NEW ZEALAND HEALTH TECHNOLOGY ASSESSMENT (NZHTA)

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Risk factors for breast cancer in women

A systematic review of the literature

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This report was authored by Robert Weir and Peter Day who conducted the critical appraisals and prepared the report.

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DISCLAIMER

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EXECUTIVE SUMMARY

Objective

This systematic review was conducted to estimate the level of increased breast cancer among women with defined risk factors as requested by the National Screening Unit (NSU), Ministry of Health. These risk factors included: previous breast cancer, at-risk lesions such as atypical ductal hyperplasia, lobular carcinoma in situ, lobular hyperplasia and sclerosing adenosis, increased breast density, childlessness, early menarche, postmenopausal obesity, exogenous hormone use, dietary factors and alcohol. The NSU specifically did not wish the scope to include genetic predisposition (especially BRCA1 and BRCA2) or family history in the scope of the review.

Data sources

Medline, Embase, Cochrane Central Register of Controlled Trials, Current Contents, and PubMed (last 60 days) were searched for both primary studies and systematic reviews/meta-analyses. Additional searches of the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), and the HTA databases were carried out for systematic reviews/meta-analyses.

Searches were limited to English language material from 1996 to end of January 2006 inclusive.

Selection criteria

Studies were included if they included women who were assessed for breast cancer, had at least 20 human participants, included a risk factor of interest and expressed their results in the form of a rate ratio, risk ratio or odds ratio. Systematic reviews were preferentially included and observational designs were only included for the time period beyond key systematic reviews.

Excluded studies included non-systematic reviews, abstracts, letters, editorials, commentaries, superseded publications and studies published before 1996.

Of more than 2,861 articles identified by the search strategy, 263 articles were retrieved as full text from which a final group of 139 studies were identified as eligible for appraisal and inclusion in the review.

Data extraction and synthesis

A systematic method of literature searching, selection and appraisal was employed in the preparation of this report. Level of evidence was assigned using the NHMRC criteria. Studies were appraised based on study design. Evidence tables were developed describing key facets and limitations of each study included in the review.

Key results and conclusions

The following conclusions are based on the current evidence available from this report's critical appraisal of literature published on risk factors for breast cancer in women.

Factors with a higher level of risk (RR>2.0) included:

- past history of breast cancer
- selected precursor lesions of breast cancer, including atypical ductal carcinoma, lobular carcinoma and ductal carcinoma *in situ* (note, the clinical management of these conditions is heterogeneous, more detail is provided in chapter 4)
- increased breast density

Other factors appeared to have a moderate level of increased risk (RR 1.5-2.0):

- heavy alcohol intake

Some risk factors appeared to have modest levels of increased risk (RR 1.0-1.5):

- nulliparity
- post menopausal obesity
- hormone replacement therapy
- current use of oral contraceptives or recent use of oral contraceptives
- high total energy intake

Finally, for some risk factors the level of increased risk was difficult to determine:

- early menarche (likely to be relatively modest)
- xenoestrogens
- phytoestrogens
- stilboestrol

MeSH headings

Breast neoplasms, risk factors, risk assessment, obesity, obesity-morbid, hormone replacement therapy, estrogen replacement therapy, exp diet, exp food, dietary fat, exp contraceptives-oral, parity, menarche, alcohol drinking, alcoholism, carcinoma in situ, carcinoma-lobular, carcinoma-lobular, fibroadenoma, neoplasms-second primary, neoplasm recurrence-local

Additional key words

Breast adj3 dens$, nullipar$, previous breast cancer, ((past history or previous history or prior history) adj5 breast cancer)), second cancer, benign adj breast adje disease

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LIST OF ABBREVIATIONS AND ACRONYMS

BBD	benign breast disease
BMD	bone mineral density
BMI	body mass index
CBD	contralateral breast cancer
CCR	California Cancer Registry
CGHFBC	Collaborative Group on Hormonal Risk Factors in Breast Cancer
CI	confidence interval
CNBSS	Canadian National Breast Screening Study
COC	combined oral contraceptive
CSP	Cancer Surveillance Program
CVD	cardiovascular disease
DCIS	ductal carcinoma in situ
DES	diethylstilbestrol
DESAD	diethylstilbestrol adenosis project
EPT	oestrogen progestin therapy
ERT	oestrogen replacement therapy
ET	oestrogen
FFQ	food frequency questionnaire
FFTP	first full term pregnancy
GIII	Guernsey III cohort
GIV	Guernsey IV cohort
HCFA	Health Care Financing Administration
HR	hazard ratio
HRT	hormone replacement therapy
HSHS	Helsinki Student Health Services
IDC	invasive ductal carcinoma
ILC	invasive lobular carcinoma
IPC	injectable progestin contraceptive
IWHS	Iowa Women's Health Study
JACC	Japan Collaborative Cohort Study
LSS	Life Span Study
MEC	multiethnic cohort
NDI	National Death Index
NHS	Nurses Health Study
NOWAC	Norwegian Women and Cancer Study
NS	not significant
NSHDC	Northern Sweden Health and Disease Cohort
NSU	National Screening Unit
OC	oral contraceptive
OR	odds ratio
PD	percent density
RDD	random digit dialling
RR	relative risk, rate ratio, risk ratio
SCC	six category classification
SIR	standardised incidence rate
SEER	Surveillance, Epidemiology and End Reports program
SFMR	San Francisco Mammography Registry
SIR	standardised incidence ratio
TCRS	Tennessee Cancer Reporting System
TNM	Tumour, node, metastasis
UBC	Unilateral breast cancer
WHI	Women's Health Initiative (trial)
WHR	Waist to Hip Ratio
WHS	women's health study

Chapter 1: Background

This systematic review was requested by Dr Madeleine Wall, Clinical Leader BreastCancer Aotearoa, National Screening Unit, Public Health Directorate, Ministry of Health, New Zealand.

The Cancer Control Strategy and the New Zealand Health Strategy are the two overarching documents that support the development of New Zealand national guidelines for women at high risk of breast cancer. Any initiatives that support the early identification of women with breast cancer and introduction of strategies to reduce the psychological, emotional and physical effects of cancer are highly valued.

The provision of mammography for women at high risk of breast cancer is a high profile media topic and an area of interest for the current Minister of Health. Numerous health reports have been written and the number of ministerial enquiries is increasing as the level of awareness around breast cancer increases.

At this time, a policy decision has been announced that allows women at high risk of breast cancer access to screening on a BreastScreen Aotearoa mobile unit in rural areas. The lack of appropriate guidelines for risk identification, surveillance and management of these women has been identified as a problem in attempting to implement the policy. The requirement for national guidelines for women at high risk of breast cancer has been identified as a priority by the BreastScreen Aotearoa Advisory Group and the National Screening Unit (NSU) Consumers Reference Group. The NSU supports the development of guidelines, which it recommends being undertaken by a representative group of interested stakeholders and not exclusively the NSU.

In order to underpin any guideline, an evidence-based review of the literature is required to identify the population at risk, methods of identifying individual risk, computer simulated risk models, and surveillance of those high risk groups. In particular, an assessment of the relevance of the international literature and risk estimates to the New Zealand population of women at high risk of breast cancer is required. This would identify gaps in our knowledge or applicability of international risk estimation tools to the NZ population which in turn will inform the development of national guidelines, or further research necessary before guideline development occurs.

This report covers the evidence-based review of the literature that examines selected risk factors for breast cancer. A subsequent evidence-based review is planned to examine surveillance of women at high risk of breast cancer. This review will include surveillance with mammography, ultrasound and MRI.

BURDEN OF DISEASE FROM BREAST CANCER IN NEW ZEALAND

Breast cancer is responsible for a significant proportion of cancer registrations, hospitalisations and deaths amongst New Zealand women. In 2001 there were 2,310 registrations for malignant neoplasms of the breast among women in New Zealand (Statistics New Zealand 2006). In 2003, the total number of registrations for malignant neoplasms of the breast increased with age to the early 50 year age group and then declined (see figure 1 for provisional data for registrations of malignant neoplasms of the breast in 2003). Age specific rates of breast cancer have been calculated using the estimated New Zealand population for 2003 (see figure 2).

During 2001/2 there were 2,370 discharges from publicly funded hospitals for malignant neoplasms of the breast (mean stay 9.7 days) and 267 discharges for carcinoma *in situ* of the breast (mean stay 2.6 days) amongst women. There were 615 deaths from malignant neoplasms of the breast among women in 2001 (Statistics New Zealand 2006).

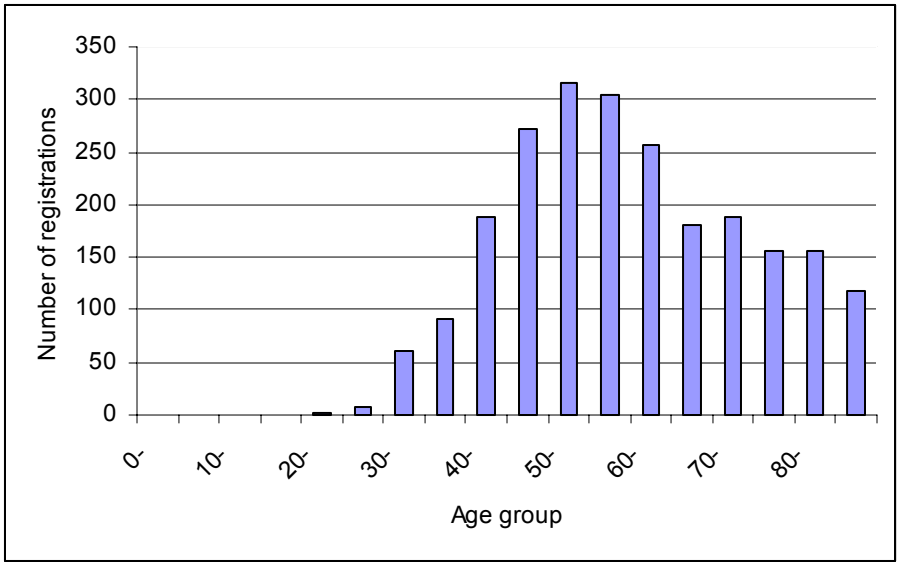

Figure 1: **Number of registrations for malignant neoplasms of the breast among women by age group, New Zealand: 2003 (provisional data)**

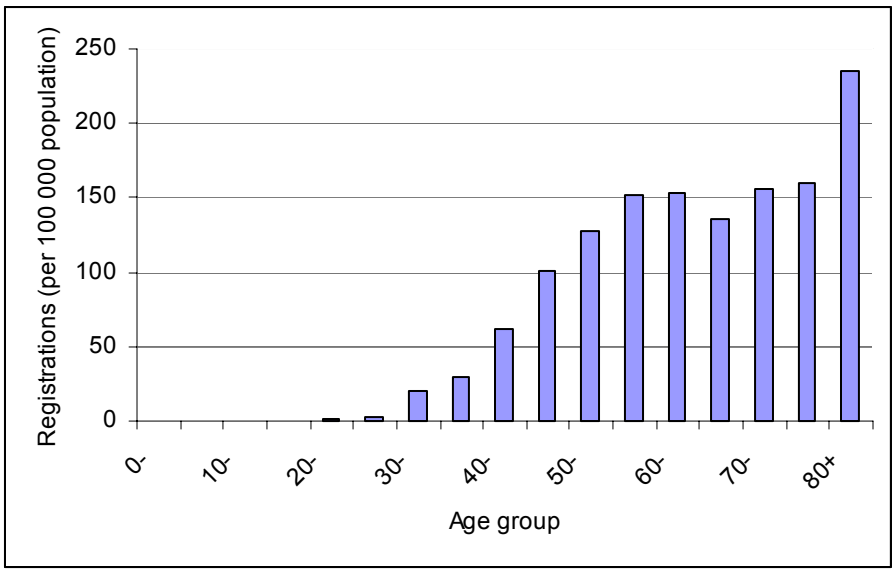

Figure 2: **Age specific rate of registrations for malignant neoplasms of the breast among women by age group, New Zealand: 2003 (provisional data)**

REVIEW QUESTION

The overarching review question for this systematic review was: What is the level of increased risk (expressed as a risk ratio, rate ratio or odds ratio) of breast cancer among women with the risk factors identified in the scope of evaluation?

REVIEW SCOPE

This systematic review focuses on the evaluation of level of risk associated with defined risk factors for breast cancer amongst women. Another report will present a review examining surveillance of women at high risk of breast cancer. The Ministry of Health requested that the scope of the present systematic review be limited to the following risk factors:

- previous breast cancer
- at-risk lesions such as atypical ductal hyperplasia, lobular carcinoma in situ, lobular hyperplasia and sclerosing adenosis
- increased breast density
- childlessness
- early menarche
- postmenopausal obesity
- exogenous hormone use
- dietary factors
- alcohol.

It is recognised that some of the above risk factors interact with each other. However, interaction of the above risk factors was outside the scope of the review.

The search was limited to full reports published in English and published between 1996 and December 2005. Full details of inclusion and exclusion criteria are provided in the next chapter.

STRUCTURE OF REPORT

This report is divided into sections. The methodology includes search strategy, inclusion and exclusion criteria, and outcomes considered. The results section of the review includes primary and secondary research considered. These results are divided into chapters for different risk factors. They are restricted to text and tables that present highly summarised and aggregated data from the studies selected and appraised. The corresponding evidence tables for the studies that were included in the review are found in the appendices. These appendices constitute the bulk of this report. This approach has been taken in recognising the need for simplicity in locating the key information in an easily used format. Thus, it is emphasised that the more detailed analyses of individual studies can be found in the appendices (again organised by risk factor). If further detail is required about individual studies, the reader is referred to the original studies. The final section summarises results, briefly discusses methodological limitations in the area, presents areas where further research is required and presents key conclusions.

Chapter 2: Methodology

SELECTION CRITERIA

Selection criteria for this systematic review are listed in Table 1. These criteria were pre-set in conjunction with the Ministry of Health.

Table 1: Inclusion/exclusion criteria for identification of risk factors for breast cancer

Characteristic	Criteria
Inclusion criteria	
Publication type	1. Systematic reviews. 2. Clinical studies with a control group for the time period beyond key systematic reviews
Population	Women who were assessed for breast cancer within the study
Sample size	At least 20 human patients in the clinical studies
Risk factors	Assessment of risk factor status, as documented in the scope of the review
Outcome	Risk or rate of breast cancer among women with versus without the risk factors of interest (measure of effect expressed as an odds ratio, risk ratio or rate ratio)
Exclusion criteria	
Publication type	Non-systematic reviews, uncontrolled studies, letters, editorials, expert opinion articles, conference proceedings, comments and articles published in abstract form
Publication topic	Limited to genetic and familial risk factors
Publication superseded	Publication superseded by a later publication with longer follow up data and overlap in the patient population
Language	Non-English language articles
Time period	Studies published before 1996

SEARCH STRATEGY

A systematic method of literature searching and selection was employed in the preparation of this review as follows:

- A search for systematic reviews and meta-analyses discussing any of the ten included risk factors for breast cancer was carried out in November 2005. The search was run on the Medline and Embase databases, the Cochrane Database of Systematic Reviews, the DARE and HTA databases
- The results from this process established the date range for the individual risk factor searches that followed – i.e. primary studies were sought only for years not already covered by satisfactory systematic reviews.
- There was enough recent information from systematic reviews to cover one of the risk factors – hormone replacement therapy. Additional primary studies were then sought for the remaining nine risk factors.
- A core search strategy encompassing the breast cancer risk factor concept was developed for each database linked with filters for trials (including randomised trials), and observational studies. The filters were adapted from the Scottish Intercollegiate Guidelines Network (SIGN) filters http://www.sign.ac.uk/methodology/filters.html for the Medline, and Embase databases. The

Medline strategy was also used for the Cochrane Central Register of Controlled Trials. The Current Contents strategy was adapted and simplified to cope with this database being without indexing and having restrictions on the number of statements per search.
- Using the core search, separate searches for primary studies on each risk factor were carried out for the range of years not covered by a relevant systematic reviews located.
- A simple search using PubMed last 60 days was also carried out for each individual risk factor to identify very recent publications.
- Further details of the search strategy are given in Appendix I included the range of years covered for each individual risk factor.
- The searches for the individual risk factors were carried out between 10 and 26 January 2006 and were limited to references in English.

Searches were limited to English language material published from 1996 onwards. The searches were completed on 26 January 2006.

Principal sources of information

The following databases were searched (using the search strategies outlined in **Appendix 1**):

Bibliographic databases

- Cochrane Central Register of Controlled Trials
- Current Contents
- Embase
- Medline
- PubMed (last 60 days)

Review databases

- Cochrane Database of Systematic Reviews
- Database of Abstracts of Reviews of Effects (DARE)
- Health Technology Assessment database

Extended Internet searching, hand searching of journals or contacting of authors for unpublished research was not undertaken in this review. A complete list of the sources searched for this review is given in **Appendix 2.**

Search terms used

- Index terms from Medline (MeSH terms): breast neoplasms, risk factors, risk assessment, obesity, obesity-morbid, hormone replacement therapy, estrogen replacement therapy exp diet, exp food, dietary fat, exp contraceptives-oral, parity, menarche, alcohol drinking, alcoholism, carcinoma in situ, carcinoma-lobular, carcinoma-lobular, fibroadenoma, neoplasms-second primary, neoplasm recurrence-local
- Index terms from Embase (where different from the MeSH terms):breast cancer, risk factor, morbid obesity, hormone substitution, second cancer, alcohol consumption, nullipara, breast fibroadenoma, breast hyperplasma, breast carcinoma
- The above index terms were used as keywords in databases where they were not available and in those databases without controlled vocabulary.
- Additional keywords (not standard index terms) were used in all databases: Breast adj3 dens$, nullipar$, previous breast cancer,((past history or previous history or prior history) adj5 breast cancer)), benign adj breast adj disease

STUDY SELECTION

Studies were selected for appraisal using a two-stage process. Initially, the titles and abstracts (where available) identified from the search strategy, were scanned and excluded as appropriate. The full text articles were retrieved for the remaining studies and these were appraised if they fulfilled the study selection criteria outlined above.

There were 2,861 studies identified by the search strategy. Two hundred and sixty-three full text articles were obtained after excluding studies from the search titles and abstracts. A further 124 of these

full text articles did not fulfil the inclusion criteria and are presented in **Appendix 3**. Therefore, 139 articles were fully appraised and are included in this report. These are presented in the **References**. No references were excluded on the basis that they could not be retrieved, either electronically or in hardcopy.

APPRAISAL OF STUDIES

The evaluation initially classified studies according to National Health and Medical Research Council (NHMRC, 2000) levels of evidence criteria, so as to rank them in terms of quality according to a pre-determined "evidence hierarchy" (see **Appendix 2**). These evidence levels are only a broad indicator of the quality of the research. The levels describe groups of research which are broadly associated with particular methodological limitations. However, these levels are only a general guide to quality because each study may be designed and/or conducted with particular strengths and weaknesses. High level evidence is provided by a well conducted randomised-controlled trial. Each study included in the review was also appraised using standard criteria for the specific study design.

Summaries of appraisal results are shown in tabular form as **Evidence Tables** and include:

- reference (authors, publication date) and country where study was principally conducted
- design
- evidence level (applying NHMRC criteria)
- study setting
- patient characteristics
- patient inclusion and exclusion criteria
- results of analyses comparing groups on eligible outcomes, including statistically tested comparisons and reporting relevant statistical data
- authors' conclusions

Systematic reviews and meta-analyses are described and critiqued in terms of their search strategy, inclusion/exclusion criteria, data synthesis and interpretation.

KEY OUTCOME MEASURES FOR PRIMARY STUDIES

The key outcome measure used was the relative risk of breast cancer in those exposed to the risk factor of interest compared with those not exposed. It should be observed that for some risk factors everyone was exposed at some level. In these cases, a reference category was assigned for comparative purposes. Usually this was the lowest level of exposure for risk factors to which everyone is exposed. The relative risk estimate could take the form of a rate ratio, risk ratio or odds ratio. In case control studies and studies presenting adjusted estimates by use of logistic regression, odds ratios were presented. Confidence intervals were also presented in association with the relative risk estimate.

LIMITATIONS OF THE REVIEW

This study has used a structured approach to review the literature. However, there were some inherent limitations with this approach. Namely, systematic reviews are limited by the quality of the studies included in the review and the review's methodology.

This review has been limited by the restriction to English language studies. Restriction by language may result in study bias, but the direction of this bias cannot be determined. In addition, the review has been limited to the published academic literature, and has not appraised unpublished work. Restriction to the published literature is likely to lead to bias since the unpublished literature tends to consist of studies not identifying a significant result.

Papers published pre-1996 were not considered and original papers were only included for the time period beyond identification of adequate quality secondary research (the specific time periods involved varied by risk factor).

The studies were initially selected by examining the abstracts of these articles. Therefore, it is possible that some studies were inappropriately excluded prior to examination of the full text article. However, where detail was lacking or ambiguous, papers were retrieved as full text to minimise this possibility.

The majority of studies included in this review were conducted outside New Zealand, and therefore, their generalisability to the New Zealand population and context may be limited and needs to be considered. However, studies would have wider generalisability if results are consistent across study populations and the association under investigation is biologically plausible.

Although two reviewers were responsible for data extraction, critical appraisal and report preparation double extraction and appraisal of the same studies was not conducted.

The review scope was developed with the assistance of Ministry of Health staff. It had the goal of providing information that was useful for identifying women at increased risk of breast cancer.

This review was conducted over a limited timeframe given the size of the topic (November, 2005 – June, 2006).

This review has greatly benefited from the advice provided by the peer reviewer (Professor Ann Richardson). However, it has not been exposed to wider peer review.

Chapter 3: Past history of breast cancer

SECONDARY RESEARCH

The search strategy identified no relevant reviews.

PRIMARY RESEARCH: STUDY RESULTS

Full details of the five papers appraised, including methods, key results, limitations and conclusions, are provided in evidence Table 4.1 (Appendix 4, pages 91-95). Studies are presented in reverse chronological order of publication.

Three of the studies were retrospective analyses of cohorts of confirmed first primary breast cancer patients from the:

- Eindhoven Cancer Registry in the Netherlands (Soerjomataram et al, 2005)
- Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute in the United States (Li et al, 2003)
- Cancer Registry of Slovenia (Volk & Pomp-Kim, 1997).

The other two studies were hospital-based, with one nested prospective cohort study set in the Nottingham city hospital (Kollias et al, 1999). The other was a retrospective cohort analysis set in the Cancer Institute in Chennai, India (Gajalakshmi et al, 1998). The aim of these studies was either to assess the risk factors associated with the development of a second primary breast cancer (contralateral breast cancer) in first primary breast cancer patients (Li et al, 2003) or to compare the incidence of second primary breast cancer among first primary breast cancer patients with the incidence of breast cancer expected in the general population (Soerjomataram et al, 2005; Volk & Pomp-Kim, 1997) or to assess both (Kollias et al, 1999; Gajalakshmi et al, 1998). General limitations with the studies reviewed included inadequate descriptions of patient characteristics of the cohort, use of the retrospective study design where study investigators were not blinded to patient status or clinical characteristics, lack of adequate control over confounders and low power to determine valid associations given the small number of CBC cases in some studies. The validity and reliability of patient data abstraction methods were also unknown.

Studies comparing the incidence of second primary breast cancer among breast cancer patients with the incidence expected in the general population

Soerjomataram et al (2005b), estimated the standardised incidence ratio (SIR) for developing a second primary breast cancer was significantly greater among women with a prior first primary breast cancer than in the general population (SIR=6.3, 95% CI 3.2-3.8). There was also increased risk for both pre-menopausal (SIR=3.5, 95% CI n/a) and postmenopausal women (SIR=2.6, 95% CI n/a). The main limitations with this study was that no confounders were adjusted for and there may have been misclassification bias due to first primary breast cancer metastases being classified as second primary breast cancer. It is likely that detection bias may have occurred, in that women with a past history of beast cancer would be followed up more closely for breast cancer than the general population group.

In another study, the mean annual metachronous contralateral breast cancer (CBC) incidence rate was reported to be 6.45 per 1000 women years (s.d. 1.61 per 1000 women years) compared to the UK standardised rate of 2.3 per 1000 women years, with a reported RR of 2.8 for CBC after previous treatment and RR 5.8 to the remaining breast (Kollias et al, 1999).

The rate ratio for first primary and second primary breast cancer age-specific incidence rates adjusted for world population showed a rate ratio of 7.4 (4.8-11.4) per single breast compared to other women in the population in the study by Gajalakshmi et al (1998). Significant increases in risk were evident at all age-groups (<45, 45-54, and ≥55 years). The main limitation with this analysis was that the Cancer Registry data for the general population were not available prior to 1982 (subjects with a first primary breast cancer diagnosed 1960-1989 were included in the CBC cohort).

In the study by Volk and Pomp-Kim (1997) the SIR for developing a second primary breast cancer was also significantly greater among women with a prior first primary breast cancer than that expected in the general population (SIR=1.4, 95% CI 1.1-1.7). This was also true for women aged <50 years (SIR=3.0, 95% CI 2.0-4.3) but was not significantly greater for those aged 50+ years (SIR=1.2, 95% CI 0.9-1.4). This study considered a range of secondary invasive cancers including breast cancer. The main study limitation was possible misclassification bias due to coding practices in use until the beginning of 1991 for multiple primaries of the breast that may have been coded as metastases of the first primary cancer.

Studies reportingon risk factors for the occurrence of second primary breast cancer (contralateral breast cancer) among breast cancer patients

Three studies were appraised that reported on risk factors for the occurrence of second primary breast cancer. They did not present estimates of relative risk comparing women with and without a past history of primary breast cancer. Rather the focus was on other risk factors responsible for elevated relative risks among study populations of women with a past history of primary breast cancer. Therefore, these studies provide some information on the way in which different risk factors for breast cancer interact.

The study by Li et al (2003) evaluated risk factors for second CBC in younger women diagnosed with first breast cancer at age < 45 years. A high body mass index (BMI) was associated with increased risk (≥ 30 kg/m^2, hazard ratio 2.6; 95% CI 1.1-3.9, and 25.0-29.9 kg/m^2, hazard ratio 2.1, 95% CI 1.1-3.9). The tumour marker expressed by c-erbB-2 in first breast cancer was also a significant risk factor for the incidence of CBC. Other risk factors that were not significant included age at menarche, gravidity, age at first live birth, number of live births, OC use, average number of drinks per week and family history of breast cancer.

A univariate analysis of risk factors associated with metachronous CBC in women with first primary breast cancer found no significant risks in the histological factors analysed except invasive tumour type (p=0.02) or in clinical factors except for family history (p=0.0001) and age of onset (p<0.05) (Kollias et al, 1999). Multivariate analysis found strong family history RR=2.5 (95% CI 1.45-4.26) and lobular tumour RR=1.9 (CI 1.1-3.13) as predictors significantly associated with CBC incidence.

The study by Gajalakshmi et al (1998) analysed various risk factors associated with an increased risk of developing CBC. Univariate analysis of risk factors associated with metachronous CBC in women with first primary breast cancer found that the risk of CBC increased with increasing education and income level, and Christian religion. Univariate and multivariate rate ratios for CBC by family history showed elevated risk if the mother had breast cancer RR=4.5 (95% CI 1.1-19.6). Apart from age 21-25 years at first childbirth other age-groups, reproductive factors, menopausal status, year of diagnosis, treatment, and time since diagnosis were not shown to be elevated risk factors.

Summary

The results of the four studies comparing the incidence of second primary breast cancer among breast cancer patients with the incidence expected in the general population consistently reported increased risk. The SIR ranged from 1.4 to 6.3 and rate ratios ranged from 2.8 to 7.4 in these studies. Breakdown by various stratified risk factors also showed elevated risk. The limited control of confounding and the increased follow-up of women with past history of breast cancer in these studies means the association is likely to be overestimated.

Three studies reported on various risk factors associated with the development of a second primary breast cancer in first primary breast cancer patients. High BMI at diagnosis of first primary breast

cancer (Hazard ratio for BMI ≥30 kg/m^2 was 2.6, 95% CI 1.1-3.9) and strong family history with an RR ranging from 2.5 to 4.5 were the most consistently elevated risk factors for the development of a second primary breast cancer in the studies considered.

Chapter 4: Lesions associated with increased risk of breast cancer

INTRODUCTION

There is variation in the nomenclature used for benign breast disease lesions. Within this section, we have retained the nomenclature used in the source article. It is noted that this may not meet currently accepted, standard classifications. It should also be noted that the cellular appearance (particularly the presence of atypia) is considered to be an important hallmark of the level of risk so, while there are various types of benign breast disease, including fibroadenoma, sclerosing adenosis, ductal lesions, and lobular lesions it is useful to also consider the cellular appearance (particularly the presence of atypia) when considering the level of increased relative risk. This section has suffered from the preset limitation of restricting the review to studies published from 1996 onwards. Specifically, the key research for the association between benign breast disease and breast cancer was published before 1996. Therefore, some of the benign breast lesions considered to be associated with a relatively small increase in relative risk have not been considered in this section simply because the relevant studies did not meet the eligibility criteria that were pre-set for this review.

SECONDARY RESEARCH

Two systematic reviews were included (El-Wakeel and Umpleby 2003; Arpino et al. 2005). One systematic review included seven observational studies (Level III-2 evidence), (El-Wakeel and Umpleby 2003). Two studies in this review were considered to provide the strongest evidence. The results of these two studies are summarised in Table 5.1 (appendix 5, page 98). In brief, both found increased levels of risk associated with fibroadenoma (both with typical and atypical hyperplasia). One of these two studies also presented results for the association between benign breast disease and breast cancer. The authors divided benign breast disease into three categories: (1) without hyperplasia, (2) with typical hyperplasia and (3) with atypical hyperplasia. In all three cases there was a significantly increased level of risk with odds ratios ranging from 1.5 (with no hyperplasia) to 2.2 (with atypical hyperplasia). The two estimates for fibroadenoma with typical hyperplasia were RR 2.16 (95% CI 1.2-3.8) and OR 3.7 (95% CI 1.5-9.2). Estimates were higher for fibroadenoma with atypical hyperplasia: RR 4.77 (95% CI 1.5-15) and OR 6.9 (95% CI 1.5-30.6). Limitations of this review and the studies included in the review are documented in Table 5.1. In brief, it was unclear how the preset quality criteria were used in determining the most robust studies and it was unclear if carcinoma *in situ* was included as an outcome in some of the included studies. Studies selected were limited to the English language.

The second review provided a more complete discussion of different precursor lesions (Arpino et al. 2005). Some general comments can be made. There are a wide range of premalignant lesions but few are thought to have premalignant potential. The best characterised lesions with premalignant potential are atypical ductal hyperplasia, atypical lobular carcinoma and lobular carcinoma *in situ*. Ductal carcinoma *in situ* is also thought to have premalignant potential and both unfolded lobules and usual ductal hyperplasia are thought to be very early premalignant lesions. A continuum can be envisaged in the development of breast carcinoma with the following stages:

1. unfolded lobules and usual ductal hyperplasia
2. atypical ductal carcinoma
3. lobular carcinoma

4. ductal carcinoma *in situ*

The review summarised relative risk estimates for each of the above lesions. Unfolded lobules and usual ductal hyperplasia were thought to present between a 1.5 and two fold increase in risk, atypical ductal carcinoma presented about a four fold increase in risk, lobular carcinoma about a six to ten fold increase in risk and ductal carcinoma *in situ* about an eight to ten fold increase in risk.

There is no current evidence to suggest increased surveillance, additional mammographic examinations or additional screening is needed for women with usual ductal hyperplasia in the absence of additional breast cancer risk factors. It is worth observing that these lesions are associated with a similar level of relative risk as those associated with fibroadenoma in the absence of atypia.

Atypical ductal hyperplasia and ductal carcinoma *in situ* are primarily differentiated on a quantitative basis and misclassification can occur given the semi-subjective differentiation required. Tamoxifen therapy should be considered for women with atypical ductal hyperplasia. Current treatment options for ductal carcinoma *in situ* include breast conserving surgery and radiation therapy (with or without tamoxifen) or total mastectomy.

Lobular neoplasia cover the spectrum from minimal lobular involvement to maximum distention of acini in several lobules. Various classification systems exist. The clinical significance and management of these conditions remains unsettled. Current thinking is that the approach should be individualised. Arpino et al. (2005), suggest women with lobular carcinoma should be followed-up with annual mammography and clinical breast examination. Tamoxifen should be considered in lobular carcinoma *in situ*. Bilateral mastectomy can be considered in women who want the greatest risk reduction while noting the negative aspects of this approach.

Limitations of this review and the studies included in the review are documented in Table 5.1 (Appendix 5, pages 97-98). While the literature search methods were well described and appropriate, the selection criteria for inclusion in the review were not fully documented. The articles selected were limited to the English language.

PRIMARY RESEARCH: STUDY RESULTS

Since the latest systematic review was published in 2005, primary research studies were not included in this review.

Summary

The results presented in El-Wakeel and Umpleby (2003) covered a narrower range of potential precursor lesions. Nevertheless, the results presented were similar to those identified in the review by Arpino et al (2005). The results of the latter review can be summarised as follows:

1. unfolded lobules and usual ductal hyperplasia (potentially very early precursor lesions): 1.5 to two fold increase in risk of breast carcinoma.

2. atypical ductal carcinoma (later precursor lesion): four fold increase in risk

3. lobular carcinoma (later precursor lesion): six to ten fold increase in risk

4. ductal carcinoma *in situ* (later precursor lesion): eight to ten fold increase in risk

Current thinking is that the lower grade lesions like fibroadenoma and ductal hyperplasia do not require enhanced surveillance. One effect of restricting this review to studies published from 1996 onwards is that the level of risk associated with other benign breast lesions has not been placed into context. Specifically, while fibroadenoma has been documented in this review (since it was the focus of a systematic review in 2003), this is not meant to imply that there are not other benign breast lesions associated with a similar level of increase in risk. Other lesions, such as sclerosing adenosis have not been documented simply because the research was published before 1996.

Chapter 5: Increased breast density

SECONDARY RESEARCH

The search strategy did not identify any relevant reviews.

PRIMARY RESEARCH: STUDY RESULTS

Study characteristics

Twelve studies (13 publications) were identified that fulfilled the eligibility criteria, examined the relationship between breast density and risk of breast cancer and were published from 1996 onwards. Evidence tables for these studies are presented in Table 6.1 (appendix 6, pages 100-116). The studies selected were characterised by variability in the:

- study design
- criteria used for classification of breast density
- number of categories used for different levels of breast density
- reference category used for estimation of relative risk
- specific type of mammography technique used for measurement of breast density
- variation in definition of a case
- controlling of masking bias.

There were two cohort studies, seven nested case control studies and three non-nested case control studies. Most of the case control studies included some form of matching: frequency matching was used in two and individual matching in six. The nested case control studies were mainly set within cohorts of women in mammography screening programmes. In the cohort studies and some of the nested case control studies, breast density was estimated before development of case status. This approach is clearly advantageous in minimising bias, although some other studies blinded the mammography reader to case status. There was variation in the co-variants included as potential confounders within the multivariate models developed to estimate level of risk. In some cases this variation may have been appropriate, however, in other cases some co-variants were not included in the models due to the lack of relevant data. Some studies also solely presented results stratified by other covariates such as parity, menopausal status and type of positive family history for breast cancer.

Classification of breast density used both qualitative and quantitative methods. Common qualitative techniques include the Wolfe classification system and the BI-RADS classification system. The Wolfe classification system is (Nagao et al. 2003):

- N1: parenchyma primarily fat
- P1: parenchyma chiefly fat with prominent ducts in anterior portion (no more than a quarter of the volume of the breast)
- P2: prominent duct pattern (more than a quarter of the volume of the breast)
- DY: increased density but without a prominent duct pattern as the dominant feature.

The BI-RADS classification system is (Vacek and Geller 2004):

- entirely fat
- scattered
- heterogeneous
- extremely dense.

Quantitative methods largely used computer assisted technology. Most commonly the percentage area of dense breast tissue was estimated. Typically these methods were based on digitisation of mammography images. Estimation of percentage area of dense breast tissue first constituted outlining the breast area and estimating size. A threshold was then set for dense breast tissue and the area of dense tissue was compared with the total area of the breast. The area of dense breast tissue was also commonly used in assessing the relationship between breast density and risk of breast cancer. Other methods used less commonly included regional skewness, fractal dimension (a measure of image texture where it is expected that dense tissue will yield more sheet like terrain), and visual assessment by a radiologist.

In most studies, breast density was categorised although some also presented estimates of the change in relative risk with a given change in breast density. The number of categories used varied between two and six. Some studies used more than one classification system with variable numbers of categories. Some studies also did not present estimated relative risks for each level of breast density with these studies tending to compare the densest classification with the least dense classification. Partly as a consequence of this variation, there was also variation in the reference category used. Although all studies used the least dense category as the reference, the precise classification of this category varied. For example, some studies used "zero percent density" based on area as the reference whereas another study used "≤25% percent density" as the reference. In consequence, estimated relative risks would be expected to be lower amongst those studies with a higher reference category cut-off.

There was variation in the type of view used from mammography in assigning breast density and also variation in the method of determining which breast mammogram side to use both amongst cases and controls. Some studies used cranio-caudal views and others used medio-lateral oblique views. However, some studies noted that there was a strong correlation in breast density classification between the views used. In some cases, the side used for assigning density was the same side as that in which breast cancer subsequently developed, in others the contralateral side was used. Typically, if the mammography film used was the one taken at the same time as diagnosis of breast cancer, then the contralateral side was used. In contrast, if some time had elapsed then the same side was used as that in which breast cancer developed. In case control studies, there was also some variation in approach, with some studies selecting the side used randomly, others using all one side and others using either side but not making use of a random selection process.

There was variation in the definition of a case with some studies restricting cases to those with histologically confirmed invasive breast cancer while others also included *in situ* cancer in their definition.

The precise status of masking bias is unclear. Masking bias is considered to be a potential issue in the assessment of the association between breast density and risk of subsequent breast cancer as it is thought that an invasive breast cancer is more likely to be masked in a mammogram of women with dense breasts. Thus cases of invasive breast cancer that develop shortly after the mammogram was taken that were used to estimate breast density may represent prevalent cases (i.e. the disease was already present when the mammogram was taken) rather than incident cases. Therefore, a number of studies disregarded cases of invasive breast cancer diagnosed within one year of the relevant mammogram. Two studies also investigated the possibility of masking bias by following the variation in relative risk between breast density and risk of breast cancer at different time intervals post mammography (Maskarinec et al. 2005; van Gils et al. 1998). If masking bias was the full explanation for an increased risk of breast cancer in women with increased breast density then we would expect an increased risk of breast cancer in the short term after mammography but this relative risk should return to unity over time. Both studies were somewhat underpowered, especially the one by van Gils that set out to also assess the role of age and more advanced mammography techniques in the role of masking bias, so it was not possible to form any firm conclusions. However, in both studies the association between breast density and breast cancer appeared to be similar at different time intervals. Thus, there was little support for masking bias as the full explanation of an increased level of risk with increased breast density in these studies.

Study results

With the variation in methods used between studies it would be inappropriate to pool all the studies in a meta-analysis. However, some general comments can be made about the study results. Most importantly, there was a consistently increased level of risk of breast cancer among women with increased breast density (irrespective of the method of measurement) across the studies appraised. The results presented in Table 2 are the association between percent area of dense tissue and risk of breast cancer. As observed in the table, all studies presenting overall results estimated a statistically significant increase in risk of breast cancer amongst women with the densest classification compared with the least dense classification. The estimated level of relative risk approximated four in these studies with the exception of the study by Kerliskowe et al (2005), where the odds ratio was lower. However, this study was characterised by having a higher cut off in its reference category, so the result remains consistent with the other four studies. One of these four studies presented results for the presence of a linear trend (Ursin et al. 2003). A highly statistically significant linear trend consistent with increased risk of breast cancer with increasing levels of breast density was identified.

The stratified results are more difficult to interpret and are not so relevant to the research question. However, it is important to consider that interaction between covariates can result in variation in the estimated association compared with when the role of interaction is not considered in developing a model of increased risk of breast cancer.

Some caution also needs to be applied when considering the generalisability of these results to New Zealand after considering the results of Maskarenic et al (2005) who suggested the level of risk may be higher amongst "Caucasian" and "Native Hawaiian" women than Japanese women. It should also be noted that there are limitations to the studies included in Table 2. These are listed in detail in Table 6.1 under the limitations and comments column. However, the level of consistency between studies, irrespective of these limitations, with studies that have used different designs, including some with prospective evaluation of breast density and others that excluded cases presenting within one year of mammography presents support for percent area of breast density as an independent risk factor of breast cancer.

Three studies used area of dense breast tissue as a surrogate for breast density. These results are presented in Table 3. These studies also showed an increased risk in breast cancer with increasing area of dense breast tissue. Given the relative dearth of studies identified few conclusions could be drawn. It was also not clear whether the percent of dense tissue or the area of dense tissue is a more appropriate measure of breast density given the lack of studies comparing the two methods.

Three studies used a qualitative method of assigning breast density (Nagao et al. 2003; Torres-Mejia et al. 2005; Vacek and Geller 2004). Two of these used the Wolfe system (Nagao et al. 2003; Torres-Mejia et al. 2005). These results are presented in Table 4. In each study the adjusted estimates that compared the densest category with the least dense category found a statistically significant increased risk of breast cancer amongst women classified in the densest category.

Table 2: Association between percent area of dense tissue and risk of breast cancer.

Reference	Study characteristics	Association between percent dense area and risk of breast cancer. RR (95% CI)
(Yaffe et al. 1998)	Nested case control study No density as reference	> 75% density: RR 4.00 (2.12-7.56)
(Byrne et al. 2001)	Nested case control study <10% density as reference	10-49: OR 2.0 (1.2-3.5) 50-74: OR 3.0 (1.7-5.4) ≥ 75: OR 4.4 (2.1-9.0)
(Ursin et al. 2003)	Case control study <1% density as reference	1-: OR 1.57 (0.81-3.03) 10-: OR 1.74 (0.91-3.31) 25-: OR 2.30 (1.24-4.28) 50-: OR 3.21 (1.65-6.25) 75+: OR 5.23 (1.70-16.13) *Ptrend* 0.0001
(Kerlikowske et al. 2005)	Nested case control study <23.9% density as reference	23.9-34.2%: OR 1.2 (0.6-2.3) 34.3-42.6%: OR 1.2 (0.6-2.4) 42.7-54.0%: OR 1.9 (1.0-3.7) 54.1-66,7%: OR 2.8 (1.5-5.4) 66.8+%: OR 2.7 (1.4-5.4)
(van Gils et al. 1998)	Nested case control study Note: results stratified by parity with reference group 1+ children and <5% density.	Among group with 1+child: 5-25% density: OR 2.7 (1.3-5.6) >25% density: OR 3.6 (1.7-7.7) Among group with no children: <5% density: OR 1.1(0.2-5.8) 5-25% density: OR 8.5 (3.1-23.0) >25% density: OR 6.6 (2.6-16.5)
(Boyd et al. 1999)	Nested case control study Note: results stratified by type of positive family history. Results compare most and least extensive categories of breast density	≥1 first degree relative with breast cancer: RR 4.67 (95% CI 0.63-34.52) ≥2 first or second degree relative with breast cancer: RR 2.42 (95% CI 0.16-37.65) ≥1 first or second degree relative with breast cancer RR 6.83 (95% CI 2.02-23.14)
(Nagata et al. 2005)	Case control study Note: results stratified by menopausal status. No density as reference	1. Premenopausal women 1-24: OR 2.27 (0.64-8.08) 25-49: OR 4.01 (1.16-13.9) 50-75: OR 4.37 (1.24-15.4) 75-100: OR 1.36 (0.31-6.06) *Ptrend* 0.22 2. Postmenopausal women 1-24: OR 1.17 (0.55-2.49) 25-49: OR 3.00 (1.20-7.48) 50-100: OR 4.19 (1.33-13.2) *Ptrend* 0.005
(Maskarinec et al. 2005)	Nested case control study Note: results stratified by timing of mammogram in original study. Only mean results presented in this table. <10% density as reference	10-24.9: OR 1.61 (1.09-2.39) 25-49.9: OR 2.16 (1.45-3.20) 50+: OR 3.59 (2.29-5.62) Per 10%: OR 1.22 (1.14-1.31)
(van Gils et al. 1998)	Nested case control study Note: results stratified by mammogram technique in the original study. Only results using the most recent technique presented in this table. ≤25% density as reference	Years between initial examination and diagnosis 0: OR 2.0 (0.3-14.0) 1-2 years: OR 2.1 (0.5-8.5) 3-4 years: OR 1.2 (0.5-3.2) 5-6 years: OR 1.2 (0.3-5.2)

Table 3: Association between area of dense tissue and risk of breast cancer.

Reference	Study characteristics	Association between size of dense area (cm^2) and risk of breast cancer. RR (95% CI)
(Torres-Mejia et al. 2005)	Cohort study. Least dense quartile as reference	Quartile 2: 2.23 (1.17-4.26) Quartile 3: 3.14 (1.65-5.97) Quartile 4: 3.73 (1.85-7.51)
(Nagata et al. 2005)	Case control study Note: results stratified by menopausal status. No density as reference	1. Pre-menopausal women 0.1-12.0: OR 1.58 (0.41-6.23) 12.1-26.3: OR 4.03 (1.14-14.2) 26.4-44.4: OR 5.14 (1.45-18.3) 44.5+: OR 2.78 (0.77-10.1) *Ptrend* 0.09 2. Postmenopausal women 0.1-9.5: OR 0.83 (0.33-2.12) 9.6-21.3: OR 1.07 (0.41-2.80) 21.4+: OR 4.02 (1.80-8.94) *Ptrend* 0.0002
(Maskarinec et al. 2005)	Nested case control study Note: results stratified by timing of mammogram in original study. Only mean results presented in this table. <15 cm^2 as reference	15-29.9: OR 1.40 (1.00-1.96) 30-44.9: OR 1.84 (1.27-2.65) 45+: OR 2.91 (2.02-4.21) Per 10 cm^2: OR 1.19 (1.12-1.26)

Table 4: Association between breast density classified using a qualitative method (Wolfe or BI-RADS classification) and risk of breast cancer.

Reference	Study characteristics	Association between percent dense area and risk of breast cancer. RR (95% CI)
(Torres-Mejia et al. 2005)	Cohort study. Wolfe classification: N1 as reference	P1: 2.06 (1.08-3.94) P2: 3.50 (1.98-6.21) DY: 3.90 (1.76-8.62)
(Nagao et al. 2003)	Case control study Wolfe classification: N1 as reference	P1: 1.03 (0.69-1.55) P2: 0.68 (0.36-1.31) DY: 2.20 (1.02-4.77)
(Vacek and Geller 2004)	Cohort study Note: results stratified by menopausal status. BI-RADS classification: entirely fat as reference	1. Premenopausal women Scattered: RR 2.50 (0.92-6.82) Heterogeneous: RR 3.62 (1.32-9.92) Extremely dense: RR 4.21 (1.49-11.80) 2. Postmenopausal women Scattered: RR 2.06 (1.47-2.89) Heterogeneous: RR 2.75 (1.93-3.92) Extremely dense: RR 3.48 (2.24-5.40)

General study limitations

All studies were observational thus all were susceptible to confounding. In general, however, appropriate methods were used to control for known potential confounders and the presence of significant unknown confounders in the relationship between breast density and breast cancer is unlikely to be high. Therefore, while confounding may explain some of the association between breast density and breast cancer, given the size of the estimated associations confounding is likely to have only a small role in the observed associations. One possible exception was the lack of control for use of HRT in a number of the included studies.

Misclassification of breast density is also possible and the degree of misclassification is likely to vary between methods. However, a lot of this misclassification is likely to be non-differential, given the use of pre-assignment of breast density in some studies (documented in three studies) and blinding of the mammography reader to case status in other studies (documented in five studies). Therefore, density was assigned in at least 67% of the studies without information about the case status of the participants.

The non-differential misclassification that is likely in these studies would tend to dilute the degree of association between breast density and breast cancer.

Misclassification of case status is also possible. As previously outlined, some studies classified cases solely on the basis of invasive cancer while three also included *in situ* cancer. The precise effect of this bias is not clear although it would seem likely that the association would be underestimated in those studies that also included *in situ* cancer in their definition.

Selection bias is also a consideration, particularly in the case control studies that did not use a nested design. There were three of these studies. In one of these studies, the control population did not appear to be representative of the population from which the cases were selected and in another the controls may not have been representative of women who did not have breast cancer. All the studies were susceptible to selection bias through non-participation and, in the cohort studies, loss to follow up.

Conclusions

Despite the limitations described, the strength of the association between breast density and risk of breast cancer and the consistency of results between studies using varying methods and designs and locations, leads one to conclude that breast density is an independent risk factor for breast cancer. High level of density, based on percent area of breast tissue appears to be associated with approximately a four fold increased of breast cancer compared with low levels of density. However, there are some unanswered questions:

- What is the best measure of breast density? It is noted that the most common measure is percent area of dense tissue
- Is there likely to be variation in the association by ethnic group in New Zealand?
- How does breast density interact with other risk factors for breast cancer?

It was observed that it would also be desirable to have consistency in the following areas when conducting further research on this topic:

- The type of view used in assigning breast density from mammograms
- The type and number of categories used in assigning breast density
- Routine estimation of the increased level of risk of breast cancer with stipulated increased levels of breast density.

Chapter 6: Nulliparity

SECONDARY RESEARCH

The search strategy identified one relevant secondary research study (Hunter et al. 1997). The study pooled data from six prospective studies across North America and Europe (Level III-2 evidence). Given the geographical restriction it has not been considered to be a robust review of all the evidence available at the time. The authors compared the rate of breast cancer among women with at least three parities compared with nulliparous women. The rate ratio was 0.72 (95% CI 0.61-0.86), indicating increased risk with nulliparity. The methods and conclusions are described in evidence table 7.1 (Appendix 7, page 118).

PRIMARY RESEARCH: STUDY RESULTS

Twenty-eight studies were identified that fulfilled the eligibility criteria, examined the relationship between nulliparity and risk of breast cancer, were not primarily investigating the relationship between another risk factor and breast cancer and were published from 1996 onwards. There were three cohort studies and 25 case control studies, including four nested case control studies. The evidence tables for these studies are presented in Table 7.2 (Appendix 7, pages 119-148).

Nulliparous was described in Dorlands Medical Dictionary as "having never given birth to a viable infant" (1988). Within the research presented various measures were used as a comparison between being nulliparous and parous. These included:

- Nulliparous versus parous (Gao et al. 2000; Gilani and Kamal 2004; Kojo et al. 2005; Kuru et al. 2002; Li et al. 2003b) (Lumachi et al. 2002) (Oran et al. 2004; Tamakoshi et al. 2005; Tryggvadottir et al. 2002; Wu et al. 1996)
- Nulliparous versus number of parities (Holmberg et al. 2005; McCredie et al. 1998a; Talamini et al. 1996)
- Stipulated level of parities versus other level of parities/nulliparity (Gomes et al. 2001)
- Nulliparous versus number of full term pregnancies (Clavel-Chapelon and Group 2002; Ramon et al. 1996)
- Nulliparous versus number of children (Gammon et al. 2002; Lambe et al. 1996; Magnusson et al. 1999; Minami et al. 1997) (Ng et al. 1997) (Nichols et al. 2005; Tavani et al. 1999; Viladiu et al. 1996; Wrensch et al. 2003)
- Nulliparous versus number of pregnancies (Ghadirian et al. 1998; Hu et al. 1997)
- Parous before a stipulated age versus parous after the stipulated age versus nulliparity (Bleiker et al. 1996)

Henceforth the following assumptions will be made:

1. Being parous is equivalent to having a full term pregnancy
2. Having a full term pregnancy is equivalent to having children.

Therefore, the studies will be discussed under four categories:

1. Nulliparity versus parity
2. Nulliparous versus number of parities: which encompasses number of full term pregnancies, number of children, stipulated level of parities versus other levels as well as number of parities
3. Nulliparous versus number of pregnancies
4. Parous before a stipulated age.

Nulliparity versus parity

There were 10 studies that investigated the relationship between being nulliparous and being parous with the risk of breast cancer. These results are summarised in Table 5. In the six studies where being nulliparous was the reference, the confidence interval for five of them included one. There was also inconsistency in the point estimate with one study having a measure of effect greater than 1, one having a measure of effect of one and the other four having an estimate under one. The point estimates ranged between 0.37 and 1.10. Similar inconsistencies were found in the four studies that used being parous as the reference (i.e. the OR for three was greater than one and for the other was less than one). The point estimates ranged between 0.66 and 1.4. The confidence interval included one in three of these studies. Overall, the results were consistent with nulliparity being a risk factor for breast cancer, but the level of risk was relatively low.

Table 5: Association between nulliparous/parous and risk of breast cancer.

Reference	Design and sample	Variables adjusted for	Key result RR/HR/OR, (95% CI)
Nulliparous as reference			
(Tamakoshi et al. 2005)	Cohort study (n=38,159)	age at baseline, study area, smoking status, alcohol consumption, exercise, meat intake, green leafy vegetable intake, family history of breast cancer, BMI at baseline, menopausal status and age at menarche	RR 0.95 (0.38-2.32)
(Tryggvadottir et al. 2002)	Nested case (n=1,120) control (n=10,537)	age at menarche, age at first birth, number of births, OC use, lactation, height and weight	OR 0.96 (0.74-1.25)
(Li et al. 2003b)	Case (n=975) control (n=1,007)	age	OR 1.0 (0.8-1.4)
(Oran et al. 2004)	Case (n=622) control (n=622)	marital status, menopausal status and age at menopause, BMI, smoking, first degree relative with breast cancer, history of benign breast disease	OR 0.37 (0.13-1.06)
(Wu et al. 1996)	Case (n=492) control (n=768)	age, area, ethnicity, and migration history	OR 0.57 (0.41-0.80)
(Kojo et al. 2005)	Nested case (n=27) control (n=517)	cumulative radiation dose, number of fertile years, family history of breast cancer, alcohol consumption, disruption of sleep rhythm, disruption of menstrual cycle	OR 1.10 (0.23-4.85)
Parous as reference			
(Gao et al. 2000)	Case (n=1459) control (n=1556)	age, education, family history of breast cancer, history of breast fibroadenoma, waist to hip ratio, menarcheal age, menopausal status, menopausal age, and physical activity.	OR 1.4 (0.8-2.4)
(Kuru et al. 2002)	Case (n=504) control (n=610)	age, residence, age at menarche, menstrual irregularity, age at first pregnancy, breast feeding, OC use, family history, BMI, education, previous benign breast biopsy, menopausal status and age at menopause	OR 1.18 (0.41-3.35)
(Gilani and Kamal 2004)	Case (n=498) control (n=996)	BMI, family history of breast cancer, consanguineous marriage, menopausal status and age at menarche	OR 0.66 (0.19-2.30)
(Lumachi et al. 2002)	Case (n=404) Control (n=780)	age, age at first birth, breastfeeding, use of oestrogen replacement therapy and use of oestrogen replacement therapy for more than 40 months	OR 5.25 (3.63-7.58).

Nulliparity versus number of parities

There were 15 studies that investigated the relationship between number of parities and the risk of breast cancer. These results are summarised in Table 6. The two cohort studies are presented in the table first then the studies are ordered by the number of cases. Studies that did not use nulliparity as the reference are presented last. The results are consistent with nulliparity being a risk factor for breast cancer. Further, the level of risk decreases with increasing levels of parity. The point estimates within the larger studies are consistent across studies and generally each additional "parity" is associated with a reduction of relative risk in the order of 0.09.

Table 6: Association between number of parities and risk of breast cancer.

Reference	Design and sample	Variables adjusted for	Key result RR/HR/OR, (95% CI)
(Holmberg et al. 2005)	Cohort (n=2,014,816)	age group, calendar period and residence	1: 0.93 (0.90-0.95) 2: 0.83 (0.81-0.85) 3: 0.74 (0.72-0.76) 4: 0.62 (0.59-0.64) 5: 0.57 (0.53-0.61) 6: 0.43 (0.39-0.48) Nulliparity as reference
(Clavel-Chapelon and Group 2002)	Cohort (n=91,260)	age at FFTP, age at menarche, number of spontaneous abortions, age, history of benign breast disease, family history of breast cancer, current BMI, ever married, educational level	1: 0.76 (0.61-0.95) 2: 0.73 (0.60-0.89) 3: 0.68 (0.55-0.83) 4+: 0.68 (0.53-0.87) *Ptrend* <0.0001 Nulliparity as reference
(Lambe et al. 1996)	Case (n=12,782) Control (n=54,347)	age	1: 0.92 (0.86-0.97) 2: 0.84 (0.80-0.97) 3: 0.76 (0.71-0.81) 4: 0.67 (0.61-0.74) 5: 0.53 (0.45-0.63) 6: 0.33 (0.24-0.46) 7: 0.33 I(0.19-0.57) 8: 0.63 (0.33-1.18) 9: 0.55 (0.20-1.58) Nulliparity as reference
(Magnusson et al. 1999)	Case (n=3,016) control (n=3,263)	age, age at menarche, age at first birth, menopausal status, age at menopause, height, BMI one year prior to data collection and use of HRT for at least one year	1: 0.69 (0.53-0.90) 2: 0.63 (0.49-0.81) 3-4: 0.50 (0.40-0.64) 5-6: 0.39 (0.26-0.58) 7+: 0.06 (0.01-0.26) *Ptrend* < 0.0001 Nulliparity as reference
(Gammon et al. 2002)	Case (n=1,508) control (n=1,556)	age	1: 0.97 (0.72-1.32) 2: 0.83 (0.65-1.05) 3: 0.78 (0.60-1.00) 4+: 0.63 (0.48-0.82) Nulliparity as reference
(McCredie et al. 1998a)	Case (n=891) control (n=1,864)	age, ethnicity, age at menarche, age at FFTP, duration of breast feeding, menopausal status, family history and previous surgery for benign breast disease	1: 0.86 (0.53-1.4) 2: 0.82 (0.54-1.3) 3: 0.81 (0.52-1.2) 4+: 0.57 (0.37-0.88) Nulliparity as reference
(Nichols et al. 2005)	Case (n=682) control (n=649)	age, hospital, age at first birth, alcohol use an spouse's education	1-2: 0.58 (0.22-1.54) 3-4: 0.43 (0.16-1.17) >5: 0.53 (0.18-1.56) *Ptrend* 0.6 Nulliparity as reference

Table 6: Association between number of parities and risk of breast cancer (continued)

Reference	Design and sample	Variables adjusted for	Key result RR/HR/OR, (95% CI)
(Tavani et al. 1999)	Case (n=579) control (n=668)	study, centre, year of recruitment, age, education, BMI, family history of breast cancer, parity and age at first birth.	1: 1.53 (1.09-2.13) 2: 1.70 (1.21-2.40) 3: 1.42 (0.86-2.36) 4+: 1.13 (0.47-2.71) *Ptrend* 0.05 Nulliparity as reference
(Viladiu et al. 1996)	Case (n=330) control (n=346)	age, family history of breast cancer, age at first birth and age at menopause.	1-3: 1.4 (0.7-2.5) 4-5: 1.4 (0.7-2.8) 6+: 1.6 (0.6-4.2) Nulliparity as reference
(Wrensch et al. 2003)	Case (n-285) control (n=286)	age, family history of breast cancer, benign biopsy history, previous radiation treatment, menopause status, reproductive history, OC use, HRT history, highest BMI, number of mammograms, socioeconomic status before age 21, highest degree obtained, religion in which raised, and alcohol and tobacco use.	1: 1.0 (0.54-2.0) 2: 1.1 (0.59-1.9) 3+: 1.3 (0.68-2.4) Nulliparity as reference
(Ng et al. 1997)	Case (n=204) control (n=882)	age, menopausal status, age at menarche, pregnant, age at first birth, age at last birth, use of HRT, use of OC, positive family history of breast carcinoma, breast feeding, breast biopsy, smoking, height, weight, BMI and waist to hip ratio.	For each additional delivery: 0.82 (0.7-0.9) Nulliparity as reference
(Minami et al. 1997)	Case (n=204) control (n=810)	age at menarche, history of benign breast disease and family history of breast cancer	1: 0.93 (0.43-1.99) 2: 0.62 (0.33-1.19) 3+: 0.56 (0.30-1.06) *Ptrend* 0.03 Nulliparity as reference
(Ramon et al. 1996)	Case (n=184) control n=368)	age	1: 1.10 (0.555-2.16) 2-3: 0.54 (0.30-1.03) >3: 0.37 (0.16-0.78) Nulliparity as reference
(Talamini et al. 1996)	Case (n=2,569) control (n=2,588)	area of residence, age, education, and menopausal status	0: 0.8 (0.7-1.0) 2: 1.0 (0.8-1.1) 3: 0.8 (0.7-0.9) 4: 0.7 (0.5-0.9) 5+: 0.7 (0.5-0.9) *Ptrend* <0.001 1 parity as reference
(Gomes et al. 2001)	Case (n=300) control (n=600)	irregular menstrual cycles, occupation, family history of breast cancer and OC use	0: 4.56 (2.69-7.73) 1-5: 2.61 (1.72-3.96) Reference: 6+.

Nulliparous versus number of pregnancies

There were two studies in this category. These studies are presented separately from the above section as it was unclear if all pregnancies were viable in the included studies. The results are summarised in Table 7. In one, the reference was 3+ pregnancies and in the other, nulliparity was the reference. In the latter, the confidence intervals were broad, so it wasn't possible to form any conclusions based on this study.

Table 7: Association between number of pregnancies and risk of breast cancer.

Reference	Design and sample	Variables adjusted for	Key result RR/HR/OR, (95% CI)
(Ghadirian et al. 1998)	Case (n=414) control n=429)	age, marital status, parity, age at FFTP, history of benign breast disease, family history of breast and ovarian cancers, personal income.	1: 0.78 (0.48-1.27) 2: 1.23 (0.80-1.89) 3: 0.74 (0.48-1.18) 4: 0.89 (0.53-1.50) 5+: 0.46 (0.29-0.75) Nulliparity as reference
(Hu et al. 1997)	Case (n=157) control (n=369)	age at menarche, BMI, age at first birth, and duration of breast feeding.	1-2: 1.83 (1.11-2.99) 0: 6.06 (2.40-15.3) Reference: 3+

Parity before a stipulated age

A single study assessed parity status using first parity before age 30 as the reference (Bleiker et al. 1996). Therefore, this study was not as useful to the research question as the studies outlined above. Nevertheless there was an elevated risk of breast cancer among women who were nulliparous compared with the group of women who were parous before age 30 (OR 2.32, 95% CI 1.39-3.89). Therefore, the results were consistent with the body of studies presented above.

Conclusions

Overall, the results were consistent with nulliparity being a risk factor for breast cancer. The most useful results were those that assessed the level of risk associated with increasing levels of parity. These studies showed increasing levels of protection with increasing parity number. In the larger studies the level of relative risk declined by approximately 0.09 for each additional parity. Some studies formally assessed the presence of a significant trend and generally such analyses revealed highly statistically significant trends. However, the lack of control for breast feeding may have influenced study estimates. For example, breast feeding was included in the multivariate models for only three of the 10 studies comparing parity with nulliparity. Breast feeding is closely associated with parity and the protective effect of parity is slightly greater for women who ever breastfed than for women who never breast fed. Thus, the protective association between parity and breast cancer may have been overestimated in the studies that did not control for breast feeding.

Chapter 7: Early menarche

SECONDARY RESEARCH

The search strategy identified one relevant secondary research study (Hunter et al. 1997). The study pooled data from six prospective studies across North America and Europe (Level III-2 evidence). Given the geographical restriction it has not been considered to be a robust review of all the evidence available at the time. The authors compared the rate of breast cancer among women with age at menarche of at least 15 years compared with age at menarche less than 12 years. The rate ratio was 0.72 (95% CI 0.62-0.82), indicating increased risk with younger age at menarche. The methods and conclusions are described in evidence table 8.1 (Appendix 8, page 150).

PRIMARY RESEARCH: STUDY RESULTS

Twenty-nine studies were identified that fulfilled the eligibility criteria, examined the relationship between nulliparity and risk of breast cancer, were not primarily investigating the relationship between another risk factor and breast cancer and were published from 1996 onwards. There were five cohort studies and 24 case control studies, including one nested case control study. The evidence tables for these studies are presented in Table 8.2 (Appendix 8, pages 151-179).

There was variation in the cut points used between categories of age at menarche and there was also variation in the reference category used. In some studies, the reference category was the stratum that consisted of the oldest age at menarche and in others it was the youngest stratum. Other studies used an intermediate category as the reference. The results are organised based on the category used as the reference.

Reference for age at menarche used the youngest age stratum

There were 20 studies that investigated the relationship between number of parities and the risk of breast cancer where the youngest age stratum was used as the reference category. These results are summarised in Table 8. The four cohort studies are presented in the table first then the studies are ordered by the number of cases. Statistically significant results were found in nine of these studies. In all but one study these results were in the direction of reduced risk with older age at menarche. Five of these studies found a statistically significant trend towards decreasing breast cancer risk with increasing age of menarche. There was variation in the categories used, including variation in the reference category across studies. Further, the confidence intervals were relatively broad. Therefore, it is difficult to estimate the level of protection associated with specific changes in the age of menarche and pooling of the studies would not be appropriate given the variation in cut-offs used. The estimates are also susceptible to bias. Probably the most significant form of potential bias would result from selection bias, given the large number of case control studies included. The magnitude of this bias is difficult to estimate. Recall bias is also a consideration and may result in over-estimation of the level of effect (assuming women are aware of the hypothesis that early menarche is associated with breast cancer). Therefore, it is likely that increasing age at menarche is a relatively modest protective factor or, conversely, decreasing age of menarche is a relatively modest risk factor for breast cancer.

Table 8: Association between age at menarche and risk of breast cancer: reference using the youngest age at menarche stratum

Reference	Design and sample	Variables adjusted for Reference category	Key result RR/HR/OR, (95% CI)
(Garland et al. 1998)	Cohort (n=396,299 person-years)	age, alcohol intake, history of benign breast disease, family history of breast cancer, quintiles of current BMI, parity, age at FFTP, menopausal status, and duration of OC use. Reference category: <12 years	12 years: RR 0.79 (0.57-1.10) 13 years: RR 0.74 (0.53-1.03) >13 years: RR 0.66 (0.44-0.99) *Ptrend* 0.03
(Clavel-Chapelon and Group 2002)	Cohort (n=91,260)	age at FFTP, number of full term pregnancies, number of spontaneous abortions, age, history of benign breast disease, family history of breast cancer, current BMI, ever married, educational level. Reference category: <12 years	12 years: RR 0.97 (0.85-1.11) 13 years: RR 0.91 (0.79-1.04) 14 years: RR 0.89 (0.77-1.04) 15+ years: RR 0.84 (0.70-1.02) Trend (each additional year at menarche): RR 0.97 (0.93-0.99), *P* < 0.05.
(Berkey et al. 1999)	Cohort (n=65,140)	age in1976, adult height, body fatness at ages 5, 10 and 20 years, maternal body fatness, family history, drinking (ages 18-22), adolescent and maternal smoking, family SES, adolescent benign breast disease. Reference category: ≤11 years	12 years: RR 0.82 13 years: RR 0.85 14 years: RR 0.78 15+years: RR 0.52 (*P* <0.05 compared with reference) *Ptrend* 0.001
(Tamakoshi et al. 2005)	Cohort (n=38,159)	age at baseline, study area, smoking status, alcohol consumption, exercise, meat intake, green leafy vegetable intake, family history of breast cancer, BMI at baseline, menopausal status and number of parity. Reference category: ≤12 years	13-14 years: RR 1.05 (0.51-2.15) 15-16 years: RR 1.15 (0.55-2.41) 17+ years: RR 1.27 (0.56-2.85) *Ptrend* 0.45
(Talamini et al. 1996)	Case (n=2,569) control (n=2,588)	area of residence, age, education, and menopausal status. Reference category: <12 years	12 years: OR 1.1 (0.9-1.3) 13 years: OR 1.1 (0.9-1.3) 14 years: OR 1.0 (0.8-1.2) 15+ years: OR 1.0 (0.8-1.2) *Ptrend* 0.56
(Gammon et al. 2002)	Case (n=1,508) control (n=1,556)	age Reference category: < 12 years	12 years: OR 1.16 (0.95-1.41) 13 years: OR 1.17 (0.96-1.43) 14+ years: OR 0.94 (0.7-1.16)
(Gao et al. 2000)	Ccase (n=1,459) Control (n=1,556)	age, education, family history of breast cancer, history of breast fibroadenoma, waist to hip ratio, ever having had a live birth, age at first live birth, and physical activity. Reference category: ≤12 years	13 years: OR 1.2 (0.9-1.6) 14 years: OR 0.9 (0.7-1.2) 15 years: OR 1.0 (0.7-1.3) 16 years: OR 0.8 (0.6-1.1) 17+ years: OR 0.7 (0.5-0.9) *Ptrend* < 0.01
(Tryggvadottir et al. 2002)	Case (n=1,120) Control (n=10,537)	parous status, age at first birth, number of births, OC use, lactation, height and weight.	Adjusted odds ratio by age at menarche (per unit change), (95% CI): OR 0.91 (0.87-0.96)
(Li et al. 2003b)	Case (n=975) control (n=1,007)	age Reference category: 8-11 years	12-13 years: OR 1.0 (0.8-1.2) 14+ years OR 0.8 (0.6-1.0)

Table 8: Association between age at menarche and risk of breast cancer: reference using the youngest age at menarche stratum (continued)

Reference	Design and sample	Variables adjusted for Reference category	Key result RR/HR/OR, (95% CI)
(McCredie et al. 1998a)	Case (n=891) control (n=1,864)	age, ethnicity, parity, age at FFTP, duration of breast feeding, menopausal status, family history and previous surgery for benign breast disease. Reference category: < 12 years	12 years: OR 0.93 (0.7-1.2) 13 years: OR 0.80 (0.6-1.0) 14 years: OR 0.80 (0.6-1.1) 15+ years: OR 0.79 (0.6-1.1) *Ptrend* 0.06
(Nichols et al. 2005)	Case ((n=682) control (n=649)	age, hospital, parity, age at first birth, alcohol use an spouse's education Reference category: <15 years	15 years: OR 0.74 (0.53-1.04) 16 years: OR 1.11 (0.80-1.53) 17+ years: OR 1.09 (0.82-1.45) *Ptrend* 0.5
(Oran et al. 2004)	Case (n=622) control (n=622)	marital status, menopausal status and age at menopause, history of benign breast disease, first degree relative with breast cancer, OC use and BMI. Reference category: < 12 years	12: OR 0.93 (0.71-1.22) 13: OR 1.03 (0.74-1.43) >13: OR 0.76 (0.47-1.23)
(Tavani et al. 1999)	Case (n=579) control (n=668)	study, centre, year of recruitment, age, education, BMI, family history of breast cancer, parity and age at first birth Reference category: < 12 years	12 years: OR 0.85 (0.61-1.18) 13 years: OR 0.79 (0.56-1.10) 14 years: OR 0.89 (0.61-1.31) 15+ years: OR 0.53 (0.31-0.89) *Ptrend* 0.06
(Gilani and Kamal 2004)	Case (n=498) control (n=996)	BMI, family history of breast cancer, consanguineous marriage, menopausal status and parity. Reference category: ≤12 years	13-14 years: OR 2.02 (1.21-3.38) 15+ years: OR 3.31 (1.63-6.73)
(Wu et al. 1996)	Case (n==492) control (n=768)	age, area, ethnicity, and migration history. Reference category: ≤12 years	13-14: OR 0.87 (0.67-1.14) 15+: OR 0.69 (0.48-1.00) Per year: OR 0.94 (0.86-1.03)
(Ghadirian et al. 1998)	Case ((n=414) control (n=429)	age, marital status, parity, age at FFTP, history of benign breast disease, family history of breast and ovarian cancers, personal income. Reference category: < 12 years	12-13: OR 0.93 (0.65-1.33) 13+: OR 0.81 (0.55-1.21)
(Yang et al. 1997)	Ccase (n=244) control (n=450)	menopausal status, family history of breast cancer, previous breast biopsy or operation, smoking history, menses history, regular menstrual cycle, breast feeding, number of full term pregnancies, BMI, age at FFTP, ever use of OCs, history of abortion. Reference category: < 13 years	13+: OR 1.20 (0.87-1.65)
(Minami et al. 1997)	Case (n=204) control (n=810)	number of parity, history of benign breast disease and family history of breast cancer Reference category: ≤13 years	14 years: OR 0.93 (0.59-1.47) 15 years: OR 1.08 (0.67-1.72) 16+ years: OR 0.67 (0.40-1.12) *Ptrend* 0.21
(Suh et al. 1996)	Case (n=190) control (n=380)	age at interview, occupation, educational attainments, family history of breast cancer, past history of benign breast disease, BMI, history of ever had a full term pregnancy Reference category: ≤14 years	1. Hospital controls 15-16 years: OR 0.83 (0.49-1.38) 17+ years: OR 0.61 (0.33-1.11) *Ptrend* > 0.05 2. Community controls 15-16 years: OR 0.31 (0.17-0.56) 17+ years: OR 0.16 (0.08-0.31) *Ptrend* <0.01
(Ramon et al. 1996)	Case (n=184) control (n=368)	age Reference category: < 12 years	12-14: OR 0.74 (0.46-1.18) >14: OR 1.07 (0.72-1.62)

Reference for age at menarche used the oldest age stratum

There were 7 studies that investigated the relationship between number of parities and the risk of breast cancer where the oldest age stratum was used as the reference category. These results are summarised in Table 9. The single cohort study is presented in the table first then the studies are ordered by the number of cases. The results are consistent with those in the section above, in that the groups with younger age at menarche were associated with increased risk of breast cancer. The estimated relative risk in the youngest age groups compared with the oldest age group ranged between 1.0 and 1.92 with a significantly increased risk in three of these studies. Similar quality considerations apply as those set out above, thus the level of association may be overestimated in these studies.

Table 9: Association between age at menarche and risk of breast cancer: reference using the oldest age at menarche stratum

Reference	Design and sample	Variables adjusted for Reference category	Key result RR/HR/OR, (95% CI)
(Goodman et al. 1997)	Cohort (n=22,200)	city, attained age, age at time of bombings and radiation dose to the breast. Reference category: 16+ years	15 years: RR 1.47 (0.90-2.38) 14 years: RR 1.58 (0.99-2.52) < 14 years: RR 1.92 (1.20-3.06) *Ptrend* 0.006
(Butler et al. 2000)	Case (n=1,647) control (n=1,505)	age, study site, race, combined age at first full-term pregnancy and parity, and family history of breast cancer. Reference category: 15+ years	14 years: OR 1.2 (0.8-1.7) 13 years: OR 1.4 (1.0-1.5) 12 years: OR 1.5 (1.1-1.9) 11 years: OR 1.1 (0.9-1.5) ≤ 10 years: OR 1.2 (0.9-1.7)
(Rockhill et al. 1998)	Case (n=830) Control (n=758)	5 year age group, race, family history of breast cancer, history of benign breast biopsy, age at FFTP. Reference category: 14+ years	13 years: OR 1.3 (1.0-1.7) 12 years: OR 1.2 (0.9-1.6) 11 years: OR 1.3 (1.0-1.9) < 11 years: OR 1.4 (0.9-2.1)
(Kuru et al. 2002)	Case (n=504) control (n=610)	age, residence, menstrual irregularity, parity, age at first pregnancy, breast feeding, OC use, family history, BMI, education, previous benign breast biopsy, menopausal status and age at menopause. Reference category: 15+ years	<15 years: OR 1.72 (1.30-2.28)
(Tung et al. 1999)	Case (n=376) control (n=430)	Multivariate model used but variables included were not clear Reference category: 16+ years	14-15 years: OR 1.75 (1.18-2.70) ≤13 years: OR 1.85 (1.82-2.78)
(Beiler et al. 2003)	Case (n=304) control (n=305)	marital status, income, education, age, religion, family history of breast cancer, history of benign breast disease, alcohol use, smoking, oral contraceptive use, age at first birth, age at first sexual intercourse, weight status by BMI, daily energy intake, physical activity, electric blanket/mattress use, history of infertility, menarche to regularity, cycle length, length of flow and menopausal status. Reference category: 16+ years	15 years: OR 1.53 (0.56-4.22) 13-14 years: OR 0.94 (0.44-2.00) ≤ 12 years: OR 1.00 (0.48-2.10) *Ptrend* not significant
(Wrensch et al. 2003)	Case (n=285) control (n=286)	age, family history of breast cancer, benign biopsy history, previous radiation treatment, menopause status, reproductive history, OC use, HRT history, highest BMI, number of mammograms, socioeconomic status before age 21, highest degree obtained, religion in which raised, and alcohol and tobacco use. Reference category: 15+ years	12-14 years: OR 1.5 (0.74-3.1) ≤11 years: OR 1.2 (0.51-2.6)

Reference for age at menarche used an intermediate age stratum

Two case control studies were identified that used an intermediate level of age at menarche as the reference category. One of these studies presented statistically significant findings. The results were consistent with the results in the above two sections.

Table 10: Association between age at menarche and risk of breast cancer: reference using an intermediate age at menarche stratum

Reference	Design and sample	Variables adjusted for Reference category	Key result RR/HR/OR, (95% CI)
(Magnusson et al. 1999)	Case (n=3,016) control (n=3,263)	age, parity, age at first birth, menopausal status, age at menopause, height, BMI one year prior to data collection and use of HRT for at least one year. Reference category: 13-14 years	≤11 years: OR 1.33 (1.06-1.67) 12 years: OR 1.00 (0.86-1.17) 15-16 years: OR 1.00 (0.87-1.15) 17+ years: OR 0.74 (0.54-1.03) *Ptrend* 0.02
(Viladiu et al. 1996)	Case (n=330) control (n=346)	age, family history of breast cancer and age at first birth. Reference category: 12-14 years	<12 years: OR 0.9 (0.6-1.3) >14 years: OR 1.4 (0.9-2.2)

Conclusions

Overall, the results were consistent with young age at menarche being a relatively modest risk factor for breast cancer. These data were complicated to interpret given variation in cut-points for categorisation of age at menarche. This was exacerbated by variation in the reference category used. The case control design was common amongst the studies included. Case control studies are relatively prone to bias, which creates further uncertainty in the results. On this basis, it is difficult to be precise about the level of risk associated with decreasing age of menarche, but it seems likely that it is a relatively modest risk factor. It should be noted that the impact of early menarche is likely to increase in New Zealand given the increasing prevalence of childhood obesity.

Chapter 8: Post menopausal obesity

SECONDARY RESEARCH

Three systematic reviews were identified that examined the relationship between postmenopausal obesity and breast cancer. Two examined the relationship between waist to hip ratio (WHR) and breast cancer (Connolly et al. 2002) (Harvie et al. 2003) while the other used BMI as a measure of obesity (Bergstrom et al. 2001). The two studies assessing the association between WHR and breast cancer did so in order to evaluate the role of central (rather than general) obesity. Of the two examining WHR, the study by Harvie et al used more robust methods. While there were limitations to this review, including publication bias, variation in the method of measuring WHR between studies and lack of knowledge on the transition from premenopausal to post-menopausal status in selected cohort studies, it was interesting that the key findings suggested there was no association between WHR and breast cancer after controlling for BMI. The implication of this result is that general obesity rather than central obesity should be viewed as a risk factor for breast cancer in postmenopausal women. Bergstrom et al (2001) found support for an association between BMI and breast cancer in post menopausal women with estimated relative risks of 1.12 and 1.25 respectively for overweight (25≤BMI<30) and obese (BMI ≥30) women.

Evidence tables for these studies are presented in Table 9.1 (appendix 9, pages 181-183).

PRIMARY RESEARCH: STUDY RESULTS

Fourteen studies were identified that fulfilled the eligibility criteria and were published from 2003 onwards. Systematic reviews examining the association between various anthropometric measures and breast cancer were identified up to and including 2003, thus the restriction of selecting original studies to those that were published from 2003 onwards. The original studies identified, examined a range of anthropometric measures for proxy measures of obesity and reported their association with the risk of breast cancer in older post-menopausal women. These measures included:

- BMI (kg/m^2) at diagnosis, at 5-years prior to diagnosis, at study defined reference date, at age 18 years, using quartile, quintile, WHO specified cut-points, and continuous BMI (14 studies with one or more of these measures)
- Annual BMI change (kg/m^2) (2 studies)
- Other measures expressed in quartiles or quintiles, at study defined reference date, or at age 18 years:

- height (cm/inches) (8 studies)
- weight (kg/pounds), at age 30, maximum weight (7 studies)
- waist Hip Ratio (WHR) (cm/cm) (5 studies)
- waist (circ -cm) (4 studies)
- hip (circ -cm) (3 studies)
- weight change (kg/pounds) from age 18 to baseline or reference date (4 studies)
- thorax (circ -cm) (1 study)
- breast (circ -cm) (1 study)
- fat mass (kg) (1 study)
- percent fat (%) (2 studies)
- percent body fat (%) (1 study).

BMI is defined as weight in kilograms divided by the square of height in metres (kg /m^2). This index mathematically relates height and weight as an indicator of body fat. This measure correlates closely with body density and thickness and is the main indicator for obesity used in the analysis of the evidence. Waist to hip ratio was also considered as an indicator for obesity and this was analysed in five of the appraised studies.

Full details of the fourteen papers appraised, including methods, key results, limitations and conclusions, are provided in evidence Table 9.2 (Appendix 9, pages 184-203). Studies are presented in reverse chronological order of publication and study alphabetical order within publication year.

Original studies examining BMI and the association with breast cancer

Fourteen studies examined the association between BMI (kg/m^2) and the risk of breast cancer at a range of time periods including at breast cancer diagnosis, at 5-years prior to diagnosis, at study defined reference date, at age 18 years, and risk at quartile, quintile, WHO specified cut-points, and for continuous BMI (Table 11).

The results of the appraised studies in table 11 were mixed in terms of the significance of the linear associations between BMI and the risk of breast cancer in postmenopausal women. The *P*trend results were significant for some expressions of BMI and not others and there was no clear pattern indicating which measures of BMI e.g. quartile, quintile, WHO, continuous cut-points at differing reference periods e.g. BMI at age 18, at breast cancer diagnosis, or study reference date, best determined the relationship between BMI and breast cancer risk.

Several large prospective cohort studies also demonstrated significant *P*trend results for RRs and HRs indicating a positive linear relationship between increased BMI and the risk of breast cancer. The *P*trend for non-HRT users in the study by Lahmann et al (2004) was p=0.002 across BMI quintiles adjusted for a range of variables. The same trends were not apparent for HRT users. The study by Sweeney et al (2004) found significant *P*trends for BMI quartiles after adjusting for a number of variables in each of the age at diagnosis categories of post-menopausal women aged 55-64 years, p=0.004, 64-74 years, p<0.0001, and 74-84 years, p=0.001. One other prospective cohort study (Lahmann et al 2003), the Malmo Diet and Cancer study based in Sweden (Lahmann et al 2004) found a significant *P*trend (p=0.023) across BMI quintiles adjusted for a range of confounders. The study by Tehard et al (2004) showed *P*trends that were close to significance (RR per unit change in category 1.06, 95% CI 1.02-1.09) for study and WHO classed BMI categories. A later study from the same population cohort of French women showed no significant *P*trends (Tehard and Clavel-Chapelon, 2006).

The case-control study by Chow et al (2005) demonstrated a significant association with a *P*trend for BMI at breast cancer diagnosis (p<0.001) but this study only adjusted for age. The matched case-control study by Zhu et al (2005) with BMI at study reference date adjusted for a wide range of variables had a *P*trend of 0.039, and the matched case-control study by Carpenter et al (2003) for BMI at study reference date also adjusted for a smaller range of variables had a *P*trend of 0.005. Other case-control studies by Pan et al (2004), Adebanowo et al (2003), and Li et al (2003) did not test for *P*trend, however in each of these studies the odds ratios for breast cancer cases at the higher BMI categories were significant i.e. the 95% CIs did not overlap 1.

In ten studies with varying degrees of adjustment for confounders the RR (Tehard and Clavel-Chapelon 2006; Lahmann et al 2004; Lahmann et al 2003), OR (Chow et al 2005; Zhu et al 2005; Pan et al 2004; Carpenter et al 2003; Li et al 2003) or hazard ratio (HR) (MacInnis et al 2004; Sweeney et al 2004) for BMI at the highest categories (dependent on BMI cut-points used in the analysis) were significant with the 95% CIs non-overlapping with 1. The analysis indicated that there is an association between severe-overweight and obesity using BMI classifications and the risk of breast cancer in post-menopausal women (Table 11).

Table 11: Comparison of original studies appraised that evaluated the association between BMI and the risk of breast cancer in post menopausal women

Reference	Design and sample	Variables adjusted for	Key result RR/HR/OR (compared with lowest BMI category at baseline), (95% CI)
(Lahmann et al 2004)	Prospective cohort study N=235,486	smoking history, age at menarche, age at first live birth, family history, history of benign breast disease, marital status, physical activity, number of years of education, BMI adjustments	BMI kg/m^2 non-HRT user 25-29 RR 1.30 (1.12-1.51) ≥30.0 RR 1.31 (1.08-1.59) *P*trend p= 0.0012 BMI kg/m^2 HRT user 25-29 RR 0.94 (0.76-1.15) ≥30.0 RR 0.66 (0.45-0.98) *P*trend p= 0.064 BMI kg/m^2 non-HRT user 23.6-25.6 RR 1.35 (1.06-1.73) 25.7-28.7 RR 1.38 (1.08-1.76) ≥28.8 RR 1.36 (1.06-1.75) *P*trend = p=0.002 BMI kg/m^2 HRT user 23.6-25.6 RR 0.91 (0.70-1.19) 25.7-28.7 RR 0.85 (0.64-1.13) ≥28.8 RR 0.71 (0.50-1.01) *P*trend *p*= 0.073
(Tehard et al 2004)	Prospective cohort study N=94,805	smoking history, age at menarche, age at first live birth, family history, history of benign breast disease, marital status, physical activity, number of years of education, BMI adjustments	BMI kg/m^2 22.2-24.2 RR 0.95 (0.81-1.08) >24.4 RR 1.06 (0.93-1.21) 4.2-26.2 RR 0.97 (0.81-1.14) >26.2 RR 1.15 (1.00-1.34) *P*trend *p*= 1.06 BMI kg/m^2 (WHO) 25-30 RR 1.05 (0.92-1.20) ≥30.0 RR 1.23 (1.00-1.59) *P*trend *p*=1.06
(Tehard and Clavel-Chapelon 2006)	Prospective cohort study N=69,116	smoking history, age at menarche, age at first live birth, family history, history of benign breast disease, marital status, physical activity, number of years of education	BMI Quartile 4 ≥24.4 kg/m^2 RR 1.21 (0.96-1.52), *P*trend = NS BMI (WHO) ≥30.0 kg/m^2 RR 1.44 (1.04-1.99), *P*trend = NS

Table 11: Comparison of original studies appraised that evaluated the association between BMI and the risk of breast cancer in post menopausal women (continued)

Reference	Design and sample	Variables adjusted for	Key result RR/HR/OR (compared with lowest BMI category at baseline), (95% CI)
(Silvera et al. 2005)	Nested Prospective cohort study N=49,613	age, smoking history, HRT use, OC use, parity, age at menarche, age at first live birth, family history, history of breast disease, study centre, randomisation group	BMI (kg/m^2) 25-29 HR 1.12 (0.91-1.38) ≥30.0 HR 1.26 (0.95-1.67) *P*trend p= 0.08
(Sweeney et al 2004)	Prospective cohort study N=36,658	age at baseline, smoking history, age at menarche, age at first live birth, parity, family history, age at menopause, education, BMI adjustments	BMI kg/m^2 55-64 years age at diagnosis 26-29.5 HR 1.26 (0.96-1.64) >29.5 HR 1.34 (1.03-1.75) *P*trend p= 0.004 BMI kg/m^2 64-74 years age at diagnosis 26-29.5 HR 1.26 (0.96-1.64) >29.5 HR 1.48 (1.26-1.73) *P*trend p< 0.0001 BMI kg/m^2 75-84 years age at diagnosis 26-29.5 HR 1.26 (1.14-1.85) >29.5 HR 1.34 (1.12-1.84) *P*trend p= 0.001
(Lukanova et al.)	Prospective cohort study N=35,362	age, calendar year, smoking status	BMI Quartile 4: ≥27.9 kg/m^2 RR 1.04 (0.80-1.36), *P*trend = 0.83 BMI (WHO) RR 1.09 (0.83-1.43), *P*trend = 0.70
(MacInnis et al 2004)	Prospective cohort study N=29,479 women	age at attendance, physical activity, education	BMI kg/m^2 highest quartile as reference <25 HR 1.2 (0.9-1.5) 25-29 HR 1.4 (1.0-1.9) Linear trend (per 5 kg/m^2 increase in BMI) HR 1.14 (1.02-1.27), p= 0.02
(Lahmann et al.)	Prospective cohort study N=12,159	age at recruitment, height, %body fat, weight at age 20 as continuous variables and categorical variables including smoking status, alcohol consumption, occupation, age at menarche, parity. age at first pregnancy, current HRT use	Age adjusted BMI kg/m^2 Quintiles RR 23.9-25.7 1.09 (0.72-1.65) 25.8-28.5 1.18 (0.79-1.77) > 28.5 1.26 (0.85-1.89) *P*trend p= 0.187 Multi-variate adjusted BMI kg/m^2 Quintiles RR 23.9-25.7 1.20 (0.78-1.85) 25.8-28.5 1.31 (0.86-2.01) > 28.5 1.54 (1.01-2.35) *P*trend p= 0.023
(Pan et al 2004)	Case control 9,522 cases, 2,492 controls	5-year age group, province of residence, education, pack years of smoking, alcohol consumption, age at menarche, age at first birth, number of live births, menopausal status, total calorific intake, vegetable intake, dietary fibre intake, physical activity	BMI kg/m^2 25-29 OR 1.17 (1.00-1.39) ≥30.0 OR 1.66 (1.33-2.06)
(Carpenter et al 2003)	Matched case control 1,883 cases, 1,628 controls	ages at menarche and menopause, age at first full-term pregnancy, family history, interviewer, average MET hours per week of lifetime exercise	BMI kg/m^2 at reference date OR 23.7-27.0 1.35 (0.95-1.46) ≥ 27.1 1.34 (1.09-1.66) *P*trend p= 0.005 Additionally adjusted for average MET hours/week of lifetime physical activity. BMI kg/m2 at age 18 OR 20.3-22.16 1.03 (0.84-1.25) ≥ 22.17 0.91 (0.74-1.13) *P*trend p= 0.74
(Li et al 2003)	Case control 975 cases, 1,007 controls	age, income	BMI Quartiles OR 23.3-26.2 1.3 (1.0-1.7) 26.2-30.1 1.4 (1.1-1.9)* ≥ 30.1 1.4 (1.0-1.8)* * p value < 0.05

Table 11: Comparison of original studies appraised that evaluated the association between BMI and the risk of breast cancer in post menopausal women (continued)

Reference	Design and sample	Variables adjusted for	Key result RR/HR/OR (compared with lowest BMI category at baseline), (95% CI)
(Zhu et al 2005)	Matched case control 304 cases, 305 controls	family history, history of benign breast disease, menstrual status, menstrual cycle length, smoking history, alcohol use, HRT, OC use, parity, age at menarche, age at first live birth, miscarriages, history of radiotherapy, use of estrogen other than birth control, history of losing weight, history of taking iron pills, age at first sexual intercourse, daily energy intake (kcal), physical activity, use of electric bedding devices, history of infertility, demographic variables	BMI (kg/m2) at reference date 25-29 OR 1.50 (0.70-3.21) ≥30.0 OR 2.32 (1.04-5.19) Ptrend = p=0.039 BMI (kg/m2) at age 18 25-29 OR 1.50 (0.40-2.48) ≥30.0 OR 2.32 (0.20-9.15) Ptrend = p=0.856
(Adebamowo et al 2003)	Case control 234 cases, 273 controls	age, age at menarche, age at first full-term pregnancy, regularity of periods	BMI kg/m2 ≥30.0 OR 1.82 (0.78-4.31) Continuous BMI (units/kg/m2) OR 1.82 (0.78-4.31)
(Chow et al 2005)	Case control 121 cases, 131 controls	age	BMI (kg/m2) at diagnosis 23-27 OR 1.73 (1.04-2.86) 27-31 OR 2.06 (1.08-3.93) >31 OR 3.82 (1.03-14.27) Ptrend = p<0.001 BMI (kg/m2) present 23-27 OR 1.51 (0.83-2.77) 27-31 OR 1.47 (0.66-3.00) >31 OR 1.22 (0.30-5.05) Ptrend = p=0.06 BMI (kg/m2) five years before diagnosis 23-27 OR 1.33 (0.69-2.55) 27-31 OR 1.64 (0.76-3.57) >31 OR 2.18 (0.63-7.60) Ptrend = p=0.12

Five studies considered waist-to-hip ratio (ratio of waist/hip circumference) and its relationship with the risk of breast cancer in post-menopausal women. Four of these studies (Tehard and Clavel-Chapelon 2006; Lahmann et al 2004; Lahmann et al 2003; MacInnis et al 2004) showed no significant *P*trends for linear trends in the association between WHR and the risk of breast cancer. The 95% CIs in these studies all overlapped 1 at the cut-points used in the analyses. Only one study showed a significant association between WHR and breast cancer risk in the *P*trend analysis (Sweeney et al, 2004). The *P*trends by 10-year age group (55-64, 65-74, 75-84 years) for WHR were p=0.01, p=0.0004, and p=0.002 respectively. The 95% CIs did not overlap 1 at the highest WHR cut points used in the analysis.

Summary

Three systematic reviews examined the relationship between postmenopausal obesity and breast cancer. Two examined the relationship between WHR and breast cancer while the other used BMI as a measure of obesity. The key findings suggested there was no association between WHR and breast cancer after controlling for BMI. The implication of this result was that general obesity rather than central obesity should be viewed as a risk factor for breast cancer in postmenopausal women. The other systematic review found support for an association between BMI and breast cancer in post menopausal women with estimated relative risks of 1.12 and 1.25 respectively for overweight (25≤BMI<30) and obese (BMI ≥30) women.

The results of the fourteen appraised primary studies in Table 11 were varied in terms of the strength of the linear associations between BMI and the risk of breast cancer in postmenopausal women. The *P*trend results were significant for some expressions of BMI and not others and there was no clear pattern indicating which measures of BMI e.g. quartile, quintile, WHO, continuous cut-points at differing reference periods e.g. BMI at age 18, at breast cancer diagnosis, or study reference date, best determined the relationship between BMI and breast cancer risk.

A number of large prospective cohort studies demonstrated significant *P*trend results for relative risks and hazard ratios indicating a positive linear relationship between increased BMI and the risk of breast cancer. A number of smaller case-control studies also demonstrated associations with significant *P*trends for odds ratios for BMI and the risk of breast cancer. In ten studies with varying degrees of adjustment for confounders the relative risks, odds ratios and hazard ratios for BMI at the highest categories (dependent on BMI cut-points used in the analysis) were significant with the 95% CIs non-overlapping with 1. This analysis indicated that there was an association between severe-overweight and obesity using BMI classifications and the risk of breast cancer in post-menopausal women. Five studies also considered WHR and its relationship with the risk of breast cancer in post-menopausal women. Four of these studies showed no significant *P*trends for linear trends in the association between WHR and the risk of breast cancer. The 95% CIs in these studies all overlapped 1 at the cut-points used in the analyses. Only one study showed a significant association between WHR and breast cancer risk in the *P*trends analysis by 10-year age group (55-64, 65-74, 75-84 years) and the 95% CIs did not overlap one at the highest WHR cut points used in the analysis.

It should be observed that most studies did not control for breast density and HRT use. Since both variables are potentially associated with both postmenopausal obesity and breast cancer risk this may have affected the estimated measure of effect although the precise magnitude and direction of this influence is difficult to determine.

Chapter 9: Hormone replacement therapy

SECONDARY RESEARCH

Eight secondary research studies were included in this systematic review. All were systematic reviews that included observational study designs (Level III-2 evidence). The studies were published between 1997 and 2005. The Collaborative Group on Hormonal Factors in Breast Cancer (1997) re-analysed data from 51 studies, using individual patient data. Most women had used oestrogen only preparations in the studies included in this re-analysis. Subsequent studies included higher proportions of women taking combined preparations. One group also suggested that the design used in the collaborative re-analysis did not adequately control for study quality. They conducted a meta-regression, adjusting for six quality variables (Garbe et al. 2004). In contrast to the Collaborative Group analysis, which identified an increased risk of breast cancer amongst current users of HRT, Garbe et al (2004) found no such association in studies that fulfilled all six quality criteria.

Evidence tables for these studies are presented in Table 10.1 (appendix 10, pages 205-214).

In general, most studies identified an increased risk of breast cancer amongst current users of HRT, increased risk with longer use, no increased risk amongst users who stopped HRT more than five years previously and no increased risk amongst short term users. The Women's Health Initiative (WHI) trial estimated a hazard ratio of invasive breast cancer among HRT users of 1.26 (95% CI 1.00-1.59). Most other observational studies estimated relative risks ranging between 0.98 and 1.5. Humphrey et al (2002) categorised studies into four groups:

1. ever or short term use of oestrogen
2. long term use of oestrogen or hormone replacement therapy
3. combined oestrogen/progestin use
4. current use of hormone replacement therapy.

They concluded that increased risk was largely confined to current and long term users (> five years) and results for other groups were conflicting. Amongst current users, the three relevant meta-analyses included in the review estimated pooled relative risks between 1.2 and 1.4. Results for long term use were similar with five meta-analyses estimating relative risks of between 1.2 and 1.5 amongst women who had used HRT for more than five years. These estimates were consistent with most other estimates in other reviews.

Shah et al (2005)provided the most comprehensive review and had the other advantage of excluding studies that included premenopausal women who were taking oral contraceptives. They concluded there were different levels of risk in women taking unopposed oestrogen (OR 1.2) and combined oestrogen-progestogen (OR 1.4). The latter also varied by duration of use with lower risk amongst women taking a combined preparation for less than five years (OR 1.4) than amongst women taking combined HRT for at least five years (OR 1.6).

Most of the literature was drawn from observational studies and there are important sources of bias and confounding in these study designs when examining the effect of HRT. Firstly, HRT users tend to be different from non-HRT users producing an important selection bias. Strong sources of confounding are associated with age at menopause and BMI. Some studies adjusted for these confounders (such as the Collaborative re-analysis) but other did not. For example, there was a lack of documentation of such adjustment in most of the studies included by Warren (2004). Randomised controlled trials control for both known and unknown confounders. The WHI trial was published in the eligible time period for this review and was included in the reviews by Warren (2004), Lee (2005b) and Shah (2005).

Conclusions

Most reviews consistently identified a low level of increased risk (relative risks up to 1.5) associated with current use of HRT and long term use of HRT. One group noted that these relative risks may be over-estimated due to limitations of study design (having observed a lack of association in studies that fulfilled all six *a priori* quality criteria). Therefore, it can be concluded that the level of risk of breast cancer associated with HRT use is unclear but is likely to be low.

PRIMARY RESEARCH: STUDY RESULTS

Since the latest systematic review was published in 2005, primary research studies were not included in this review.

Chapter 10: Hormonal contraceptives

SECONDARY RESEARCH

The Collaborative Group examined the relationship between oral contraceptives (OCs) and breast cancer in a 1996 publication (Collaborative Group on Hormonal Factors in Breast Cancer 1996). This was the only secondary research publication identified. The evidence table for this review is included in Table 11.1 (Appendix 11, page 216)

The Collaborative Review concluded "that recency of use was a useful variable to consider in relation to the use of OCs and risk of breast cancer." The original studies investigating time since last use of OCs that were included in the present review presented results that were consistent with the results of the Collaborative Review. This is the key result of this section. Specifically, the Collaborative Review estimated:

- current users: RR 1.24 (95% CI 1.15-1.33)
- 1-4 years after stopping: RR 1.16 (95% CI 1.08-1.23)
- 5-9 years after stopping: RR 1.07 (95% CI 1.02-1.13)
- $\geq$ 10 years after stopping: RR 1.01 (95% CI 0.96-1.05).

PRIMARY RESEARCH: STUDY RESULTS

Thirty-seven studies were identified that fulfilled the eligibility criteria and were published from 1996 onwards. The Collaborative Group examined the relationship between oral contraceptives (OCs) and breast cancer in a 1996 publication. No other systematic reviews of relevance were identified, hence the inclusion of original studies from 1996 onwards.

Four of the studies used a cohort design and the remaining 33 were case control studies. Of these 33 case control studies, four used the nested design. The four cohort studies all used large sample sizes with each one variously including:

- 87,084 participants,
- 106,844 participants,
- 1.6 million person-years follow up, and
- 15,373 participants and 610,328 women years of observation.

The case control studies varied in size with the two smallest studies each having 100 cases and controls. The largest study included 6751 cases and 9311 controls. Eighteen of the 33 (55%) included less than 1000 cases and less than 1000 controls.

The association between breast cancer and the use of OCs was examined using a range of approaches, with variables studied including:

- ever use
- duration of use
- recency of use
- timing of use in relation to timing of first full term pregnancy (FFTP)
- timing of use by defined ages
- age at first use
- time since first use
- oestrogen dose
- type of OC

Other types of contraceptive were also studied, including:

- injectable progestogen contraceptives
- contraceptive implant.

Ever use of oral contraceptives

There were 26 studies that explored the relationship between ever use of OCs and risk of breast cancer. These studies are summarised in Table 12.

Table 12: Comparison of original studies appraised that evaluated the presence of an association between ever OC use and risk of breast cancer

Reference	Design	Adjusted	*in situ* disease	Key results (95% CI)
(Heinemann et al. 2002)	Cohort (n=610,328)	Yes	No	RR 0.6 (0.5-0.8)
(Kumle et al. 2002)	Cohort (n=106,844)	Yes	No	RR 1.3 (1.1-1.5)
(Newcomb et al. 1996)	Case (n=6,751) control (n=9,311)	Yes	No	RR 1.1 (1.0-1.2)
(Marchbanks et al. 2002)	Case (n=4,576) control (n=4,682)	Yes	No	OR 0.9 (0.8-1.0)
(Rosenberg et al. 1996)	Case (n=3,540) control (n=4,488)	Yes	No	RR 1.1 (1.0-1.3)[1]
(Magnusson et al. 1999)	Case (n=3,016) control (n=3,263)	Yes	No	OR 0.98 (0.86-1.12)
(Althuis et al. 2003)	Case (n=1,640) control (n=1,429)	Yes	No	RR 1.24 (1.0-1.5)
(Gammon et al. 2002)	Case (n=1,508) control (n=1,556)	Yes	Yes	OR 1.21 (0.99-1.49)
(Brinton et al. 1998)	Case (n=1,031) control (n=919)	Yes	Yes	OR 1.14 (0.9-1.4)
(Ursin et al. 1998)	Case (n=744) control (n=744)	Yes	Yes	OR 0.83 (0.62-1.12)
(Ursin et al. 1999)	Case (n=597) control (n=966)	Yes	No	OR 0.91 (0.72-1.15)
(Tavani et al. 1999)	Case (n=579) control (n=668)	Yes	No	OR 1.05 (0.81-1.36)
(Rossing et al. 1996)	Case (n=537) control (n=545)	Yes	Yes	RR 1.1 (0.8-1.4)
(Suter et al. 2003)	Case (n=524) control (n=461)	Yes	No	OR 1.3 (0.9-1.8)
(Kuru et al. 2002)	Case (n=504) control (n=610)	Yes	No	OR 1.51 (1.10-2.08)
(Shapiro et al. 2000)	Case (n=419) control (n=1,625)	Yes	No	OR 1.2 (1.0-1.5)
(Van Hoften et al. 2000)	Nested case (n=309) control (n=610)	Yes	No	OR 1.31 (0.96-1.79)
(Yavari et al. 2005)	Case (n=303) control (n=303)	Variables unclear	No	OR 1.95 (1.32-2.87)
(Gomes et al. 2001)	Case (n=300) control (n=600)	Variables unclear	No	OR 1.93 (1.19-3.11)
(Price et al. 1999)	Case (n=298) control (n=1,926)	Yes	No	OR 1.44 (1.04-2.00)
(Levi et al. 1996)	Case (n=230) control (n=507)	Yes	No	OR 1.5 (1.0-2.3)
(Jernstrom et al. 2005)	Case (n=222) control (n=735)	Yes	No	OR 1.65 (0.95-2.87)
(Chie et al. 1998)	Case (n=174) control (n=453)	Yes	No	OR 1.7 (0.9-3.2)
(Hemminki et al. 2002)	Case (n=150) control (n=316)	Yes	No	OR 2.1 (1.1-4.2)
(Norsa'adah et al. 2005)	Case (n=147) control (n=147)	Yes	No	RR 2.5 (1.3-4.8)
(Petro-Nustas et al. 2002)	Case (n=100) control (n=100)	No	No	OR 6.28 (3.14-12.55)

[1] Reference category: < 1 year of use

The reviewers conducted a meta-analysis to explore this relationship. Additional restrictions were placed on the studies selected to be included in the meta-analysis. Studies were only included on the following basis (in addition to the general criteria set out in the methods section):

- reference category was never use of OCs
- estimates were adjusted for at least two potential confounders
- the outcome was restricted to invasive disease (i.e. did not include in situ disease)
- not restricted to progestogen only OCs

Application of these criteria resulted in the inclusion of 18 studies in the meta-analysis.

The pooled random effects estimate, comparing the risk of breast cancer amongst ever users of OCs versus never users was 1.17 (95% CI 1.05-1.31). There was significant heterogeneity between studies (P<0.001), hence the use of a random effects model. The forest plot for this analysis is shown in Figure 3.

Pooled estimates varied by study design but confidence intervals overlapped amongst studies using different designs:

- cohort studies: OR (random effects model) 0.89 (0.42-1.89)
- non-nested case control studies: OR (random effects model) 1.19 (1.07-1.33)
- all case control studies: OR (random effects model) 1.20 (1.08-1.33)

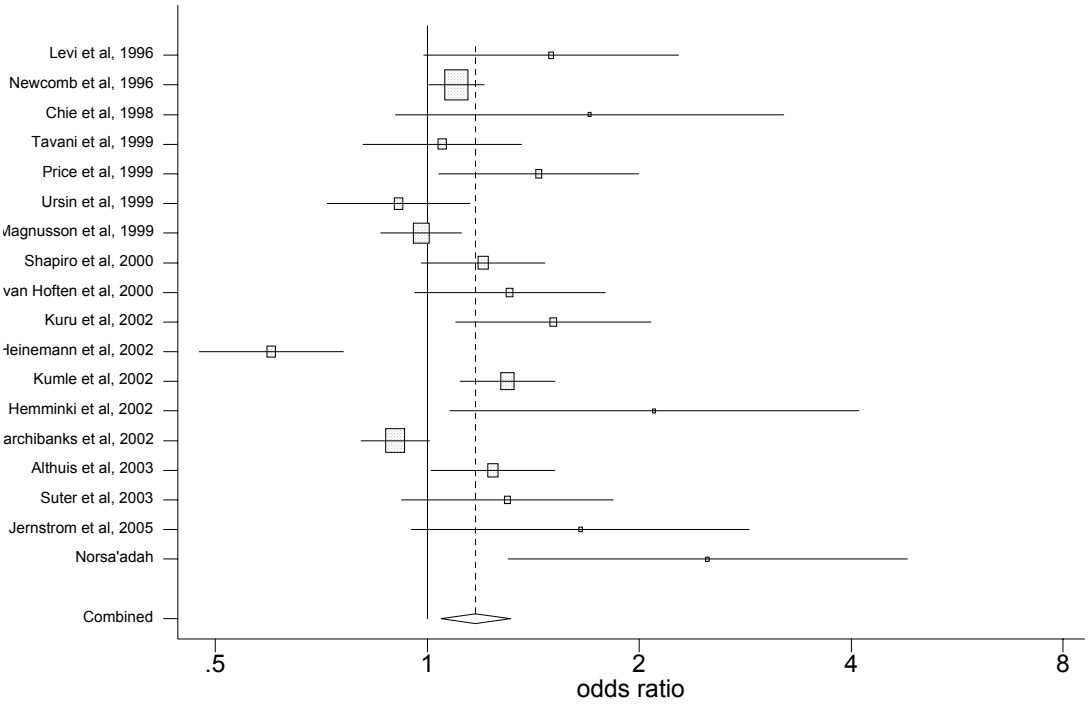

Figure 3: Forest plot examining the association between ever use of oral contraceptives and risk of breast cancer

Duration of use of oral contraceptives

There were 23 studies that explored the relationship between duration of use of OCs and risk of breast cancer. These studies are summarised in Table 13.

Table 13: Comparison of original studies appraised that evaluated the presence of an association between duration of OC use and risk of breast cancer

Reference	Design	Adjusted	*In situ* disease	Key results (95% CI)
(Heinemann et al. 2002)	Cohort (n=610,328)	Yes	No	< 5 years: RR 0.7 (0.5-0.9) 5-10 years: RR 0.7 (0.5-1.0) 10+ years: RR 0.6 (0.4-0.8)
(Kumle et al. 2002)	Cohort (n=106,844)	Yes	No	≤12 months: RR 1.4 (1.0-1.8) 13-60 months: RR 1.2 (0.9-1.5) 61+ months: RR 1.0 (0.6-1.7)
(Dumeaux et al. 2004)	Cohort (n=87,084)	Yes	No	0-4 yrs use: RR 1.19 (1.03-1.38) 5-9 yrs use: RR 1.16 (0.95-1.41) 10+ yrs use: RR 1.29 (1.05-1.60) *Ptrend* 0.01
(Hankinson et al. 1997)	Cohort (n=1.6 million person-years follow up)	Yes	No	< 1 year: RR 1.01 (0.89-1.14) 1-2 years: RR 1.01 (0.89-1.14) 3-4 years: RR 1.08 (0.93-1.26) 5-9 years: RR 1.12 (0.99-1.27) 10+ years: RR 1.11 (0.94-1.32)
(Newcomb et al. 1996)	Case (n=6,751) control (n=9,311)	Yes	No	< 1 year: RR 1.1 (1.0-1.3) 1-4 years: RR 1.0 (0.9-1.1) 5-9 years: RR 1.1 (0.9-1.2) 10-14 years: RR 1.1 (0.9-1.3) 15+ years RR 1.0 (0.8-1.4)
(Marchbanks et al. 2002)	Case (n=4,576) control (n=4,682)	Yes	No	<1yr: OR 0.9 (0.8-1.1) 1-4 yrs: OR 0.9 (0.8-1.0) 5-9 yrs: OR 0.9 (0.8-1.0) 10-14 yrs: OR 0.8 (0.7-1.0) 15+ yrs: OR 1.0 (0.8-1.3)
(Rosenberg et al. 1996)	Case (n=3,540) control (n=4,488)	Yes	No	1-4 years: RR 1.1 (1.0-1.3)[3] 5-9 years: RR 1.2 (1.0-1.5)[3] 10+ years: RR 0.9 (0.7-1.1)[3]
(Magnusson et al. 1999)	Case (n=3,016) control (n=3,263)	Yes	No	5+ years: OR 0.98 (0.82-1.18)[1]
(Tryggvadottir et al. 2002)	Nested case (n=1,120) control (n=10,537)	Yes	No	OR (12 weeks increased use) 1.00 (0.99-1.01)
(Tomasson and Tomasson 1996)	Nested case (n=1,062) control (n=5,662)	Yes	No	1-48 mths: OR 0.92 (0.73-1.16) 49-96 mths: OR 0.89 (0.64-1.24) 97+ mths: OR 0.96 (0.69-1.33)
(Brinton et al. 1998)	Case (n=1,031) control (n=919)	Yes	Yes	6 mths-<5yrs: OR 1.11 (0.9-1.4) 5-9 yrs: OR 1.09 (0.8-1.4) 10+ yrs: OR 1.27 (0.9-1.7)
(Li et al. 2003b)	Case (n=975) control (n=1,007)	Age only	No	< 5 years: OR 0.9 (0.7-1.2) 5+ years: OR 1.1 (0.8-1.5)
(Ursin et al. 1998)	Case (n=744) control (n=744)	Yes	Yes	1-48 mths: OR 0.85 (0.62-1.16) 49-96 mths: OR 0.71 (0.49-1.02) 97-144 mths: OR 0.79 (0.52-1.18) 145+ mths: OR 1.40 (0.81-2.40)
(Ursin et al. 1999)	Case (n=597) control (n=966)	Yes	No	1-12 mths: OR 1.20 (0.86-1.69) 13-60 mths: OR 0.81 (0.58-1.12) 60+ mths: OR 0.71 (0.47-1.07) *Ptrend* 0.03
(Tavani et al. 1999)	Case (n=579) control (n=668)	Yes	No	≤ 2 years: OR 1.19 (0.87-1.36) > 2-5 years: OR 0.96 (0.63-1.48) > 5 years: OR 0.86 (0.53-1.40)
(Rossing et al. 1996)	Case (n=537) control (n=545)	Yes	Yes	≤ 12 mths: RR 1.0 (0.7-1.4) 13-48 mths: RR 1.4 (0.9-2.2) 49-120 mths: RR1.3 (0.8-1.9) 120+ mths: RR 0.8 (0.5-1.3)
(Suter et al. 2003)	Case (n=524) control (n=461)	Yes	No	< 5 years: OR 1.3 (0.9-1.8) 5-<10 years: OR 1.4 (0.9-2.1) 10+ years: OR 1.2 (0.7-1.8)
(McCredie et al. 1998b)	Case (n=467) control (n=408)	Yes	No	< 12 months: OR 0.8 (0.4-1.6) 12-59 months: OR 0.7 (0.4-1.2) 60-119 months: OR 1.0 (0.6-1.7) 120+ months: OR 1.1 (0.6-1.9)

Table 13: Comparison of original studies appraised that evaluated the presence of an association between duration of OC use and risk of breast cancer (continued)

Reference	Design	Adjusted	*In situ* disease	Key results (95% CI)
(Van Hoften et al. 2000)	Nested case (n=309) control (n=610)	Yes	*No*	1-10 years: OR 1.27 (0.92-1.77) > 10 years: OR 1.43 (0.92-2.22)
(Traina et al. 1996)	Case (n=300) control (n=300)	Age only	*No*	< 12 mths: OR 0.84 (0.49-1.41) 12-35 mths: OR 0.71 (0.41-1.20) 36-59 mths: OR 0.88 (0.39-1.97) 60+ mths: OR 0.76 (0.35-1.64)
(Price et al. 1999)	Case (n=298) control (n=1,926)	Yes	*No*	< 1 year: OR 1.11 (0.63-1.96) 1-3 yrs: OR 1.32 (0.83-2.09) 4-6 yrs: OR 1.53 (0.97-2.42) 7-10 yrs: OR 1.36 (0.83-2.22) 10+ yrs: OR 1.73 (1.13-2.65)
(Tryggvadottir et al. 1997)	Nested case (n=204) control (n=1,183)	Yes	*No*	> 4 years use: RR 1.1 (0.8-1.6)2
(Chie et al. 1998)	Case (n=174) control (n=453)	Yes	*No*	< 1 year: OR 2.0 (0.8-4.7) 1-4 years: OR 0.9 (0.3-3.0) 5+ years: OR 2.1 (0.8-5.6)

[1] Reference category: < 5 years of use
[2] Reference category: < 4 years of use
[3] Reference category: < 1 year of use

The hallmark of the results in the studies investigating the relationship between duration of OC use and risk of breast cancer is inconsistency. These inconsistencies exist at several levels:

1. For some studies, all estimates are less than 1 (implying ever use of OCs is protective) but in others, all estimates are greater than 1 (implying ever use of OCs is harmful).
2. For some studies the relative risk increases with increasing duration of use but in others it decreases.
3. Two studies were identified with a statistically significant trend with increasing duration of use (Dumeaux et al. 2004; Ursin et al. 1999). However, the trend was in opposite directions in these two studies.
4. In some studies, there was no consistent change in relative risk with changing duration of use.
5. There was no pattern observable by study design.

It was also noted that most confidence intervals encompassed 1, thus adding to the uncertainty about the significance of duration of OC use as a variable impacting on risk of breast cancer.

Given the above issues, a meta-analysis has not been conducted, and it is concluded that based on current evidence, duration of OC use is not a helpful variable to consider in relation to risk of breast cancer. If any true association between duration of OC use and risk of breast cancer does exist, then the magnitude of this association is likely to be small.

Recency of use of oral contraceptives

There were 16 studies that explored the relationship between recency of use of OCs and risk of breast cancer. These studies are summarised in Table 14. The Collaborative Group review concluded that recency of use was a useful variable to consider in relation to the use of OCs and risk of breast cancer.

Table 14: Comparison of original studies appraised that evaluated the presence of an association between recency of OC use and risk of breast cancer

Reference	Design	Adjusted	*In situ* disease	Key results (95% CI)
(Heinemann et al. 2002)	Cohort (n=610,328)	Yes	No	Current use: RR 0.5 (0.3-0.7) <5 years: RR 0.7 (0.5-0.9) 5-10 years: RR 0.6 (0.4-0.9) 10+ years: RR 0.6 (0.5-0.8)
(Kumle et al. 2002)	Cohort (n=106,844)	Yes	No	<2 years: OR 1.6 (1.2-2.3) 2-4 years: OR 1.2 (0.8-1.8) 5-9 years: OR 1.4 (1.0-1.8) 10-14 years: OR 1.2 (1.0-.6) 15+ years: OR 1.3 (1.0-1.5)
(Hankinson et al. 1997)	Cohort (n=)	Yes	No	< 5 years: RR 1.20 (1.00-1.44) 5-9 years: RR 1.02 (0.89-1.16) 10-14 years: RR 1.07 (0.96-1.20) 15-19 years: RR 1.07 (0.95-1.22) 20+ years: RR 0.91 (0.77-1.09)
(Newcomb et al. 1996)	Case (n=6,751) control (n=9,311)	Yes	No	< 2 years: RR 1.3 (0.9-2.0) 2-4 years: RR 1.2 (0.8-1.7) 5-9 years: RR 1.1 (0.9-1.3) 10-14 years: RR 1.1 (0.9-1.2) 15-19 years: RR 1.0 (0.9-1.2) 20+ years: RR 1.0 (0.9-1.2)
(Marchbanks et al. 2002)	Case (n=4,576) control (n=4,682)	Yes	No	Current use: OR 1.0 (0.8-1.3) Former use: OR 0.9 (0.8-1.0)
(Magnusson et al. 1999)	Case (n=3,016) control (n=3,263)	Yes	No	< 10 years: OR 1.00 (0.69-1.44) 10-19 years: OR 0.95 (0.78-1.16) 20+ years: OR 1.02 (0.87-1.18)
(Althuis et al. 2003)	Case (n=1,640) control (n=1,429)	Yes	No	< 5 years: RR 1.47 (1.2-1.9) 6-10 years: RR 1.33 (1.0-1.7) >10 yrs: RR 1.13 (0.9-1.4)
(Brinton et al. 1998)	Case (n=1,031) control (n=919)	Yes	Yes	< 5 years: OR 1.26 (0.9-1.8) 5-9 years: OR 1.22 (0.8-1.8) 10+ years: OR 1.11 (0.9-1.4)
(Ursin et al. 1999)	Case (n=597) control (n=966)	Yes	No	< 5 years: OR 0.68 (0.41-1.14) 6-10 years: OR 0.85 (0.57-1.27) 11-15 years: OR 0.92 (0.64-1.33) 16+ years: OR 1.09 (0.75-1.59)
(Tavani et al. 1999)	Case (n=579) control (n=668)	Yes	No	< 5 years: OR 1.17 (0.84-1.63) 5-9 years: OR 1.11 (0.75-1.65) 10+ years: OR 0.85 (0.54-1.36)
(Rossing et al. 1996)	Case (n=537) control (n=545)	Yes	Yes	≤ 10 years: OR 1.1 (0.6-2.0) 11-15 years: OR 1.4 (0.9-2.1) 16-20 years: OR 1.1 (0.7-1.7) 21-25 years: OR 0.9 (0.6-1.4) 26+ years: OR 0.9 (0.6-1.5)
(Suter et al. 2003)	Case (n=524) control (n=461)	Yes	No	10+ years ago: OR 1.3 (0.9-1.8) 5-<10 years ago: OR 1.2 (0.8-1.9) < 5years/current: OR 1.4 (0.9-2.1)
(McCredie et al. 1998b)	Case (n=467) control (n=408)	Yes	No	Current: OR 1.2 (0.7-2.0) < 12 mths: OR 0.5 (0.2-1.0) 12-59 mths: OR 0.8 (0.5-1.5) 60-119 mths: OR 0.8 (0.5-1.5) 120+ mths: OR 0.7 (0.4-1.2)
(Shapiro et al. 2000)	Case (n=419) control (n=1,625)	Yes	No	Current: OR 1.1 (0.6-2.1) 1-4 years: OR 1.6 (1.1-2.3) 5-9 years: OR 1.3 (0.9-2.1) 10-14 years: OR 1.4 (1.0-2.1) 15+ years: OR 0.9 (0.7-1.2)
(Traina et al. 1996)	Case (n=300) control (n=300)	Age only	No	< 35 mths: OR 0.65 (0.36-1.17) 35+ mths: OR 0.89 (0.89-1.33)
(Levi et al. 1996)	Case (n=230) control (n=507)	Yes	No	< 5 years: OR 1.9 (0.9-3.6) 5-14 years: 2.4 (1.4-4.4) 15+ years: OR 1.0 (0.6-1.8)

Examination of the individual study results revealed a level of consistency with the findings in the Collaborative Review. In general, the measure of association was similar between the above original studies and the Collaborative Review when results were presented for a similar timeframe after stopping OC use. In some studies, when data were presented for a similar time period after stopping OCs, the association was stronger but confidence intervals encompassed the overall estimates in the Collaborative Review. There were also three studies, where the measure of association appeared to be protective (as opposed to the findings in the Collaborative Review). However, the confidence intervals were broad in these three studies, and they encompassed the key estimates in the Collaborative Review.

Given, this level of consistency, and the advantages of using the Collaborative Review findings (given the robustness of the re-analysis that made use of the original study data), it is suggested that there is little need to change the conclusion formed in the Collaborative Review. This was: "There is a small increase in the risk of breast cancer while taking oral contraceptives and during the 10 years thereafter." The key results were:

- current users: RR 1.24 (95% CI 1.15-1.33)
- 1-4 years after stopping: RR 1.16 (95% CI 1.08-1.23)
- 5-9 years after stopping: RR 1.07 (95% CI 1.02-1.13)
- $\geq$ 10 years after stopping: RR 1.01 (95% CI 0.96-1.05).

It should be observed that, since recent use of oral contraceptives will apply mostly to younger women, adjustment for family history may be important. Some studies did not adjust for family history but the Collaborative Study did. This adjustment in the Collaborative Study made little difference to the level of risk.

Timing of use in relation to timing of first full term pregnancy

There were 13 studies that explored the relationship between timing of use of OCs in relation to the FFTP and risk of breast cancer. These studies are summarised in Table 15.

Table 15: Comparison of original studies appraised that evaluated the presence of an association between timing of OC use in relation to first full term pregnancy and risk of breast cancer

Reference	Design	Adjusted	*In situ* disease	Key results (95% CI)
(Kumle et al. 2002)	Cohort (n=106,844)	Yes	No	Duration of use before first birth ≤12 months: RR 1.4 (1.0-1.8) 13-60 months: RR 1.2 (0.9-1.5) 61+ months: RR 1.0 (0.6-1.7)
(Hankinson et al. 1997)	Cohort (n=1.6 million person-years follow up)	Yes	No	Duration of use before first birth < 1 year: RR 1.00 (0.80-1.24) 1-2 years: RR 0.95 (0.77-1.17) 3-4 years: RR 0.86 (0.59-1.26) 5+ years: RR 0.96 (0.65-1.43)
(Newcomb et al. 1996)	Case (n=6,751) control (n=9,311)	Yes	No	User before first birth RR 1.1 (0.9-1.3)
(Skegg et al. 1996)	Case (n=891) control (n=1,864)	Yes	No	User before first birth RR 1.2 (0.46-2.9)
(Ursin et al. 1998)	Case (n=744) control (n=744)	Yes	Yes	Duration of use before first birth 1-48 mths: OR 0.85 (0.62-1.18) 49-96 mths: OR 0.71 (0.47-1.06) 97+ mths: OR 0.78 (0.51-1.21)
(Ursin et al. 1999)	Case (n=597) control (n=966)	Yes	No	User before first birth OR 0.80 (0.54-1.19)
(Tavani et al. 1999)	Case (n=579) control (n=668)	Yes	No	User before first birth OR 0.90 (0.57-1.44) User during same year OR 1.19 (0.60-2.37) User after first birth OR 0.95 (0.67 – 1.33)
(McCredie et al. 1998b)	Case (n=467) control (n=408)	Yes	No	User before first birth OR 0.8 (0.6-1.0)
(Traina et al. 1996)	Case (n=300) control (n=300)	Age only	No	Duration of use before first birth < 12 mths: OR 1.11 (0.57-2.20) 12-35 mths: OR 0.55 (0.26-1.11) 36-59 mths: OR 0.94 (0.28-3.12) 59+ mths: OR 0.60 (0.21-1.72)
(Levi et al. 1996)	Case (n=230) control (n=507)	Yes	No	User before first birth OR 1.3 (0.7-2.5) User after first birth OR 1.6 (1.0-2.6)
(Jernstrom et al. 2005)	Case (n=222) control (n=735)	Yes	No	User before first birth OR 1.63 (1.02-2.62) User after first birth OR 1.03 (0.66-1.61)
(Chie et al. 1998)	Case (n=174) control (n=453)	Yes	No	User before first birth OR 1.3 (0.3-6.0) User after first birth OR 1.8 (0.9 – 3.5)
(Hemminki et al. 2002)	Case (n=150) control (n=316)	Yes	No	User before first birth OR 1.0 (0.5-1.7) User after first birth OR 0.8 (0.2-2.5)

Nine studies estimated the association between use before FFTP, five between use after FFTP and four between duration of use before FFTP and risk of breast cancer. The pooled OR using a fixed effects ratio (there was no evidence of between study heterogeneity based on Q statistic testing) for use before FFTP and risk of breast cancer was 1.01 (95% CI 0.89-1.14). As observed in the forest plot (figure 4), the point estimates varied on either side of one with confidence intervals crossing one in all but a single study. The studies examining duration of use before FFTP showed estimates consistent with the above findings, in that in one study, it was apparent the overall estimate for use before FFTP was greater than 1, in two others, the overall estimate would have been below one, and in the final study it was unclear given the changing estimates by duration of use before first birth. In relation to use after FFTP, similar findings existed to those shown for use before FFTP (forest plot not presented). The pooled OR using a fixed effects model (there was no evidence of between study heterogeneity based on Q statistic testing) for use after FFTP and risk of breast cancer was 1.15 (95% CI 0.92-1.43).

In conclusion, examination of the use of OCs in relation to timing of FFTP did not produce results consistent with a significant risk factor for breast cancer.

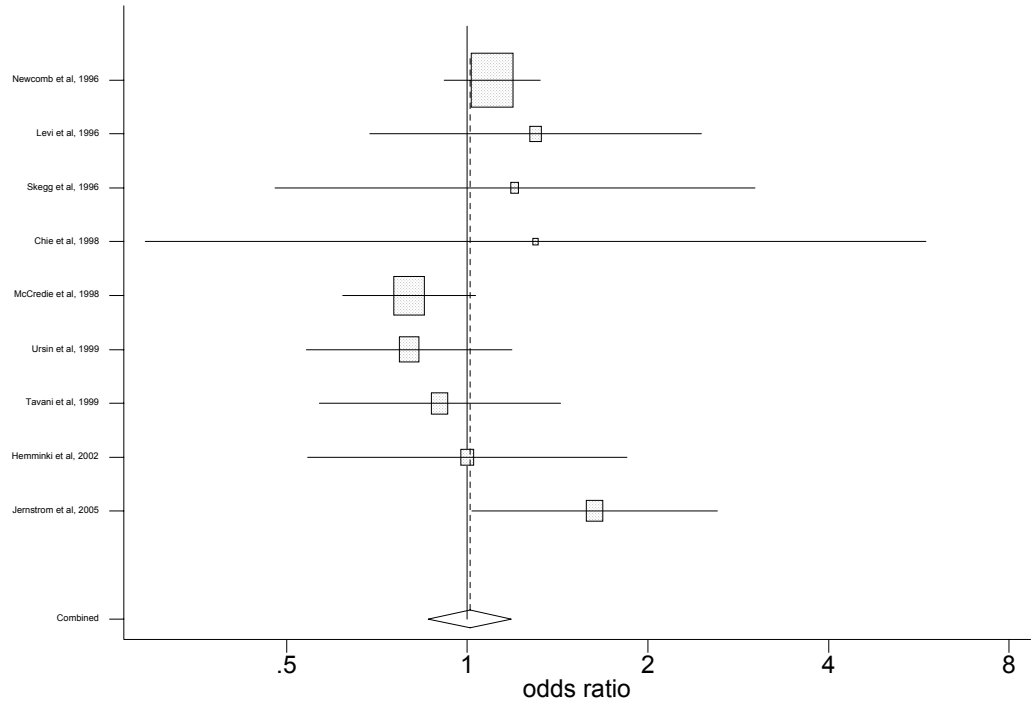

Figure 4 **Forest plot examining the association between use of oral contraceptives before first full term pregnancy and risk of breast cancer**

Timing of use by defined age groups

One study was identified that explored the relationship between timing of use of OCs in relation to defined age groups and risk of breast cancer (Jernstrom et al. 2005). This study found a statistically significant association between OC use before age 20 and risk of breast cancer (OR 2.10, 95% CI 1.32-3.33). However, this finding would need to be explored in other studies before forming any conclusions about timing of OC use by defined ages.

Age at first use and time since first use

There has been less interest in age and time since first use than there has in time since last use of OCs. Nevertheless, six studies were identified that examined age at first use and four that examined time since first use. These results are summarised in Tables 16 and 17 respectively.

In most studies investigating age at first use, the measure of effect was under one for most age groups. There was one exception in the study by Chie et al (1998), where the youngest two groups were associated with increased risk of breast cancer. There was also a significant trend in this study, with decreasing risk being associated with older starting ages. Significant trends were not documented in the other six studies, and eyeballing of estimates did not reveal differences in the degree of association across different starting age groups. Therefore, the results presented do not suggest that age at starting OC use is a discriminating risk factor for breast cancer.

There were also mixed results when examining time since first use of OCs. It appears that increasing duration since first use had lower measures of effect than shorter times but there were no significant trends identified within the individual studies. There was also variation between the direction of association, with some studies suggesting protective effects and others harmful effects. Interpretation of the findings is further complicated by the use of different categorisation cut offs between studies.

In summary, age since first use and time since first use of OCs do not appear to provide useful methods of identifying women at increased risk of breast cancer, based on the current research in the area.

Table 16: Comparison of original studies appraised that evaluated the presence of an association between age of first OC use and risk of breast cancer

Reference	Design	Adjusted	*In situ* disease	Key results (95% CI)
(Marchbanks et al. 2002)	Case (n=4,576) control (n=4,682)	Yes	No	<15 yrs: OR 0.9 (0.6-1.2) 15-19 yrs: OR 1.0 (0.8-1.1) 20-24 yrs: OR 0.9 (0.8-1.0) 25-29 yrs: OR 0.9 (0.8-1.1) 30-34 yrs: OR 0.8 (0.6-1.) 35-39 yrs: OR 1.2 (0.8-1.6) 40+ yrs: OR 1.0 (0.6-1.6)
(Ursin et al. 1998)	Case (n=744) control (n=744)	Yes	Yes	< 17 yrs: OR 0.96 (0.60-1.55) 17-19 yrs: OR 0.84 (0.60-1.17) 20-24 yrs: OR 0.78 (0.56-1.09) 25+ yrs: OR 0.86 (0.51-1.44)
(Ursin et al. 1999)	Case (n=597) control (n=966)	Yes	No	≤ 21 yrs: OR 0.46 (0.24-0.87) 22-24 yrs: OR 0.86 (0.56-1.32) 25-29 yrs: OR 1.10 (0.77-1.58) 30-35 yrs: OR 0.87 (0.59-1.28) > 35 yrs: OR 1.23 (0.62-2.44)
(Traina et al. 1996)	Case (n=300) control (n=300)	Age only	No	< 25 years: OR 0.63 (0.38-1.01) 25+ years: OR 0.87 (0.56-1.36)
(Chie et al. 1998)	Case (n=173) control (n=453)	Yes	No	< 25 years: OR 3.5 (1.2-9.7) 25-29 years: OR 1.7 (0.7-4.1) 30 + years: OR 0.7 (0.2-2.4) *Ptrend* 0.019
(Hemminki et al. 2002)	Case (n=150) control (n=316)	Yes	No	16-19 years: OR 0.5 (0.2-1.6) 20-24 years: OR 0.9 (0.5-1.9)

Table 17: Comparison of original studies appraised that evaluated the presence of an association between time since first OC use and risk of breast cancer

Reference	Design	Adjusted	*In situ* disease	Key results (95% CI)
(Brinton et al. 1998)	Case (n=1,031) control (n=919)	Yes	Yes	<15 yrs: OR 1.26 (0.9-1.8) 15-19 yrs: OR 1.32 (0.9-1.8) 20+ yrs: 1.09 (0.9-1.4)
(Tavani et al. 1999)	Case (n=579) control (n=668)	Yes	No	< 10 years: OR 1.19 (0.86-1.64) 10+ years: OR 0.92 (0.66-1.28)
(Rossing et al. 1996)	Case (n=537) control (n=545)	Yes	Yes	≤ 20 yrs: RR 1.9 (1.1-3.2) 21-25 yrs: RR 1.1 (0.7-1.6) 26-30 yrs: RR 0.9 (0.6-1.3) 30+ yrs: RR 1.0 (0.5-1.8)
(McCredie et al. 1998b)	Case (n=467) control (n=408)	Yes	No	Current: OR 1.2 (0.7-2.0) < 12 months: 0R 0.5 (0.2-1.0) 12-59 months: OR 0.8 (0.5-1.5) 60-119 months: OR 1.1 (0.6-2.0) 120+ months: OR 0.7 (0.4-1.2)

Oestrogen dose and type of oral contraceptive

There were three studies identified that presented estimates by oestrogen dose and three that examined different types of oral contraceptive. These are presented in Tables 18 and 19 respectively.

Although there was a significant trend between oestrogen dose and risk of breast cancer in one study (Dumeaux et al. 2004), examination of the point estimates suggest it wasn't linear. Furthermore, comparison of the estimated odds ratios in a second study that stratified by high and low oestrogen dose did not suggest any difference in the association with breast cancer based on these two dose categories. Thus, there were no data identified that supported the use of oestrogen dose as a discriminating factor for identifying women at high risk of breast cancer.

Three studies were identified that considered specific types of oral contraceptive. One compared progestin only with combined contraceptives, one was restricted to progestin only contraceptives and

the other examined a wide range of oral contraceptive types. These disparate studies did not allow for an assessment of consistency between studies. Therefore, at this time it is not possible to conclude that oral contraceptive type is a useful discriminating factor for identifying women at high risk of breast cancer.

Table 18: Comparison of original studies appraised that evaluated the presence of an association between oestrogen dose and risk of breast cancer

Reference	Design	Adjusted	*In situ* disease	Key results (95% CI)
(Heinemann et al. 2002)	Cohort (n=610,328)	Yes	No	Low oestrogen dose Ever use: RR 0.8 (0.5-1.2)
(Dumeaux et al. 2004)	Cohort (n=87,084)	Yes	No	0.1-49.9 mg: RR 1.26 (1.05-1.52) 50.0-99.9 mg: RR 1.21 (0.96-1.54) 100.0+ mg: RR 1.28 (1.00-1.64) *Ptrend* 0.01
(Marchbanks et al. 2002)	Case (n=4,576) control (n=4,682)	Yes	No	High oestrogen dose Any use: OR 0.8 (0.7-0.9) Current use: OR 0.7 (0.2-1.8) Former use: OR 0.8 (0.7-0.9) Low oestrogen dose Any use: OR 0.9 (0.8-1.0) Current use: OR 1.0 (0.8-1.3) Former use: OR 0.9 (0.8-1.0)

Table 19: Comparison of original studies appraised that evaluated the presence of an association between specific types of OC use and risk of breast cancer

Reference	Design	Adjusted	*In situ* disease	Key results (95% CI)
(Kumle et al. 2002)	Cohort (n=106,844)	Yes	No	Progestin only: RR 1.1 (0.8-1.7) Combined OC: RR 1.3 (1.1-1.6)
(Althuis et al. 2003)	Case (n=1,640) control (n=1,429)	Yes	No	Multiple results were presented, statistically significant results are reproduced here. Ethinyl estradiol > 35 µg: RR 1.99 (1.2-3.2) Progestin low potency: RR 1.40 (1.1-1.8) Oestrogen low potency: RR 1.38 (1.1-1.8)
(Skegg et al. 1996)	Case (n=891) control (n=1,864)	Yes	No	Ever use progestin only: OR 1.1 (0.73-1.5)

Non-oral, hormonal contraceptives

There were two studies identified that presented estimates by use of injectable progestin contraceptive (IPC), other types of injectable contraceptive and implantable contraceptives. The two studies examining IPC are presented in Table 20. The point estimates for an association between IPC use and breast cancer risk were widely varying between these two studies. The study by Parvez et al (2001) had significant limitations and little could be concluded from it.

One study examined injectable and implantable contraceptives (Strom et al. 2004). This study used a case control design, the results presented were crude (unadjusted) estimates and *in situ* cases were not included in the outcome measure. A range of co-variants were examined and these are summarised below:

- Ever use of contraceptive injection: OR 0.87 (0.66-1.15)
- Recent use of contraceptive injection:
  - ≤ 1 year: OR 0.67 (0.35-1.30)
  - >1 years: OR 0.67 (0.68-1.26)

- Duration of use of contraceptive injection:
  - < 6 mths: OR 0.60 (0.37-0.98)

- 6 - < 12 mths: OR 0.89 (0.50-1.57)
- 12-<24 mths: OR 0.94 (0.50-1.77)
- 24+mths: OR 1.38 (0.77-2.47)
- use of contraceptive implant: OR 0.67 (0.21-2.13)

Based on the limited data, at this time it is not possible to conclude that discrimation by injectable/implantable contraceptive type is a useful factor for identifying women at high risk of breast cancer.

Table 20: Comparison of original studies appraised that evaluated the presence of an association between injectable progestin contraceptive use and risk of breast cancer

Reference	Design	Adjusted	*In situ* disease	Key results (95% CI)
(Shapiro et al. 2000)	Case (n=419) control (n=1,625)	Yes	No	Ever use IPC: OR 0.9 (0.7-1.2) Ever use COC: OR 1.2 (1.0-1.5)
(Parvez et al. 2001)	Case (n=100) control (n=100)	No	Unclear	Ever use of IPC: OR 25, *P*<0.001

Study limitations

Most studies in this section on hormonal contraceptives used non-nested case control designs. Standard limitations of such studies included potential selection and recall bias. The latter would tend to result in overestimation of the degree of association with breast cancer risk although is likely to vary by specific variables considered. For example, most participants would recall use of oral contraceptives with a high level of certainty but there may be greater uncertainty, potentially leading to an increased risk of recall bias, when the duration of use of oral contraceptives was considered. It is also recognised that the accuracy of retrospectively recalling the use of particular brands of contraceptive is lower than desirable. The issue of recall bias is pertinent to discussions around the association between time since last use of oral contraceptives and the risk of breast cancer. It is also noted that the pooled association between ever use of OCs and risk of breast cancer was less than one in the cohort studies and greater than one in the case control studies (although the confidence intervals were consistent with the same true association).

In relation to selection bias, some case control studies used designs that may have resulted in an increased risk of selection bias. For example, a number of studies used hospital-based controls, thus not necessarily being representative of the population from which the cases were derived. The direction of such a bias is difficult to derive. Cohort studies are also prone to selection bias, particularly through loss to follow-up. However, the cohort studies included in this review were all large, and had substantial person-years of follow up data.

Exposure misclassification may have occurred in the cohort (and case control designs). In the cohort studies, this was likely to be non-differential, given the prospective timing of classification, which would result in dilution of the association.

Outcome misclassification may also have occurred. However, in most studies, careful consideration was given to the accuracy of the outcome, so the size of this bias is likely to be small. A few studies included *in situ* disease, as well as invasive disease, as an outcome measure. These studies may have resulted in bias as the level of risk may vary between these two outcomes. However, the overall impact of this bias is likely to be small given the small number of studies where *in situ* disease was included in the outcome.

Potential confounders were handled in different ways in the studies included. Some did not present adjusted estimates, whereas some included multiple *a priori* confounders in the multivariate models used. Others determined the appropriateness of including potential confounders as part of the multivariate model development process. Where possible, pooled estimates have relied on selecting studies that appeared to handle potential confounding in a robust manner.

There was also variation in classification of specific variables between studies, with different categories being used in different studies. This resulted in difficulty comparing estimates across studies.

There were also limitations to the review process, including:

- Original studies considered were limited to 1996 onwards, leading to a potential publication bias
- The size of this subtopic was relatively large compared with the time available
- Study selection and data extraction was conducted by one reviewer.

Conclusions

The Collaborative Review, conducted in 1996 concluded "that recency of use was a useful variable to consider in relation to the use of OCs and risk of breast cancer." The original studies investigating time since last use of OCs that were included in the present review found results that were consistent with the results of the Collaborative Review. This is the key result of this section. Specifically, the Collaborative Review estimated:

- current users: RR 1.24 (95% CI 1.15-1.33)
- 1-4 years after stopping: RR 1.16 (95% CI 1.08-1.23)
- 5-9 years after stopping: RR 1.07 (95% CI 1.02-1.13)
- $\geq$ 10 years after stopping: RR 1.01 (95% CI 0.96-1.05).

It is noted that the degree of association between time since last use of OCs and risk of breast cancer is relatively modest. This is also a theme for other exposures of interest. Exposures considered in a reasonable number of studies can be summarised as follows:

- Ever use of OCs: pooled effect 1.17 (95% CI 1.05-1.31) but with significant heterogeneity between studies. Suggests, at best a relatively modest association with breast cancer
- Duration of use of OCs was characterised by inconsistencies both within and between studies. It was not possible to draw any firm conclusions about this exposure.
- Timing of use in relation to FFTP: no significant association with risk of breast cancer so this exposure is unlikely to be a useful variable when determining the level of risk of breast cancer
- Age and time since first use of OCs: based on the small number of studies that were eligible for this review, these factors did not appear to be usefully discriminating for determining a group at increased risk of breast cancer.

Other exposures were considered, including, timing of use by defined age groups, oestrogen dose, type of oral contraceptive and use of non-oral hormonal contraceptives but the number of studies eligible in these categories was not large enough to enable the formulation of any conclusions.

Given the high prevalence of OC use in New Zealand and the relatively low risk of breast cancer in young women, the relevance of recent OC use may be questionable. The benefits of OC use also need to be considered.

Chapter 11: Other exogenous hormones

SECONDARY RESEARCH

Xenoestrogens and endocrine disruptors

No systematic reviews were identified examining the relationship between xenoestrogens and breast cancer.

Phytoestrogens

Three systematic reviews were identified that examined the role of phytoestrogens on risk of breast cancer (Cassidy et al 2006; Qin et al 2006; Trock et al 2006). The evidence table for these reviews is included in Table 12.1 (appendix 12, pages 263-267). The three reviews came to inconsistent conclusions with one suggesting insufficient evidence for the role of isoflavones due to the lack of RCTs (Cassidy et al. 2006), another suggesting it is premature to conclude that isoflavone supplementation reduces the risk of breast cancer but a third study concluding that soyfood intake may be associated with a decreased risk of breast cancer (Qin et al. 2006). The latter study included the highest number of research studies. However, it was notable that the 95% confidence intervals comparing isoflavone intake with risk of breast cancer (RR 0.81, 95% CI 0.67-0.99) only just excluded one, so the result should be considered as borderline significant. Similar estimates were found for the comparison of soyfood intake and breast cancer in the same study (RR 0.75, 95% CI 0.59-0.95). There were also limitations to the primary studies included in the review, such as the reliance on self report food frequency data, which may have produced exposure misclassification.

Trock et al (2006) estimated an OR of 0.86 (95% CI 0.75-0.99) when comparing the risk of breast cancer among women with the highest category of soy intake compared with the lowest category. They noted there was no evidence of a dose response effect.

Cassidy et al (2006) considered various categories of studies. Eight case control studies that analysed the effect of soyabean intake among Asian women were examined and the pooled odds ratio from these studies was 0.67 (95% CI 0.48-0.93). However, results were less clear cut in studies of "Caucasian" women (pooled OR 0.96, 95% CI 0.71-1.2). Two studies of adolescent dietary exposure showed a strong inverse relationship with breast cancer risk (OR 0.49, 95% CI 0.33-0.74; OR 0.41, *p* for trend 0.007).

Thus overall, there was uncertainty about the effect of isoflavones/soy on breast cancer although the balance of results suggests they are protective if any true effect exists.

Diethylstilbestrol (DES)

No systematic reviews were identified examining the relationship between DES and breast cancer.

Xenoestrogens and endocrine disruptors

Ten studies were identified that fulfilled the eligibility criteria for xenoestrogens or endocrine disruptors as exposures of interest. Eight were case control studies (including one nested case control study) and two were cohort studies. A range of xenoestrogens were studied with various pesticides being commonly studied. Some studies included the same xenoestrogen and these will be presented first.

Three case control studies included various PCBs and these results are presented in Table 21. There was no clear association between PCB and breast cancer based on the three studies presented.

Table 21: Comparison of original studies appraised that evaluated the presence of an association between PCBs and risk of breast cancer

Reference	Design	Adjusted	PCB	Key results (95% CI)
(Demers et al. 2000)	Case n=315 Control n=307 population based, n=219 hospital based	Yes	153	OR compared with lowest quintile: Quintile 2: 1.12 (0.66-1.88) Quintile 3: 0.94 (0.55-1.62) Quintile 4: 1.18 (0.68-2.05) Quintile 5: 1.28 (0.74-2.19)
(Hoyer et al. 1998)	Case n=240 Control n=477	Yes	Total	OR compared with lowest quartile Quartile 2 0.92 (0.58-1.45) Quartile 3: 0.78 (0.48-1.26) Quartile 4: 1.11 (0.70-1.77)
(Aschengrau et al. 1998)	Case n=261 Control n=753	Yes	Any	OR compared to non-exposed 3.2 (0.8-3.2)

Three case control studies examined the association between DDE and breast cancer. These are summarised in Table 22. There was no clear association between DDE and breast cancer based on the three studies presented.

Table 22: Comparison of original studies appraised that evaluated the presence of an association between DDE and risk of breast cancer

Reference	Design	Adjusted	DDE	Key results (95% CI)
(Ibarluzea et al. 2004)	Case n=198 Control n=260	Yes		OR compared with low exposure (ng/g of lipid) 201.73-397.67: 1.04 (0.59-1.84) 397.68-675.97: 1.23 (0.69-2.17) 675.98+: 1.22 (0.68-2.21) *P* for trend 0.40
(Demers et al. 2000)	Case n=315 Control n=307 population based, n=219 hospital based	Yes	*p, p'*-DDE	OR compared with lowest quintile: Quintile 2: 0.75 (0.45-1.25) Quintile 3: 1.06 (0.62-1.79) Quintile 4: 0.86 (0.52-1.42) Quintile 5: 1.00 (0.60-1.67)
(Hoyer et al. 1998)	Case n=240 Control n=477	Yes	*p, p'*-DDE	OR compared with lowest quartile Quartile 2 0.83 (0.53-1.31) Quartile 3: 0.77 (0.49-1.22) Quartile 4: 0.88 (0.56-1.37)

Three case control studies examined the association between DDT and breast cancer. These are summarised in Table 23. The results from Charlier et al (2003) were inconsistent with those in the other two studies. Charlier et al suggested total DDT increased the risk of breast cancer whereas DDT was not associated with increased risk in the other two studies and the measure of effect was in the opposite direction.

Table 23: Comparison of original studies appraised that evaluated the presence of an association between DDT and risk of breast cancer

Reference	Design	Adjusted	DDT	Key results (95% CI)
(Charlier et al. 2003)	Case n=159 Control 250	Yes	Total	OR compared with non-exposed 5.64 (1.81-17.65)
(Demers et al. 2000)	Case n=315 Control n=307 population based, n=219 hospital based	Yes	*p, p'*-DDT	OR compared with lowest quintile: Quintile 2: 0.57 (0.34-0.95) Quintile 3: 0.50 (0.30-0.84) Quintile 4: 0.71 (0.43-1.19) Quintile 5: 0.81 (0.48-1.37)
(Hoyer et al. 1998)	Case n=240 Control n=477	Yes	*p, p'*-DDT Total DDT	OR compared with lowest quartile Quartile 2 1.07 (0.68-1.68) Quartile 3: 0.91 (0.56-1.47)) Quartile 4: 1.19 (0.76-1.87) OR compared with lowest quartile Quartile 2 0.79 (0.45-1.39) Quartile 3: 0.92 (0.54-1.58) Quartile 4: 0.84 (0.49-1.45)

Two case control studies classified the substances studied under the general heading of xenoestrogens. One of these studies investigated the effect of exposure to a range of xenoestrogens on breast cancer risk. These studies are included in Table 24. There was no clear association between xenoestrogens and breast cancer based on the two studies presented.

Table 24: Comparison of original studies appraised that evaluated the presence of an association between xenoestrogens and risk of breast cancer

Reference	Design	Adjusted	Xenoestrogens	Key results (95% CI)
(Ibarluzea et al. 2004)	Case n=198 Control n=260	Yes	Excess burden of type alpha Excess burden of type beta	OR compared with low exposure (picomolar of estradiol equivalent/g of lipid) 0.26-41.00: 1.15 (0.64-2.05) 41.01-197.50: 1.33 (0.76-2.33) 197.51+: 1.31 (0.74-2.31) OR compared with low exposure (picomolar of estradiol equivalent/g of lipid) 9.96-100.00: 1.08 (0.61-1.90) 100.01-550.00: 1.05 (0.59-1.86) 550.01+ 0.99 (0.55-1.79)
(Aschengrau et al. 1998)	Case n=261 Control n=753	Yes		OR compared to non-exposed 1: 1.1 (0.8-1.7) 2: 0.6 (0.3-1.2) 3: 0.9 (0.5-1.9) 4+: 0.9 (0.5-1.9)

Two case control studies examined the association between β-HCH and breast cancer. These are summarised in Table 25. There were no statistically significant results and the measures of effect were inconsistent between the two studies.

Table 25: Comparison of original studies appraised that evaluated the presence of an association between β-HCH and risk of breast cancer

Reference	Design	Adjusted	Key results (95% CI)
(Demers et al. 2000)	Case n=315 Control n=307 population based, n=219 hospital based	Yes	OR compared with lowest quintile: Quintile 2: 0.60 (0.35-1.01) Quintile 3: 0.62 (0.37-1.04) Quintile 4: 0.86 (0.50-1.49) Quintile 5: 0.80 (0.47-1.35)
(Hoyer et al. 1998)	Case n=240 Control n=477	Yes	OR compared with lowest quartile Quartile 2 1.13 (0.69-1.86) Quartile 3: 1.35 (0.79-2.30) Quartile 4: 1.36 (0.79-2.33)

Other chemicals included as an exposure of interest were only included in single studies. These included nitrate-N, metalworking fluid, aldrin, endosulfanether, lindane, HCB, TCDD (dioxin), oxychlordane, nonachlor, dieldrin methoxychlor, endosulfanether, butylphenol, hydroxybiphenol, nonlyphenol, octylphenol, butyl benzyl phthalate, BHA and bisphenol A.

There were three significant associations found between these xenoestrogens and increased risk of breast cancer. Thompson et al (2005) estimated exposure to soluble metal working fluid within 10 years of breast cancer diagnosis was associated with an increased risk of breast cancer (OR 1.18, 95% CI 1.02-1.35). Charlier et al (2003) studied the association between HCB, an environmental xenoestrogen, and breast cancer in one of their studies. There was a significantly increased odd of breast cancer in the group exposed to HCB (OR 9.14, 95% CI 2.84-29.41). Hoyer et al (1998) also found increased risk of breast cancer in a group exposed to high levels of dieldrin (*p* for trend 0.01).

One study also evaluated classes of pesticides (Reynolds et al. 2004). They included:

- Probably/likely human carcinogens
- Possible/suggestive human carcinogens
- Mammary carcinogens
- Endocrine disruptors
- Anticholinesterases
- Organochlorines.

There were no significant associations found between any of these groups and breast cancer.

In summary, there were few associations detected between xenoestrogens and breast cancer. Most analyses did not achieve statistical significance. Some of the results were conflicting between studies. In the few analyses where there was a significant association, this was in the direction suggesting the xenoestrogen was associated with increased risk of breast cancer. It should be noted that there were limitations associated with the studies. These included potential misclassification of exposure due to:

- Exposure measurement of specimens collected after diagnosis of breast cancer may not represent exposure levels experienced pre diagnosis
- Assignment of exposure based on occupational history may result in inaccuracy
- Use of extrapolation to estimate exposure level at a certain time may result in inaccurate assessment.

It should be noted that non-differential misclassification was likely in a number of studies. Such misclassification would result in dilution of any association between exposure and outcome.

There were also potential sources of selection bias including:

- Selection of controls from a population that didn't best represent the population from which cases were drawn
- Non-participation of some eligible women.

All the studies were susceptible to confounding although the magnitude of confounding was likely to vary between studies given the variation in potential confounders considered by different authors. All studies conducted multivariate analyses thus exerting some control on potential confounders.

Phytoestrogens

No primary research studies examining the relationship between phytoestrogens and breast cancer were examined since systematic reviews were identified that were published in 2006.

Diethylstilbestrol (DES)

This review identified five studies published between 1997 and 2002 that fulfilled the eligibility criteria. Three of the studies were cohort studies (Palmter et al 2002; Titus-Ernstoff et al 2001; Hatch et al 1998) and the remaining two used a case control design (Sanderson et al 1998; Weiss et all 1997). The studies were all evidence level III-2. The three cohort studies were large, consisting of:

- 6,916 participants, including 83,370 and 29,224 person-years of follow-up among women exposed to DES and unexposed to DES respectively (Palmer et al. 2002)
- 7,758 participants, including 3879 exposed and 3879 not exposed to DES (Titus-Ernstoff et al. 2001)
- 6,080 participants, including 4536 exposed and 1544 not exposed to DES (Hatch et al. 1998).

The two case control studies were population-based. One study included 510 cases and 436 controls (Sanderson et al. 1998) while the other included 534 cases and 497 controls (Weiss et al. 1997).

The studies used various approaches to examine the association between maternal (or *in utero)* DES exposure and risk of breast cancer. Four studies looked at the risk of breast cancer in daughters of women who took DES during pregnancy (*in utero* exposure) (Palmer et al 2002; hatch et al 1998; Sanderson et al 1998; Weiss et al 1997) whereas only one looked at the risk of breast cancer on the mothers themselves (Titus-Ernstoff et al. 2001) . A summary of the results of these studies is presented below:

Summary of cohort studies

Palmer et al 2002

Palmer et al (2002) did not identify a significant association between DES exposure and invasive breast cancer (RR 1.4, 95% CI 0.7-2.6) or invasive plus *in situ* tumours (RR 1.3, 95% CI 0.7-2.1). However, when restricting the analysis to women at least 40 years of age there was a borderline significant association between DES exposure and breast cancer incidence (RR 2.5, 95%CI 1.0-6.3) after adjusting for year of birth, age at first birth and parity. There was a non-significant increase in breast cancer risk when the timing of first exposure to DES was at ≥ 13 weeks of gestation (RR 1.7, 95% CI 0.7-3.8).

In summary, the results suggest that *in-utero* exposure to DES may lead to an increased risk of breast cancer, but the data were not definitive. There was a statistically significant association between DES exposure and risk of breast cancer at ages 40 and older; this increase was a 2.5 fold. This result however was based on a small number of cases (27 exposed women and 7 unexposed women). DES exposure was not associated with higher grade or advanced disease based on data on the size of tumour and nodal involvement.

Titus-Ernstoff et al 2001

This 19-year follow-up study assessed the long-term cancer risk, particularly breast cancer risk, among women who were exposed to DES during pregnancy using combined analysis of results from two cohorts of DES exposed women, the Mothers Study cohort, and the Dieckmann Study cohort (Titus-Ernstoff et al. 2001).

The following results are from the combined analysis from the two cohorts:

- There was a statistically significant association between DES exposure and breast cancer risk (RR 1.27, 95% CI 1.07-1.52)
- The age-standardized breast cancer rates per 100 000 were 106.9 for exposed women versus 83.9 for non exposed women.
- In comparison with the general US population, the incidence rate of breast cancer was slightly increased among DES-exposed women (SIR= 1.10, 95% CI 0.98-1.23), and slightly but significantly reduced among unexposed women (SIR =0.86, 95% CI 0.75-0.98).

- The RR for breast cancer associated with DES exposure during a first pregnancy was higher than that in subsequent pregnancies (RR 1.15, 95%CI 0.9-1.47).

The study results demonstrated a modest association between DES exposure and breast cancer risk (27% increase), among results based on over 500 breast cancer cases. This increased risk of breast cancer was relative both to unexposed women and to the general US population The influence of DES on breast cancer risk was fairly constant in the presence of other hormonal factors, including oral contraceptives, menopausal status, and HRT. The presence of a dose-response relationship between DES exposure and breast cancer could not be evaluated.

Hatch et al 1998

Hatch et al (1998) aimed to test the hypothesis that breast cancer risk may be associated with *in utero* exposure to elevated oestrogen levels due to the oestrogenicity itself rather than to the chemical structure of the oestrogen. Some associations have been reported for variables that may reflect endogenous *in utero* oestrogen levels, such as maternal age, twin status, and pre-eclampsia during the index pregnancy. The study particularly assessed the risk of breast cancer and other cancers in a group of daughters who were exposed to DES *in utero* an average of 16 years after that exposure using mailed questionnaires and medical record review of reported cancer outcomes. This study also combined different population cohorts and the median DES dose varied between cohorts. In the Dieckmann & Horne cohorts the median dose was 12g whereas in the DESAD cohort the incomplete data provided indicated a range of 1.5-4.5g.

There was no significant association between *in-utero* DES exposure and risk of breast cancer (RR 1.18, 95% CI 0.56-2.49). Age stratified analyses were also conducted:

- Breast cancer risk in daughters exposed to DES who were aged under 40 years: rate ratio 0.66 (95% CI 0.26-1.68)
- Breast cancer risk in daughters exposed to DES who were aged 40 years and over: rate ratio 3.17 (95% CI 0.73-13.83)

Among the entire cohort, there was no evidence of an increased risk of breast cancer among *in utero* DES-exposed women. However, there was a non-significant increased risk of breast cancer among DES-exposed daughters aged 40 years and older compared to non exposed daughters. It should be noted that the observations with respect to breast cancer were related to cancers occurring at a young age as the majority of women included in this study were aged less than 50 years at study time.

Summary of case-control studies

Sanderson 1998

Sanderson et al (1998) evaluated the association between *in utero* DES exposure and risk of breast cancer. This case-control study aimed to further investigate the relationship between intrauterine oestrogen exposure and risk of breast cancer. The study data were collected from mothers of women in two population-based case control studies of breast cancer for those perinatal factors thought to be related to pregnancy oestrogen levels in women under the age of 45 years who were diagnosed with breast cancer between 1983 and 1992.

There was no significant association between the use of DES and risk of breast cancer overall (OR = 2.3, 95% CI 0.8-6.4) or when the analysis was restricted to women with no first-degree family history of breast cancer (OR= 2.0, 95% CI 0.7-5.9).

It should be noted that only 18 women reported using DES during pregnancy (13 case women and 5 control women). The study provided limited support for the oestrogen hypothesis as it relates to subsequent breast cancer risk among young women.

Weiss 1997

Weiss et al (1997) conducted a population-based case-control study that assessed early life risk factors for breast cancer (including maternal exposure to diethylstilbestrol) in women aged less than 55 years.

There was no significant association between *in-utero* DES exposure and risk of breast cancer (RR 0.75, 95%CI 0.4-1.6).

These results were restricted to "white women" under the age of 45 years with completed mothers' questionnaires. Results showed no evidence of an increased breast cancer risk from exposure to diethylstilbestrol *in utero*. However, the number of women who reported exposure to diethylstilbestrol was small (n=14) compared with the number of women with unknown exposure status (n=34).

Study limitations

The studies included in this section on diethylstilbestrol (DES) were observational (three studies used a cohort design and two used a case-control design). Such designs are more prone to bias and confounding than randomised controlled trials. They do not for the control of unknown confounders. Both designs are also prone to selection bias. Lack of blinding can also result in information bias particularly when a long period of time has elapsed since exposure. The case control design is also prone to recall bias. Another problem with case-control studies is the selection of control groups where there is no control group which is optimal for all situations (Rothman 1998). There is a further risk of misclassification as many women may have not known whether their mothers took DES during pregnancy.

In cohort studies another important source of bias is loss to follow-up. In general it was not always clear from the study description how losses to follow up were handled.

Detection bias may have arisen from lack of blinding in cohort studies and from imprecise case-definitions in the case-control studies. In both types of studies performance bias may arise from the absence of data on diethylstilbestrol dose (measurement of exposure). In epidemiological studies an important issue in exposure assessment is the quality and accuracy of the exposure estimate as this in turn will determine the validity of the results. Most of the studies included used questionnaires to collect data on DES exposure. Information on the dose of DES used among exposed women was often not provided or was missing. Studies also did not give clear information on the duration and frequency of the DES exposure.

There was also overlap in the cohorts included in the different studies. For example, the DESAD cohort was included in the studies by Palmer et al (2002) and Hatch et al (1998). The Dieckman cohort was included in Palmer et al (2002), Titus-Ernstoff et al (2001) and Hatch et al (1998).

Specific limitations from the appraised studies included:

For the study by Palmer et al (2002):

- The median age of the cohort included was only 43 years and the incidence of breast cancer may have been under estimated
- there was lack of statistical power to detect relative risks lower than two.

For the study by Titus-Ernstoff et al (2001):

- The study compared the results from two cohorts (one cohort identified through prenatal record review whereas the second were based on a clinical trial of the effectiveness of DES). The Mothers Study participants had higher parity, younger age at first full-term birth, younger age at menarche, and higher frequency of cigarette smoking than the Dieckmann Study participants.
- There was a long period of time between evaluations of the Dieckmann cohort and consequent losses to follow-up.
- The modest increase in breast cancer risk associated with DES exposure was not supported by a dose-response relationship as this could not be evaluated. There were missing details of DES doses from the obstetrics records of the Mothers Study participants and were administered through a

standard protocol in the Dieckmann Study participant. The authors cited other research that had not identified a dose response relationship between DES levels and risk of breast cancer.

For the study by Hatch et al (1998):

- The major limitation of this study was the relatively young age of the cohort members leading to lack of statistical power to detect a relative risk of 2 for breast cancer.
- This study showed similar results to Palmer et al in that there was a higher risk in the DES exposed daughters compared to unexposed daughters among women aged ≥ 40 years but results were not statistically significant due to the lower rate of breast cancer among unexposed women in this age group.

For the study by Sanderson et al (1998):

- Selection bias as a result of the increased availability of data on maternal factors for case/proxy mothers (77.6%) compared with control mothers (72.7%) and the exclusion of proxy respondents for deceased mothers (26.2% case/proxy mothers, 21.2% control mothers).
- Difficulty in recalling the circumstances of the mothers' individual pregnancies, which occurred 25-50 years before the study (recall bias).
- The study also has the potential for misclassification bias
- The study lacked statistical power to detect significant associations between DES exposure and breast cancer risk.
- There lies a possibility of underestimation or overestimation of the odd ratios because of the effect of differential measurement error of maternal factors.

For the case-control study by Weiss et al (1997):

- Many possible sources of bias may be identified from the mothers' questionnaire with recall bias being evident as the time from pregnancy to the interview was long. The potential for response bias arose from a high proportion of non-respondents to the mothers' questionnaire.

Conclusions

Due to the above limitations, data should be interpreted cautiously as the measure of exposure may be affected by the potential biases described. In general, results from the four studies of daughters of mothers who used diethylstilbestrol during pregnancy suggests that *in utero* exposure may have a slight increased risk of breast cancer after the age of 40 years. Further follow-up with the aging of the cohorts would be essential to provide adequate number of cases for testing the causal relationship further. The one study of exposure to diethylstilbestrol during pregnancy showed a slight increase of risk of breast cancer compared with the general population.

Chapter 12: Dietary factors

SECONDARY RESEARCH

Four systematic reviews were identified that examined the association between breast cancer and various diet related factors. All included observational studies so provided Level III-2 evidence. Zock et al (1998) investigated the association between linoleic acid and breast cancer. They concluded that it was unlikely a high intake of linoleic acid increased the risk of breast cancer substantially. Missmer et al (2002) examined risk of breast cancer by various food groups. There were no statistically significant findings by red meat, white meat, dairy fluid, dairy solid and egg consumption in this review. Unfortunately sources of data were not documented in this review. In contrast, Boyd et al (2003) found a significant association between meat consumption and risk of breast cancer (RR 1.17; 95% CI 1.06-1.43). They also found significantly increased risks of breast cancer by total fat intake (RR 1.13; 95% CI 1.03-1.25) and saturated fat intake (RR 1.19; 95% CI 1.06-1.35). A review by Saadatian-Elahi et al (2004) was restricted to studies measuring dietary fat intake with biomarkers, so in contrast to the earlier studies was not reliant on self-report data. However, results were conflicting. Saturated fatty acid intake was significantly associated with breast cancer in the three cohort studies selected (RR 1.74; 95% CI 1.15-2.63) but not in the seven case-control studies selected (RR 0.91; 95% CI 0.66-1.28).

The evidence table for these reviews is included in Table 13.1 (Appendix 13, pages 292-295)

PRIMARY RESEARCH: STUDY RESULTS

Nine studies were identified that fulfilled the eligibility criteria and were published from 2004 onwards. Systematic reviews examining the association between dietary factors and breast cancer were identified up to and including 2004, hence the restriction of selecting original studies to those that were published from 2004 onwards. The original studies identified examined a heterogeneous group of dietary factors. These included:

- total fat (5 studies)
- specific types of fat (3 studies)
- beta carotene (2 studies)
- total carotene (2 studies)
- total energy (2 studies)
- serum triglycerides
- serum cholesterol
- total protein
- retinoids
- tocopherol
- carbohydrates
- vegetable pattern
- pork, processed meat and potatoes pattern

Full details of the nine papers appraised, including methods, key results, limitations and conclusions, are provided in evidence table 13.2 (Appendix 13, pages 296-310).

Original studies examining total fat intake and association with breast cancer

Five studies evaluated the effect of total fat intake on risk of breast cancer (Alothaimeen et al. 2004; Frazier et al. 2004; Lee et al. 2005a; Mattisson et al. 2004; Wakai et al. 2005). These studies are compared in Table 21. Examination of the key results reveals inconsistent results between studies. However, there were important design differences between studies. Most notably, Frazier et al (2004) examined the effect of adolescent diet in a retrospective study. Given that 15-35 years had elapsed since the participants had been at school, the risk of misclassification was high. It is also unclear whether adolescent diet is the most relevant time to study. Irrespective, no association was found between total fat intake and risk of breast cancer. In contrast to Frazier et al (2004), the other retrospective studies examined diet for the period up to 1-2 years preceding diagnosis of breast cancer while the mean follow up period in the two prospective cohort studies were 7.6 and 7.7 years.

The two prospective cohort studies provided inconsistent results (Mattisson et al. 2004; Wakai et al. 2005). The former was conducted in Sweden and the latter in Japan. Mattison et al (2004) presented two multivariate models, one comparing fat to total energy intake and the other comparing fat to non-alcohol energy intake. In contrast, Wakai et al (2005) adjusted for total energy intake in their model. The mean age was slightly lower in the Wakai study. Mattison et al (2004) found significant trends toward increasing risk of breast cancer with increasing fat intake in both models, although the model comparing fat with non-alcohol energy intake was of borderline significance. There was no significant difference between the specific quintiles and the baseline quintile in this study for either analysis (total non-alcohol energy intake). Wakai et al did not identify a significant trend or any difference between quartiles of fat intake and risk of breast cancer. However, higher quartiles of fat intake resulted in non-significantly lower risk of breast cancer.

Two case control studies were also identified and appraised (Alothaimeen et al. 2004; Lee et al. 2005a). Alothaimeen et al found a significantly increased risk of breast cancer among women classified in the third quartile of fat intake. Lee et al found an increased risk of breast cancer among women classified in quartile four of fat intake. There was no assessment of trend in the latter study.

These conflicting results were similar to the findings of the systematic reviews presented earlier. Boyd et al (2003) estimated an increased risk of breast cancer with increased total fat intake (RR 1.13, 9%% CI 1.03-1.25) and Saadatian-Elahi et al (2004) noted conflicting results in a study using biomarkers.

The difficulties associated with evaluating the role of dietary fat in breast cancer should be noted. Common issues included:

- The difficulty ascribing any association to one particular dietary factor as change of one dietary factor inevitably results in change to the intake of other dietary factors
- Change in weight after altering diet
- Measurement error – particularly associated with self-report data.

Overall, the role of dietary fat in breast cancer is unclear. Results are conflicting between reviews but it seems unlikely that dietary fat is a strong risk factor for breast cancer based on current evidence.

Table 21: Comparison of original studies appraised that evaluated the presence of an association between total fat intake and risk of breast cancer

Reference	Design and sample	Variables adjusted for	Key result (lowest category of intake as baseline), (95% CI)
(Frazier et al. 2004)	Retrospective cohort N=47,355	Age, time period, height, parity, age at first birth, BMI at age 18, age at menarche, family history of breast cancer, history of benign breast disease, menopausal status, alcohol intake, oral contraceptive use, and weight gain since age 18	Quintile 2: 0.72 (0.52-1.00) Quintile 3: 0.61 (0.43-0.85) Quintile 4: 0.74 (0.53-1.02) Quintile 5: 0.91 (0.67-1.24) *Ptrend* 0.68
(Mattisson et al. 2004)	Prospective cohort study N=28,098	Two models. Both adjusted for: diet interviewer, method version, season of diet interview, age at baseline, change of dietary habits, height, waist, current hormone use, age at first child, age at menarche, leisure time physical activity, smoking habits and educational level. One model compared fat with total energy intake, the other with non-alcohol energy intake.	Total energy intake Quintile 2 0.81 (0.55-1.18) Quintile 3 1.36 (0.97-1.92) Quintile 4 1.26 (0.89-1.79) Quintile 5 1.36 (0.96-1.94) *Ptrend* = 0.02 Non-alcohol energy intake Quintile 2 1.05 (0.73-1.51) Quintile 3 1.23 (0.86-1.76) Quintile 4 1.38 (0.97-1.96) Quintile 5 1.35 (0.94-1.93) *Ptrend* = 0.05
(Wakai et al. 2005)	Prospective cohort study N=26,291	Age, study area, educational level, family history of breast cancer, age at menarche, age at menopause, age at first birth, parity, use of exogenous female hormones, alcohol consumption, smoking, consumption of green leafy vegetables, daily walking, height, BMI and total energy intake.	Quartile 2: 1.29 (0.80-2.08) Quartile 3: 0.95 (0.57-1.59) Quartile 4: 0.80 (0.46-1.38) *Ptrend* 0.32
(Alothaimeen et al. 2004)	Case (n=499) control (n=498)	age, nationality, province and menopause	Quartile 2: OR 1.65 (0.90-3.02) Quartile 3: OR 2.67 (1.47-4.83) Quartile 4: OR 1.64 (0.92-2.95)
(Lee et al. 2005a)	Case (n=250) control (n=219)	Age and education	Quartile 2: OR 0.9 (0.5-1.6) Quartile 3: OR 1.5 (0.9-2.6) Quartile 4: OR 1.9 (1.1-3.2)

Original studies examining specific types of fat and association with breast cancer

Data were extracted from three studies in relation to specific types of fat (Alothaimeen et al. 2004; Frazier et al. 2004; Wakai et al. 2005).

Alothaimeen et al (2004), in their case control study, examined for any association between breast cancer and various fat related factors, including serum triglyceride, serum cholesterol, saturated fat and polyunsaturated fat. There was a statistically significant association between high serum triglyceride level (highest quartile of serum triglyceride level compared with lowest quartile) and breast cancer (adjusted OR 2.16; 95% CI 1.21-3.88), high saturated fat (quartile three and quartile four versus lowest quartile) and breast cancer (Quartile 3: adjusted OR 2.43; 95% CI 1.30-4.53; Quartile 4: adjusted OR 2.43; 95% CI 1.36-4.34), and polyunsaturated fat (quartiles two to four versus quartile one) and breast cancer (Quartile 2: adjusted OR 2.19; 95% CI1.18-4.07, quartile 3: adjusted OR 2.73; 95% CI 1.53-4.87, quartile 4: adjusted OR 2.12; 95% CI 1.17-3.83).

Frazier et al (2004) investigated the role of animal fat and vegetable fat within their retrospective cohort study. This study assessed the role of adolescent diet in breast cancer. There was a highly significant trend with decreasing risk of breast cancer across increasing quintiles of vegetable fat intake. In contrast, Wakai et al (2005) found a non-significant increased risk of breast cancer with increasing levels of vegetable fat intake.

Two of the systematic reviews examined saturated fats and risk of breast cancer. Boyd et al (2003) found a moderately increased risk of breast cancer with increasing saturated fat intake (RR 1.19) and Saadatian-Elahi et al (2004) found mixed results with an overall increased risk in cohort studies (RR 1.74) but not case control studies (RR 0.91). Thus, the case control study by Alothaimeen et al (2004) presents inconsistent findings from the pooled estimate for case control studies in Saadatian-Elahi et al

(2004) but is consistent with the increased risk suggested by Boyd et al (2003). Boyd et al did not find a significant association between polyunsaturated fat intake and breast cancer (RR 0.94, 95% CI 0.80-1.10), thus the findings presented by Alothaimeen et al (2004) indicated a lack of consistency from earlier research.

Considering the primary and secondary research studies we can conclude that the role of vegetable fat intake and polyunsaturated fat intake in breast cancer is unclear. There are also inconsistencies across studies examining saturated fat intake and breast cancer. However, pooled estimates presented in this review indicated an increased risk of breast cancer, as do pooled estimates of cohort studies and the single case control study appraised for this review. These results suggest an increased risk of breast cancer in association with increased saturated fat intake, although the study limitations and inconsistencies are noted.

Original studies examining beta carotene and association with breast cancer

Data were extracted from two studies in relation to beta carotene and risk of breast cancer (Nkondjock and Ghadirian 2004; Zaroukian et al. 2005). Both were case control studies. There were 223 cases and 85 controls in Zaroukian et al (2005) and 414 cases and 429 controls in Nkondjock et al (2004). Zaroukian et al classified beta carotene levels into terciles from three types of sample: adipose tissue, cheek tissue and plasma. The samples were taken following diagnosis of breast cancer so may represent altered dietary behaviour or altered metabolism as a result of the breast cancer diagnosis. There was a significant association between increased level of beta carotene in both adipose and cheek tissue and risk of breast cancer. No such association was found with plasma. However, the increased level of risk appeared to be more significant in the intermediate than the highest level of beta carotene in both adipose and cheek tissue.

In contrast to Zaroukian et al, Nkondjock et al (2004) found no significant association between beta carotenoid intake and risk of breast cancer. In this study, the intake of beta carotene was estimated over the two year period before interview. It was noted that carotenoid supplementation was common in the source population for this study.

In conclusion, the role of beta carotene in breast cancer was not clear from the studies appraised. Further research is required in this area.

Original studies examining total carotene and association with breast cancer

Data were extracted from two studies in relation to total carotene and risk of breast cancer (Nkondjock and Ghadirian 2004; Zaroukian et al. 2005). These were the same studies as those examining beta carotene. The results were similar to those documented for beta carotene. Specifically, Zaroukian et al estimated an increased risk of breast cancer among women with high levels of total carotene in adipose tissue and cheek tissue, although, with adipose tissue it was only those in the intermediate tercile who were associated with a statistically significant increased risk. Nkondjock et al did not identify a statistically significant association between total carotene and risk of breast cancer. Further research is required in this area.

Original studies examining total energy and association with breast cancer

Data were extracted from two studies in relation to total energy and risk of breast cancer (Frazier et al. 2004; Lee et al. 2005a). One of these examined the role of adolescent diet in breast cancer (Frazier et al. 2004). In both studies an increased risk of breast cancer was found with increasing levels of total energy intake. Lee et al, in their case control study found a significantly increased risk of breast cancer among women with a total energy intake in the upper quartile of intake levels compared with the lowest quarter (OR 2.1, 95% CI 1.2-3.6). Frazier et al, found a statistically significant trend towards increasing risk of breast cancer with increasing quintiles of total energy intake (P=0.01) and also found an increased risk in quintile 4 compared with quintile 1 (RR 1.48, 95% CI 1.06-2.07). The relative risk for quintile 5 compared with quintile 1 also neared significance (RR 1.39, 95% CI 0.99-1.96).Other dietary factors and risk of breast cancer

Other dietary factors and risk of breast cancer

Other dietary factors were investigated in single studies. In general, it was not possible to form any robust conclusions in relation to the association between these variables and the risk of breast cancer, due to the limited data identified.

Chapter 13: Alcohol

SECONDARY RESEARCH

Three systematic reviews consisting of studies that used observational study designs were included (Level III-2 evidence). The studies were published between 2001 and 2004. The Collaborative Group on Hormonal Factors in Breast Cancer (2002) re-analysed data from 51 studies, using individual patient data. A total of 66,426 women with invasive breast cancer and 126,953 without breast cancer were included in the analysis. The authors observed a 7.1% increase in risk of breast cancer for each additional 10g per day intake of alcohol. This result fits with the results of Ellison et al (2001). In their review the risk ratios for development of breast cancer comparing specified levels of alcohol intake with no intake were 1.05 for 6g per day, 1.10 for 12g per day and 1.21 for 24g per day. However, there was variation by study characteristics, including study design, publication year (lower risk in later publications) and length of follow up (lower risk with longer follow up). Corrao et al (2004) updated their earlier reviews (Bagnardi et al. 2001; Corrao et al. 1999). This was a well conducted review that made use of a model to estimate risk at specified levels of alcohol intake. The estimated risk ratio at 25g alcohol per day was 1.25, at 50g/day was 1.55 and at 100g per day was 2.41. Their results were consistent with the results in the other two systematic reviews and extend the estimates to higher levels of alcohol intake. These latter results are likely to be the most reliable.

The evidence table for these reviews is included in Table 14.1 (Appendix 14, pages 312-314)

PRIMARY RESEARCH: STUDY RESULTS

Ten studies were identified that fulfilled the eligibility criteria, examined the relationship between alcohol intake and risk of breast cancer and were published from 2004 onwards. Systematic reviews examining the association between alcohol and breast cancer were identified up to and including 2004, hence the restriction of selecting original studies to those that were published from 2004 onwards. The original studies identified had four main purposes:

1. To examine the relationship between alcohol intake and risk of breast cancer (Lin et al. 2005; Mattisson et al. 2004; Petri et al. 2004; Suzuki et al. 2005);
2. To examine the influence of timing of exposure to alcohol and risk of breast cancer (Horn-Ross et al. 2004; McDonald et al. 2004; Tjonneland et al. 2004);
3. To examine the effect of folate on modifying the effect of alcohol on risk of breast cancer (Baglietto et al. 2005; Tjonneland et al. 2006);
4. To examine the interaction between use of oral contraceptives and alcohol and risk of breast cancer (Dumeaux et al. 2004).

The evidence tables for the original research studies are found in table 14.2 (Appendix 14, pages 315-327).

Relationship between alcohol intake and risk of breast cancer

Four of the ten selected studies were primarily examining the relationship between alcohol intake and risk of breast cancer without considering the role of timing of alcohol exposure. Two studies used non-drinkers as the reference group (Lin et al. 2005; Suzuki et al. 2005) and two used light drinkers as the reference group (Mattisson et al. 2004; Petri et al. 2004). All four studies used the cohort design.

Under the assumption that there is not a J shaped curve type relationship between alcohol intake and risk of breast cancer, it is expected that the estimated relative risk comparing the risk of breast cancer amongst heavy drinkers with non-drinkers would be higher than the relative risk amongst those same heavy drinkers if light drinkers had been used as the reference group. This assumption is supported by the use of linear trend relationships presented in the reviews identified under secondary research. Lin et

al (2005) had a smaller sample size than Suzuki et al (2005) and, most importantly, 74.5% of the cohort were non-drinkers. Therefore, the study estimates were associated with wide confidence intervals. The only significant association identified was a relative risk of 2.93 (95% CI 1.55-5.54) when comparing the consumption of at least 15 grams of alcohol per day compared with non-drinkers. Suzuki et al found a significant trend towards increased risk of breast cancer with increasing alcohol intake (P=0.001) and also a statistically increased risk when comparing the consumption of at least 10 grams of alcohol per day compared with non-drinkers (RR 1.43, 95% CI 1.16-1.76). The intermediate results in this study also showed a more consistent dose-response relationship than those in Lin et al.

The two studies using light drinkers as a reference group did not identify any statistically significant associations with the risk of breast cancer when considering the overall study populations. In part this may have been due to the use of light drinkers rather than non-drinkers as the reference group. Another contributing factor may have been that both studies had relatively small sample sizes (13,074 for Petri et al and 11,726 for Mattison et al) compared with Lin et al and Suzuki et al (35,844 and 51,847 respectively). Mattison et al focussed on postmenopausal women and Petri et al presented results by menopausal status. There were no statistically significant results identified among postmenopausal women in Petri et al.

In addition to these four studies, other studies presented results of relevance to the association between alcohol and breast cancer (Baglietto et al. 2005; Dumeaux et al. 2004; Horn-Ross et al. 2004; McDonald et al. 2004; Tjonneland et al. 2006).

Tjonneland et al (2006), in their nested case control study, aimed to investigate the role of folate in attenuating the effect of alcohol. Amongst women with low total folate intake (≤300μg/day) the relative risk of breast cancer for each additional 10 grams of alcohol per day was estimated to be 1.19 (95% CI 0.99-1.42).

Likewise, Baglietto et al (2005) also primarily investigated the role of folate in attenuating the effect of alcohol. However, they presented estimates adjusted for folate intake in their relatively small cohort study. No statistically significant associations were found, even when comparing heavy drinkers (>40g alcohol/day compared with non-drinkers).

Dumeaux et al (2004) primarily investigated the interaction between oral contraceptives and alcohol with the risk of breast cancer in their large cohort study (n=86,948). They found a statistically significant trend with increasing risk of breast cancer as alcohol intake increased (P<0.001) and all categories of alcohol intake had a significantly higher risk of breast cancer compared with non-drinkers. The estimated relative risk amongst women consuming at least 10 grams of alcohol per day was 1.69 (95% CI 1.32-2.15).

Horn-Ross et al (2004) primarily investigated the effect of age at drinking. They used a cohort design with a large sample size (n=103,460). In one of their analyses they examined the drinking pattern in the year before study entry. Heavy drinkers (20+ grams of alcohol/day) had an increased risk of breast cancer compared with non-drinkers (RR 1.28, 95% CI 1.06-1.54).

McDonald et al (2004) examined the timing of alcohol intake and risk of breast cancer in a population based case control study. They found an increased risk of breast cancer with the consumption of at least seven drinks per week two years before the time of diagnosis when compared with the reference group of non-drinkers. The estimated odds ratio was 1.2 (95% CI 1.01-1.3).

Overall, these results are consistent with moderately increased risk of breast cancer with increasing levels of alcohol intake. The results of the original studies therefore show some consistency with the systematic reviews presented earlier. We have not attempted to pool the results of these original studies given the different methods of presenting results in the individual studies but the individual study results do suggest similar overall results to those outlined under secondary research. In those reviews, the increase risk was in the order of 10% for 10g alcohol/day, 25% for 25g/day and 55% for 50g/day.

Effect of timing of exposure to alcohol on risk of breast cancer

The effect of timing of alcohol exposure on risk of breast cancer was examined in three studies (Horn-Ross et al. 2004; McDonald et al. 2004; Tjonneland et al. 2004). Two were cohort studies and the other was a population based case control study. Horn-Ross et al, in their cohort study included a large population sample (n=103,460). The sample size in the other cohort study was smaller, with 29,875 participants (Tjonneland et al. 2004). There were 4,575 cases and 4,682 controls in the case control study (McDonald et al. 2004). The studies supported recent exposure being more relevant than earlier lifetime exposure. However, the importance of recent exposure may be at least partially explained by study design features. In particular, misclassification of alcohol intake level could be expected to increase with increasing time since the exposure period. These studies relied on recall of alcohol intake over the period of decades so it might be expected that misclassification (which is likely to be non-differential in the two cohort studies) would be greater for the early exposure periods of interest. Such misclassification would dilute the association between alcohol and breast cancer.

Effect of folate on the association between alcohol and risk of breast cancer

Two studies examined whether folate had an attenuating effect on the risk of breast cancer associated with alcohol intake (Baglietto et al. 2005; Tjonneland et al. 2006). One was a cohort study with a sample size of 17,447 (Baglietto et al. 2005), the other was a nested case control study with 388 cases and 388 controls (Tjonneland et al. 2006). Both studies supported folate having an attenuating role in the association between alcohol and breast cancer. Tjonneland et al stratified by four levels of folate intake in their study. In the low folate category (≤300μg/day) the estimated relative risk for each additional 10g of alcohol per day was 1.19 (0.99-1.42) compared with the highest folate intake category (>400μg/day) where the relative risk was 1.01 (95% CI 0.85-1.20). As an example of the effects estimated by Baglietto et al among the group consuming at least 40 grams of alcohol per day, the estimated hazard ratios for intakes of 200μg/day, 330μg/day and 400μg/day of folate were 2.00 (95% CI 1.14-3.49), 1.08 (95% CI 0.60-1.93) and 0.77 (95% CI 0.33-1.80) respectively. Limitations of these studies are shown in Table 13.2 and should be considered when interpreting these results.

Interaction between use of oral contraceptives and alcohol and the risk of breast cancer

One study was identified that primarily aimed to examine the interaction between oral contraceptive use and alcohol intake in relation to the risk of breast cancer (Dumeaux et al. 2004). This was a cohort study with a sample size of 86,948. A negative interaction was observed with oral contraceptive use and alcohol intake implying antagonistic effects on breast cancer risk through a common pathway. This one-off finding is interesting of itself but it also emphasises that overall risk of breast cancer should not simply consider risk factors in isolation. Rather the interaction of risk factors may produce a different level of risk.

Chapter 14: Discussion

SUMMARY OF EVIDENCE

This report systematically reviewed the international evidence for risk factors for breast cancer in women.

Two thousand, eight hundred and sixty-one articles were identified by the search strategy. From 143 articles identified as potentially eligible for inclusion, a final group of 262 papers were selected for appraisal. The results were organised by chapter, with each chapter presenting a risk factor for breast cancer. The focus was on the level of independent risk associated with each risk factor considered. Main results are presented below.

A past history of breast cancer was a risk factor for a second primary breast cancer. In the four primary research studies identified, the relative risk estimates that compared women with a past history of breast cancer with women who had no past history ranged between 2.8 and 7.4.

A range of lesions associated with increased risk of breast cancer were considered in two systematic reviews. The results of the review providing the broadest consideration of the subject suggested usual ductal hyperplasia was potentially a very early precursor lesions and was associated with between a 1.5 and two fold increase in risk of breast carcinoma. Atypical ductal carcinoma was considered to be a later precursor lesion and was thought to be associated with a four fold increase in risk. In turn lobular carcinoma was a later precursor lesion associated with a six to ten fold increase in risk and ductal carcinoma *in situ* was associated with an eight to ten fold increase in risk. The clinical management of these conditions varies by both histological and individual patient characteristics.

The association between increased breast density and risk of breast cancer was considered in 12 primary research studies. All studies comparing percent area of dense tissue found an increased risk of breast cancer among women in the densest category compared with the least dense category (typically the relative risk approximated four). The relative risk approximated four across these studies. Similar results were found for studies that used other measures of breast density.

Nulliparity was considered in one secondary research study and 28 primary research studies. The results were consistent with nulliparity being a risk factor for breast cancer. Among the larger studies, the relative risk estimates appeared to decrease by approximately 0.09 for each additional birth.

Early menarche was also associated with increased risk of breast cancer in the one secondary research study and 29 primary research studies that were included in this review. The data were complicated to interpret given variation in cut-points for categorisation of age at menarche and uncertainty due to potential biases. On this basis, it is difficult to be precise about the level of risk associated with decreasing age of menarche, but it seems likely that it is a relatively modest risk factor.

Post menopausal obesity was considered in three systematic reviews and 14 primary research studies. The systematic review that compared BMI with risk of breast cancer estimated a relative risk of 1.12 for the association with the overweight category and 1.25 for the obese category. The results from primary research studies were largely consistent with this relatively low level of increased risk.

Hormone replacement therapy was considered in eight systematic reviews. Primary research studies were not considered in this section given the up to date nature of the secondary research. Most studies found an increased risk of breast cancer amongst current users and with longer duration of use. The estimated relative risk for current users seemed to be in the region of 1.2-1.4 with similar levels amongst long term users.

Hormonal contraceptives were considered in 37 primary research studies. The analyses were complicated by the use of different categories of oral contraceptive use. However, others have suggested that recency of use is a variable of key importance. Fifteen studies considered this variable. The results were consistent with the findings of the Collaborative Review (which re-analysed primary data from over 50 relevant studies). The results from this reanalysis were:

- current users: RR 1.24 (95% CI 1.15-1.33)
- 1-4 years after stopping: RR 1.16 (95% CI 1.08-1.23)
- 5-9 years after stopping: RR 1.07 (95% CI 1.02-1.13)
- $\geq$ 10 years after stopping: RR 1.01 (95% CI 0.96-1.05).

The chapter on exogenous hormones considered three different subtopics: stilboestrol, xenoestrogens and phytoestrogens. There were 10 primary studies in the xenoestrogens section. Most studies did not identify a statistically significant association between xenoestrogens and breast cancer. In the few studies where there was a statistically significant finding these were in the direction of an increased risk of breast cancer in association with increased xenoestrogen levels. There were five primary research studies in the stilboestrol section. There were overlaps in the study populations across these studies. In general there was an increased estimated risk of breast cancer following exposure to stilboestrol (usually *in utero*) but these results rarely reached statistical significance. Four studies estimated a relative risk (or odds ratio) of greater than one suggesting a harmful effect (range 1.18-2.3). One study found a non-significant protective effect from *in utero* DES exposure (OR 0.75). The section of phytoestrogens was limited to three recent systematic reviews. Overall, there was uncertainty about the effect of phytoestrogens in the form of isoflavones/soy on breast cancer although the balance of results suggests they are protective if any true effect exists.

Various dietary factors were considered in four systematic reviews and nine primary research studies. Results of dietary fat, vegetable fat and polyunsaturated fat were conflicting or unclear but there appeared to be an increased risk with saturated fat intake in the limited evidence base available. In the two studies that considered total energy intake, there was an increased level of risk with increasing intake. The highest intake category compared with the lowest was associated with relative risk estimates in the order of 1.4-2.1 in these two studies.

Alcohol intake as a risk factor for breast cancer was considered in three systematic reviews and 10 primary research studies. The primary research studies presented results that were consistent with those in the systematic reviews appraised. In the latter, the increased risk was in the order of 10% for 10g alcohol/day, 25% for 25g alcohol/day and 55% for 50g alcohol/day.

LIMITATIONS OF CURRENT RESEARCH BASE

The evidence considered in this review exhibited methodological limitations which are summarised below. These limitations can be divided into two categories: limitations of the research included in the review and limitations of the review process.

The majority of studies included in the review used the case-control design. Case control studies are characterised by susceptibility to selection bias and recall bias. Recall bias would be expected to result in over-estimation of the true level of association between the specific risk factor and risk of breast cancer. Some of the case control studies were more likely to suffer from selection bias than others due to variation in the methods of control selection. The magnitude and direction of this source of bias is more difficult to estimate. The remaining designs used in the primary research studies were nested case control studies and cohort studies. Nested case control studies are more robust than non-nested case control studies given the reduced risk of selection bias (both cases and controls are selected from the same population) and recall bias is usually controlled since exposure is recorded before development of the outcome of interest. Cohort studies are also susceptible to bias, including selection bias (due to low participation and follow-up rates) and information bias (due to misclassification of exposure or outcome). Misclassification of exposure is most likely to be non-differential, thus diluting the level of association with breast cancer. Despite these limitations, the findings across studies were relatively consistent for specific risk factors.

All observational studies are susceptible to confounding. However, risk factors for breast cancer are relatively well known and many of the studies included in this review included a wide range of these

risk factors in their multivariate models. On that basis, confounding should be relatively well controlled and is unlikely to result in a substantial influence on the estimated level of association.

There are also limitations in the review process used. The review has been limited by restriction to English language articles and to articles that were published over restricted time periods. Both of these factors may have resulted in publication bias. Publication bias may also have resulted from restriction to the published literature. The restriction to the selection of studies from 1996 onwards was particularly limiting for the benign breast disease section. Published literature is more likely to have identified an association with the outcome of interest.

There was no double selection of relevant research and double extraction of data was not used. This increases the chance of missing relevant literature and incorrectly extracting data.

Considering the size of the topic, a limited timeframe was available to conduct the review.

It should also be noted that the review did not include some key risk factors in its scope. Most notably these included genetic mutations such as the BRCA1 and BRCA2 mutations and a strong family history. Another factor that was outside the scope of the review was the way in which different risk factors interact. Nevertheless, some limited results were included in the review that illustrated the difficulties of estimating a specific level of risk for a given profile. For example, it should not be assumed that combinations of two risk factors will result in either additive or multiplicative levels of increased risk. The precise method of interaction is likely to be based on the mechanisms by which each risk factor operates. When two risk factors operate using the same physiological pathway then the level of increased risk is likely to be higher than risk factors that use different physiological pathways. Another possibility also exists that was documented in the alcohol chapter. One study was documented in that section that assessed interaction between OCs and heavy alcohol intake. The results suggested antagonistic effects from these two factors in relation to the risk of breast cancer. The authors postulated these two factors acted through a common pathway (Dumeaux et al. 2004).

DIRECTIONS FOR FUTURE RESEARCH

There were specific limitations in the research base that varied by risk factor considered. In general, more certainty in the level of risk from specific variables would result if:

- There was consistency in the methods of measurement of exposure
- Results were expressed separately for invasive breast cancer and in situ disease when both were assessed
- Cut-points were similar for specific variables across studies
- Reference categories were the same for specific risk factors.

In relation to the issue of interaction across risk factors, research examining the use of specific models estimating overall risk would be useful.

Finally, careful consideration of research design is required before starting another study investigating the level of risk associated with specific risk factors.

CONCLUSIONS

This report systematically reviewed the evidence for risk factors for breast cancer in women. After considering the results and limitations outlined above, it appears likely that the specific risk factors considered have different levels of association with breast cancer.

Factors with a higher level of risk (RR>2.0) included:

- past history of breast cancer
- lesions associated with increased risk of breast cancer (especially in the presence of atypia)
- increased breast density

Other factors appeared to have a moderate level of increased risk (RR 1.5-2.0):

- heavy alcohol intake

Some risk factors appeared to have more modest levels of increased risk (RR 1.1-1.4):

- nulliparity
- post menopausal obesity
- hormone replacement therapy
- current use of oral contraceptives or recent use of oral contraceptives
- high total energy intake

Finally, for some risk factors the level of increased risk was difficult to determine:

- early menarche (likely to be relatively modest)
- xenoestrogens
- phytoestrogens
- stilboestrol.

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Appendix 1: Search strategies

A two phase approach was taken for the search. This was described in Chapter 2.

PHASE 1: STRATEGIES TO IDENTIFY SYSTEMATIC REVIEWS AND META-ANALYSES

Medline

1 breast neoplasms/ (63829)
2 risk assessment/ or risk factors/ (242149)
3 1 and 2 (7268)
4 limit 3 to yr=1996-2005 (7094)
5 (systematic$ adj3 (review$ or overview)).tw. (9742)
6 meta-analysis/ or meta-analysis.pt. or metaanaly$.tw. or meta-analy$.tw. (19341)
7 5 or 6 (25858)
8 4 and 7 (189)
9 alcohol$.mp. (71255)
10 exp diet/ or exp food/ (189961)
11 hormone replacement therapy/ or estrogen replacement therapy/ (11334)
12 exp contraceptives, oral/ (8628)
13 parity/ (4978)
14 (nulliparous or nulliparity or childless$).mp. (2403)
15 menarche/ (941)
16 menarche.tw. (1671)
17 exp obesity/ (33725)
18 (breast adj3 dens$).mp. (498)
19 carcinoma in situ/ (3790)
20 ductal hyperplasia.mp. (400)
21 lobular hyperplasia.mp. (86)
22 sclerosing adenosis.mp. (95)
23 previous breast cancer.tw. (47)
24 neoplasms, second primary/ (4353)
25 or/9-24 (316683)
26 8 and 25 (68)

Embase

1 exp breast cancer/ (74049)
2 risk.mp. (488784)
3 1 and 2 (18305)
4 (systematic$ adj3 (review$ or overview)).mp. (16726)
5 (metaanaly$ or meta-analy$).tw. (11937)
6 meta-analysis/ or meta-analysis.pt. (22456)
7 or/4-6 (36416)
8 3 and 7 (794)
9 alcohol.tw. or alcoholism/ (57088)
10 alcohol drinking/ (5886)
11 parity/ (3410)
12 (nullipar$ or childless$).mp. (2858)
13 morbid obesity/ or obesity/ (44696)
14 menarche/ or menarche.mp. (2105)
15 (breast adj3 dens$).mp. (681)
16 second cancer/ (1725)
17 previous breast cancer$.mp. (54)
18 hormone substitution/ (13979)
19 (hormone replacement or estrogen replacement or hrt).tw. (11148)
20 exp diet/ (28811)
21 exp food/ (114669)

22 fat intake/ (8613)
23 exp oral contraceptive agent/ (12670)
24 carcinoma in situ/ (4579)
25 (ductal hyperplasia or sclerosing adnenosis or lobular hyperplasia).mp. (441)
26 or/9-25 (269656)
27 8 and 26 (328)
28 limit 27 to yr=1996-2005 (320)

The Cochrane Database of Systematic Reviews, the DARE and HTA databases were also searched in this phase using simplified strategies adapted from those given above.

PHASE 2: STRATEGIES TO IDENTIFY PRIMARY STUDIES

Core search strategy for Medline

1 breast neoplasms/ (60487)
2 risk.mp. (441462)
3 risk assessment/ or risk factors/ (227453)
4 1 and (2 or 3) (12746)
5 randomized controlled trial.pt. and randomized controlled trials/ (778)
6 controlled clinical trials/ or controlled clinical trial.pt. (27176)
7 exp clinical trials/ or clinical trial.pt. (295983)
8 random allocation/ or (random$ adj2 allocat$).tw. (25012)
9 single blind method/ or double blind method/ (46370)
10 (clinic$ adj trial$).tw. (57780)
11 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$ or dumm$)).tw. (37219)
12 exp epidemiologic studies/ (493380)
13 exp case control studies/ (200344)
14 exp cohort studies/ (295101)
15 exp cross sectional studies/ (43673)
16 (case control or cohort analy$ or cross sectional).tw. (60467)
17 (longitudinal or retrospective).tw. (106455)
18 (cohort adj (study or studies)).tw. (19303)
19 ((follow up or observational) adj (study or studies)).tw. (18865)
20 or/5-19 (808324)
21 letter.pt. (239331)
22 case report.tw. (48779)
23 21 or 22 (286889)
24 20 not 23 (784164)

Core strategy for Embase

1 exp breast cancer/ (70294)
2 risk.mp. (460847)
3 risk Factor/ (128580)
4 risk Assessment/ (98427)
5 1 and (2 or 3 or 4) (17309)
6 clinical trial/ (295121)
7 randomized controlled trial/ (88547)
8 randomization/ (15546)
9 single blind procedure/ or double blind procedure/ (43760)
10 crossover procedure/ (13066)
11 placebo/ (44852)
12 (randomized controlled trial$ or randomised controlled trial$).tw. (16330)
13 rct.tw. (1164)
14 (random$ adj2 allocat$).tw. (6057)
15 ((singl$ or doubl$ or tripl$ or trebl$) adj (blind$ or mask$ or dummy)).tw. (39146)
16 prospective study/ (44640)
17 case study/ (1918)
18 case report.tw. (51202)
19 abstract report/ or letter/ (190022)
20 or/17-19 (242064)

21 or/6-16 (356796)
22 21 not 20 (345513)
23 clinical study/ (6243)
24 case control study/ (10655)
25 family study/ (3824)
26 longitudinal study/ (10121)
27 retrospective study/ (55165)
28 prospective study/ (44640)
29 cohort analysis/ (28380)
30 (cohort adj (study or studies)).mp. (19096)
31 (case control adj (study or studies)).mp. (20255)
32 (observational adj (study or studies)).tw. (9519)
33 (epidemiologic$ adj (study or studies)).tw. (17250)
34 (follow up adj (study or studies)).tw. (10077)
35 (cross sectional adj (study or studies)).tw. (13025)
36 or/23-35 (201804)
37 22 or 36 (488513)
38 5 and 37 (6696)

Core strategy for Current Contents

1 breast cancer
2 risk
3 #1 AND #2
4 trial*
5 random*
6 control*
7 single blind* OR double blind*
8 case control* OR cohort
9 longitudinal OR retrospective
10 cross sectional OR observational
11 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

Strategies for individual risk factors (linked with the core strategies)

Strategies for Medline and Embase are given. Strategies for Current Contents made use of substantially the same vocabulary, allowing for the lack of indexing on this database

Alcohol (2004 onwards)

Medline: alcohol drinking/ or alcoholism/
Embase: alcohol consumption/ or alcohol/

Dietary fat (2004 onwards)

Medline: dietary fat/
Embase: fat intake/ or dietary fat.tw.

Breast density (1996 onwards)

Medline and Embase: (Breast adj3 dens$).mp

Parity (1996 onwards)

Medline: Parity/ or (Nullipar$ or multipar$ or childless$).mp
Embase: parity/ or nullipara/

Early menarche (1996 onwards)

Medline and Embase: menarche/ or menarche.tw.

Obesity (2003 onwards)

Medline: Obesity/ or obesity, morbid/
Embase: Morbid obesity/ or obesity/

Other exogenous hormones (1996 onwards)

Medline

1 xenoestrogen$.mp. (476)
2 xenooestrogen$.mp. (4)
3 xeno-estrogen$.mp. (38)
4 xeno-oestrogen$.mp. (17)
5 (xenobiotic adj3 hormone$).mp. (20)
6 Xenobiotics/ae, po, to [Adverse Effects, Poisoning, Toxicity] (1169)
7 (estrogen adj3 disrupt$).mp. (120)
8 (oestrogen adj3 disrupt$).mp. (8)
9 (endocrine adj3 disrupt$).mp. (2499)
10 or/1-9 (3995)
11 phytoestrogens/ (1366)
12 (phyto-estrogen$ or phytoestrogen$).tw. (1625)
13 (phyto-oestrogen$ or phytooestrogen$).tw. (123)
14 soybeans/ (4463)
15 (soy or soya or soybean$ or soyabean$ or soyfood$ or soyafood$).tw. (11323)
16 red clover.mp. or trifolium/ or trifolium.tw. (496)
17 genistein/ (3164)
18 (exogenous adj hormone$).mp. (295)
19 or11-18 (16025)
20 diethylstilbestrol/
21 (diethylstilbestrol or stilbestrol or stilboestrol)
22 20 or 21

Embase

1 xenoestrogen$.mp. (526)
2 xenooestrogen$.mp. (4)
3 xeno-estrogen$.mp. (49)
4 xeno-oestrogen$.mp. (21)
5 (xenobiotic adj3 hormone$).mp. (19)
6 Xenobiotics/ae, po, to [Adverse Effects, Poisoning, Toxicity] (977)
7 (estrogen adj3 disrupt$).mp. (119)
8 (oestrogen adj3 disrupt$).mp. (7)
9 (endocrine adj3 disrupt$).mp. (2727)
10 or/1-9 (4105)
11 Phytoestrogen/ (2481)
12 (phytoestrogen$ or phytooestrogen$).tw. (1723)
13 (phyto estrogen$ or phyto oestrogen$).tw. (145)
14 Soybean/ (4577)
15 (soy or soya or soybean$ or soyabean$ or soyfood$ or soyafood$).tw. (8855)
16 GENISTEIN/ (6078)
17 Red Clover/ (135)
18 clover/ (131)
19 trifolium.tw. (209)
20 (exogenous adj hormone$).mp. (278)
21 or/11-20(16363)
22 diethylstilbestrol/
23 (diethylstilbestrol or stilbestrol or stilboestrol)
24 22 or 23

Fibroadenoma (2003 onwards)

Medline

1 ductal hyperplasia.mp.
2 carcinoma in situ/
3 lobular hyperplasia.mp.
4 sclerosing adenosis.mp.
5 Carcinoma, Ductal/
6 Carcinoma, Lobular/

7 FIBROADENOMA/
8 Benign adj breast adj disease.tw.
9 or/1-8

Embase

1 Breast Fibroadenoma/ (654)
2 Breast Hyperplasia/ (784)
3 Carcinoma in Situ/ (4345)
4 Breast Carcinoma/ (15229)
5 breast sclerosing adenosis/ (8)
6 (lobular hyperplasia or sclerosing adenosis or ductal carcinoma or lobular carcinoma).tw.
7 Benign adj breast adj disease.tw.
8 or/1-7

Oral contraceptives (1996 onwards)

Medline: exp contraceptives, oral/
Embase: exp oral contraceptive agent/

Previous history of breast cancer (1996 onwards)

Medline

1 Neoplasms, Second Primary/
2 neoplasm recurrence, local/
3 Recurrence/
4 relaps$.tw.
5 or/1-4
6 (relative risk or risk ratio).mp.
7 Odds Ratio/
8 (rate ratio or rr).tw.
9 or/6-8
10 5 and 9
11 ((past history or previous history or prior history) adj5 breast cancer).tw.
12 second breast cancer.tw.
13 10 or 12

Embase

1 ((past history or previous history or prior history) adj5 breast cancer).mp.
2 second primary.mp.
3 second cancer/
4 second breast cancer.mp.
5 or/1-4
6 cancer recurrence/
7 recurrence risk/
8 relaps$.mp.
9 or/6-8
10 (risk ratio or relative risk or rate ratio or rr or odds ratio).mp.
11 9 and 10
12 9 or 11

Appendix 2: Sources of information

SOURCES SEARCHED

Bibliographic databases

Medline
Embase
Current Contents
Cochrane Central Register of Controlled Trials
PubMed (last 60 days)

Review databases

Cochrane Database of Systematic Reviews
Database of Abstracts of Reviews of Effects
Health Technology Assessment database

Appendix 3: Excluded references

RETRIEVED STUDIES EXCLUDED FOR REVIEW

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Backman, T., Rauramo, I., Jaakkola, K., Inki, P., Vaahtera, K., Launonen, A., & Koskenvuo, M. (2005). Use of the levonorgestrel-releasing intrauterine system and breast cancer. *Obstetrics & Gynecology*, 106, 813-817.

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Becher, H., Schmidt, S., & Chang-Claude, J. (2003). Reproductive factors and familial predisposition for breast cancer by age 50 years. A case-control-family study for assessing main effects and possible gene-environment interaction. *International Journal of Epidemiology*, 32, 38-48.

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Castiglione-Gertsch, M. (2004). Hormone replacement and breast cancer. *Annals of Oncology*, 15 Suppl 4, iv275-277.

Cellini, C., Huston, T. L., Martins, D., Christos, P., Carson, J., Kemper, S., & Simmons, R. M. (2005). Multiple re-excisions versus mastectomy in patients with persistent residual disease following breast conservation surgery. *American Journal of Surgery*, 189, 662-666.

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Chang-Claude, J., Dunning, A., Schnitzbauer, U., Galmbacher, P., Tee, L., Wjst, M., Chalmers, J., et al. (2003). The patched polymorphism Pro1315Leu (C3944T) may modulate the association between use of oral contraceptives and breast cancer risk. *International Journal of Cancer*, 103, 779-783.

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Appendix 4: Evidence tables for past history of breast cancer

Table 4.1: Evidence tables for primary studies of past history of breast cancer

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Soerjomataram et al. 2005a) Netherlands	Retrospective cohort study Level III-2.	Study setting. Population based Cancer Registry in Eindhoven, covering 2.4 million individuals in 2004. To determine the incidence of second primary breast and urogenital cancers among breast cancer patients and to compare this with incidence expected in the general population. Sample 9,919 first primary breast cancer cases, patients diagnosed between 1972-2000, over 25 years of age. Exclusions: patients with less than one year follow-up, *in situ* primary breast cancer, other malignancies diagnosed before breast cancer. 29% of subjects < 50 years of age.	Data collection Records retrospectively reviewed from population based Cancer Registry. Outcome measures Analysis stratified according to age at diagnosis, initial treatment combination for breast cancer, further treatments, and follow-up period. Follow-up interval. Average follow-up 6.6 years, median 4.9 years. A person years analysis corrected for age, and calendar-year period to the date of death, date of last follow-up, date of diagnosis of second cancer, or end of study 31st December 2001, whichever came first. Compared incidence of second primary breast cancer among patients with a diagnosis of breast cancer (observed) with incidence for the same tumours in the general population (expected) expressed as SIR. The absolute excess risk (AER) calculated by subtracting the expected number from the observed number and then dividing the difference by person-years at risk (per 10,000 breast cancer patients/year).	<u>Overall 588 breast cancer patients developed a second breast cancer.</u> SIR = 3.5 (3.2-3.8)* Premenopausal primary n=255 SIR = 6.3* Post-menopausal primary n=333 SIR = 2.6* <u>Breast cancer treatment and development of second breast cancer</u> Surgical (n=152) SIR = 3.4* Radiotherapy (n=327) SIR = 3.9* Chemotherapy (n=8) SIR = 2.3 Hormonal therapy (n=18) SIR = 2.3* Radio+ chemo (n=44) SIR = 5.0* Radio+ hormonal (n=27) SIR = 1.6* Others (n=12) SIR = 6.3* * Significant, 95% CI excludes 1.	Limitations ▪ Exposure data on other important risk factors associated with increased risk of a second breast cancer not available e.g. reproductive or lifestyle factors. ▪ Potential confounders were not adjusted for in this observational study. ▪ Changes in cancer treatments over time given the long follow-up period. ▪ Validity and reliability of patient data abstraction methods unknown. ▪ Misclassification bias due to metastases of primary breast cancer being classified as a second primary. ▪ Study investigators not blinded to patient status, clinical characteristics etc. Comments ▪ Retrospective evaluation of 28 years of Cancer Registry records. Information about the data collection and assessment methodology not specified in this paper. Reported conclusions (by authors). Breast cancer patients are at an increased risk of developing a second breast cancer (and ovarian cancer). Treatments play a limited role in causing a second breast cancer, suggesting a larger role for common risk factors that precipitate first and second breast cancers.

Table 4.1: Evidence tables for primary studies of past history of breast cancer (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Li et al. 2003a) USA	Retrospective cohort study Level III-2.	Study setting Women resident in the Seattle-Puget Sound, Western Washington State area diagnosed with breast cancer from 1983 to 1992. Study aim to evaluate risk factors for second primary contralateral breast cancer (CBC) among women diagnosed with a first breast cancer at an age younger than 45 years. Sample 1,488 women previously interviewed in two population based case-control studies. Subjects with *in situ* disease alone were excluded leaving 1,285 subjects with invasive primary breast cancer in the cohort. Data from 907 participants (70.6%) available for immunoperoxide assays. Mean age at first diagnosis 37.7 years, mean follow-up time was 9.0 years. Average age at first live birth 24.3 years and BMI was 23.9 kg/m^2	Data collection The Cancer Surveillance System (CSS), part of the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute was used by both studies to ascertain all incident first and *in situ* breast cases diagnosed between 1983-1990 in non-Hispanic white women 45 years or younger (83% of eligible cases) in one study and in all incident first and *in situ* breast cases diagnosed between 1983-1992 in all women 45 years or younger in the other study (84% of eligible cases). Data on cohort obtained from cancer registry with information on tumour stage, histology, and size. Tumour specimens were requested from hospital and commercial hospital and commercial pathology laboratories. Data from 907 participants (70.6%) available for immunoperoxide assays. Outcome measures CBC considered to have developed if diagnosed greater than 6 months after first breast cancer diagnosed, was diagnosed in the opposite breast, and was invasive. Follow-up interval. 6 months after diagnosis of first breast cancer to diagnosis of CBC, date of last follow-up, death, or the end of the study period (December 2001) which ever occurred first. Analysis Cox proportional hazards models used.	<u>Number of CBC cases</u> n=77 <u>Risk of CBC by patient characteristics at the time of first cancer diagnosis.</u> 95% confidence intervals overlapped 1 for all categories of age at menarche, gravidity, age at first live birth, number of live births, OC use average number of drinks per week, family history of breast cancer and for AJCC stages, histology categories and tumour size. Also 95% confidence intervals overlapped 1 for all categories of tumour marker expressed by first breast cancer except c-erbB-2. <u>Age at diagnosis</u>, BMI and weight categories were significant (did not overlap 1 for 95% CIs) <u>Weight (lb) HR (95% CI)</u> <u>Quartiles</u> < 123 1 reference 124-135 1.5 (0.7-3.0) 136-155 2.8 (1.4-5.3) ≥ 156 2.2 (1.1-4.4) <u>BMI</u> <u>Bray's criteria</u> < 19.9 1 reference 20.0-24.9 1.6 (0.8-3.1) 25.0-29.9 1.5 (0.6-3.6) ≥30.0 2.6 (1.1-5.9) <u>BMI Quartiles</u> < 20.6 1 reference 20..7-22.4 1.2 (0.6-2.4) 25.0-29.9 2.1 (1.1-3.9) ≥30.0 1.6 (0.9-3.2)	Limitations ▪ Self-reported patient characteristics data, including weight and BMI. ▪ Residual confounding likely in this observational study both with known confounders not adjusted for and unknown confounders. ▪ Validity and reliability of patient data abstraction methods unknown. ▪ Study may lack sufficient power to determine valid associations given small number of CBC cases. Comments ▪ Pathologist reviewer for tissue collection, review, and testing for markers blinded to CBC status and clinical and personal characteristics of women. Reported conclusions (by authors). High BMI at time of first breast cancer diagnosis and c-erbB-2 expression by this tumour, both appear to be important risk factors for CBC.

Table 4.1: Evidence tables for primary studies of past history of breast cancer (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Kollias et al. 1999) UK	Retrospective cohort study Level III-2.	Study setting. Nottingham city hospital, breast cancer clinic. Aim of study to determine the incidence of metachronous contralateral breast cancer (CBC) in breast cancer patients treated at one hospital in a 20-year period. To identify factors associated with increased risk of developing a subsequent CBC following treatment for primary breast cancer. Sample 3,240 women ≤ 70 years who had treatment for primary operative invasive breast cancer with histological tumour diameter of ≤ 5.5 cm or ductal carcinoma *in situ* (DCIS) between 1975-1995. Median age at diagnosis 54 years (24-70), a total of 3,211 women followed up.	Data collection Locoregional recurrence was certified by histological or cytological examination. Death due to breast cancer certified by autopsy, death certificate, or by death of patient admitted for asymptomatic metastatic disease. Patients without CBC were censored at time of last follow-up or death. Outcome measures Metachronous contralateral breast cancer (CBC) defined as histologically confirmed CBC not detected and treated at the time of initial breast cancer primary, demonstration of in situ change and different histological features to first primary. Follow-up interval. At regular intervals. Median follow-up 108 months, range (1-252 months). Indefinite follow-up for those with locoregional recurrence. Univariate and multivariate analysis with Cox regression models. Multivariate models adjusted for age of onset <50, 50-70 years, family history, and lobular histology in one model and in another previous radiotherapy, tumour grade, were in addition also entered into a second model. RR for CBC determined by comparing median breast cancer incidence with age-standardised incidence for breast cancer amongst general population in the UK.	There were 2,874 women included in the analysis, and 83 CBC cases identified. The cumulative CBC rate was 5.6% over 10 years, 9.9% over 15 years. The RR for CBC after previous treatment was 2.8 (RR=5.6 to the remaining breast). <u>Multivariate analysis</u> RR 95% CI Age <50, 50-70 1.6 (0.98-2.4) Strong family hist 2.5 (1.45-4.26)** Lobular tumour 1.9 (1.1-3.13)* * p<0.05; **p=0.001.	Limitations ▪ Patient characteristics of cohort not adequately described. ▪ Exposure data on other important risk factors associated with increased risk of a second breast cancer not available e.g. some reproductive and lifestyle factors. Residual confounding likely with known confounders not adjusted for and unknown confounders. ▪ Study investigators not blinded to patient status, clinical characteristics etc. ▪ Validity and reliability of patient data abstraction methods unknown. ▪ Study may lack sufficient power to determine valid associations given small number of CBC cases. Comments Retrospective evaluation of 20 years of Cancer Registry records. Reported conclusions (by authors). This study confirms the high incidence of metachronous contralateral breast cancer (CBC) post treatment for primary breast cancer. The annual hazard rates appear to be constant up to 15 years. Three important predictors of CBC recurrence were apparent. Family history, early age of onset, and lobular histology of the primary tumour. These are suggestive of a possible link to genetic predisposition.

Table 4.1: Evidence tables for primary studies of past history of breast cancer (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Gajalakshmi et al. 1998) India	Retrospective cohort study Level III-2.	Study setting. The Cancer Institute in Chennai, India. Aim of study was to determine whether or not patients with a first primary breast cancer are at increased risk of developing CBC, to determine risk factors associated with CBC, and to evaluate the carcinogenic effects of treatment for first primary breast cancer. Sample Subjects with a first primary breast cancer diagnosis between 1960-89, n=3,492. Patients who did not develop a second primary cancer during follow-up and those who had CBC >12 months after primary diagnosis were analysed. Exclusions: patients developing second cancer sites other than breast cancer, CBC occurrence within 12-months of primary breast cancer diagnosis, patients who had not completed at least one treatment modality for primary breast cancer, those not surviving >12 months since diagnosis of first primary breast cancer.	Data collection Exposure information from the first primary breast cancer was collected at time of admission for treatment, oncologists recorded treatment, complications and side effects data. Patients were staged retrospectively according to the Tumour Node Metastasis (TNM) classification. The ICD-O was used to code histology and site of first and second primary cancers. Patient data were abstracted from case records in a standard form. Study rules to differentiate a first and second primary from a metastasis to the contralateral breast were documented in the report. Follow-up interval. Period at risk was defined as 1 year after diagnosis of first primary breast cancer to date of diagnosis of CBC for those who developed CBC, to date of death or last known date to be alive or 31 December 1994 whichever was first for those who did not develop CBC. Analysis Comparisons made for age-group specific incidence rates adjusted for world population were compared for both unilateral (UBC) breast cancer cases in the general Chennai population and CBC in the study cohort. Rate ratio per single breast calculated as double the ratio of incidence rate of CBC in the study cohort to the incidence rate of UBC in Chennai.	Mean follow-up time was 7.4 years and 39 patients developed CBC >12 months after initial primary breast cancer and 2,665 patients did not develop CBC <u>Age-specific incidence rates adjusted for world population-rates ratio of first primary and second primary breast cancers by age at time of diagnosis</u> <u>Age Rate ratio 95% CI</u> <45 20.2 11.8-34.4 45-54 9.8 7.4-13.0 ≥55 9.0 7.0-11.6 All ages 7.4 4.8-11.4 Univariate and adjusted rate ratios for contralateral breast cancer CBC by family history, showed elevated risk if mother had breast cancer.	Limitations ▪ About 5% of first primary and CBC cases were not confirmed by histology. ▪ Cancer Registry cancer incidence data not available prior to 1982. Also average annual age-specific rates adjusted for world population for the years 1982-1993 were used for UBC in general population. ▪ Patient characteristics of cohort not adequately described for source populations for UBC and CBC patients, or full participants and those lost to follow-up. ▪ Loss to follow-up was 10% among initial breast cancer patients and among patients with CBC 7.5%. ▪ Study may lack sufficient power to determine valid associations given small number of CBC cases. Comments Validation of data extraction was determined by randomly re-abstracting 10% of case records by first author as were treatment details of all patients. Retrospective evaluation of 30 years of Cancer Registry records. Reported conclusions (by authors). There was a seven-fold increase in risk (per single breast) compared with other women in Chennai India. A positive family history of breast cancer and a late age at first childbirth were greater risk factors for a second primary breast cancer compared to a first primary breast cancer. Hormone therapy for first primary breast cancer offered a protective effect and reduced risk of CBC significantly. Other risk factors associated with first primary breast cancer (age at menarche, number of children, age at menopause, menopausal status, radiotherapy treatment) were shown not to be significantly different in their association with CBC.

Table 4.1: Evidence tables for primary studies of past history of breast cancer (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Volk and Pompe-Kirn 1997) Slovenia	Retrospective cohort study Level III-2.	Study setting. Cancer Registry of Slovenia. Study aim to determine whether or not the incidence of second primary cancers in patients with first primary cancer differs from the incidence expected in the general population. Sample All beast cancer patients diagnosed between 1961 and 1985 with invasive breast cancer as the first primary. During study period 8,917 patients with breast cancer as a first primary were identified. Exclusions: breast cancer diagnosed at death, or at same time as another primary. A total of 8,791 patients included in the analysis. Mean age 57 years.	Data collection Cancer registry data, reporting of cases is compulsory. Primary sites coded with ICD-8, morphology, stage and diagnosis verification, and treatment codes used since 1961. Second primary cancers defined as invasive cancers with codes (ICD-8 140-209) diagnosed after the first primary breast cancer. Second cancers at autopsy were included. Outcome measures Standardised Incidence Ratios (SIR) as observed number of second cancers by the expected ones. All cancer sites analysed by age at diagnosis of first breast cancer, and sub-period of follow-up. Follow-up interval. Until 31 December 1994. Mean time for follow-up 7.3 years. Analysis Observed and expected numbers of second primary cancers were compared using person-years calculated as the interval between breast cancer diagnosis and the date of the diagnosis of the second primary cancer, the date of death or 31 December 1994, whichever came first.	A total of 547 second primary cancers were observed and 410 were expected. <u>Breast cancer</u> Obs n= 108 Exp n= 77.4 95% CI SIR 1.4 (1.1-1.7) <u>Age <50 years</u> Obs n= 30 Exp n= 9.9 95% CI SIR 3.0 (2.0-4.3) <u>Age 50+ years</u> Obs n= 78 Exp n= 67.5 95% CI SIR 1.2 (0.9-1.4)	Limitations ▪ Patient characteristics of cohort not adequately described for source population or full participants and those lost to follow-up. ▪ Exposure data on other important risk factors associated with increased risk of a second breast cancer not available e.g. some reproductive and lifestyle factors. ▪ Validity and reliability of patient data abstraction methods unknown. ▪ Second primary cancers covered a broad range (invasive cancers with codes (ICD-8 140-209)). ▪ Potential misclassification due to coding practices in use until the beginning of 1991 for multiple primaries of the breast that may have coded these as metastases of the first primary cancer. According to IACR rules no second primary cancer of the breast of the same histology as the first one has been counted as a new primary. Comments For data quality the registry had 8% of cases verified as death certificate only (DCO) and 73% confirmed microscopically in the period 1961-1965 and 3.5% DCO and 92% confirmed microscopically in the period 1991-1994. Retrospective evaluation of 24 years of Cancer Registry records. Reported conclusions (by authors). Breast cancer patients were at increased risk of developing second primary cancers, and excess risk of any site was greatest after 10 years since diagnosis of first primary and was higher in younger groups. Breast cancer was the most common secondary cancer.

Appendix 5: Evidence tables for lesions associated with increased risk of breast cancer

Table 5.1: Evidence tables for secondary studies of lesions associated with increased risk of breast cancer

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(El-Wakeel and Umpleby 2003)	Level III-2.	Medline, Cinahl and Embase for papers published between 1960 and 2001. Manual search of "The Breast" journal between February 1997 and February 2001. On line search of Cochrane Collaboration library for systematic reviews. Key words used were breast cancer, FA, breast, risk factor, aetiology, epidemiology, and research methods.	Inclusion criteria Cohort or case-control design. Fibroadenoma as a primary exposure and breast cancer as a primary outcome. English Language Data extraction Criteria developed to compare the strength of evidence across studies. For cohort studies these criteria were: ▪ observed over a meaningful period of time in the natural history of disease (10 years considered appropriate) ▪ all members of the cohort observed over the full period of follow up ▪ Prospective and incidence studies ▪ Measures of population attributable risks ▪ For case-control studies, criteria were: ▪ studied population based cases ▪ Incident and not prevalent cases were used ▪ Both cases and controls were selected from the same defined population using the same inclusion/exclusion criteria. Data analysis Study specific results presented. Meta-analysis was not conducted	<u>Results for two key studies:</u> Dupont (cohort study) and McDivitt (case-control) <u>Dupont. Relative risk of breast cancer (registry as a control group)</u> Non-complex FA: RR 2.07 (95% CI 1.4-3.2) Complex FA: 2.24 (95% CI 1.6-3.2) FA with typical hyperplasia: RR 2.16 (95% CI 1.2-3.8) FA with atypical hyperplasia: RR 4.77 (95% CI 1.5-15). Results also available for sisters-in-law control group. McDivitt FA with typical hyperplasia: OR 3.7 (95% CI 1.5-9.2) FA with atypical hyperplasia: OR 6.9 (95% CI 1.5-30.6) FA with no hyperplasia: OR 1.7 (95% CI 1.1-2.5) Benign breast disease without hyperplasia: OR 1.5 (95% CI 1.2-1.9) Benign breast disease with typical hyperplasia: OR 1.6 (95% CI 1.2-2.2) Benign breast disease with atypical hyperplasia: OR 2.2 (95% CI 1.4-3.7)	Limitations ▪ Some uncertainty about the review methodology – for example, unclear if data were double extracted and if studies were double selected ▪ Potential publication bias from limitation to English ▪ no details about number of titles identified from search and number assessed in full text ▪ Limited sources of studies evaluated ▪ Pre-set quality criteria did not appear to be the key determinant for study emphasis (e.g. one cohort study that fulfilled all the quality criteria was considered to be a weak design). ▪ Inconsistencies in results presented in tables and text for one of the two key studies ▪ However, there was consistency in results between studies. ▪ Limitations were noted in the key studies. For example, there were no definitions of breast cancer and whether carcinoma *in situ* was included. Comments ▪ Study designs considered were appropriate for the question Reported conclusions (by authors). The relative risk of developing breast cancer in patients who had surgically excised FAs increases in the presence of atypical hyperplasia or a family history of breast cancer (in a first degree relative). None of the studies have produced results that can be used reliably to quantify the risks of a history of both excised, non-excised and asymptomatic FA

Table 5.1: Evidence tables for secondary studies of lesions associated with increased risk of breast cancer (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Arpino et al. 2005)		Sources: MEDLINE (1966-2005), CancerLit (1966-2005) and EMBASE (1990-2005). Computertised search of the proceedings of the annual meetings of the American Society of Clinical Oncology held between 1998 and 2004. Hand searched references of all review articles and cross-referenced studies from retrieved articles. Textwords: premalignant lesions of the breast, atypical ductal hyperplasia, ductal carcinoma *in situ,* atypical lobular hyperplasia, lobular carcinoma *in situ*, lobular neoplasia, unfolded lobules, usual ductal hyperplasia	Studies limited to English language articles published between 1966 and February 2005. Selection criteria not further described. Data extraction Not described Quality evaluation Molecular studies: relevance and reproducibility of the methods and findings and the number of samples analysed were the most important variables used to assess quality Large scale RCTs with clinically relevant endpoints were used whenever possible (especially for treatment and management issues).	Of the many types of premailgnant lesions, few are thought to have premalignant potential. Premalignant lesions Best characterised pre-malignant lesions include atypical duictal hyperplasia, atypical lobular carcinomaand lobular carcinoma *ion situ.* Ductal carcinoma *in situ* is also thought to be premalignant. Unfolded lobules and usual ductal hyperplasia are thought to very early premaligant epithelial abnormalities. Premalignant lesions are defined by their histologic lesions and not all progress to invasive cancer.	Limitations • Selection criteria were not well documented • Restriction to English language articles • Few estimates of level of risk provided Comments • Good description of literature sources and documentation of text words used Reported conclusions (by authors). Recent studies indicate that cancer evolves by highly diverse genetic mechanisms, and research into these altered pathways may identify specific early defects that might be targeted to prevent progression of premalignant lesions to invasive cancer. Current clinical management is heterogeneous and depends on histologic examination and individual patient factors. Options for breast cancer risk reduction and prevention are available.

Appendix 6: Evidence tables for increased breast density

Table 6.1: Evidence tables for primary studies of increased breast density

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Kerlikowske et al. 2005) USA	Cross sectional study and nested, matched case control study Level III-2.	Study setting. Women participating in the San Francisco Mammography Registry (SFMR) – which is a population based registry. Sample Average age (years): 60.1 BMI (kg/m^2): 24.1 Family history of breast cancer in a first degree relative (%): 16 Age at first live birth (%): Nulliparous: 36 Age under 30 years at first birth: 47 Age 30+ at first birth: 17 Postmenopausal HRT (%): 57 Postmenopausal (%): 89 Race (%): White 65 Asian/Pacific 23 Other 12	Inclusion criteria. Women aged 28+ years who underwent bilateral mammography in San Francisco for screening and a bone mineral density (BMD) measurement within 2 years of each other. Exclusion criteria. Diagnosis of breast cancer before their first screening exam. Breast augmentation, reduction or reconstruction. History of mastectomy. Bilateral breast cancer. Cases (n=208). Invasive breast cancer or ductal carcinoma *in situ* if screening mammogram and BMD measurement occurred before diagnosis. Subjects identified by linkage of the SFMR with the Northern California SEER program and the California Cancer Registry. Controls (n=436). At least two women without breast cancer selected from the same mammography and BMD facilities as the case subject.	<u>Adjusted odds ratio (95% CI) by percent area of dense tissue as predictor of breast cancer (<23.9% as reference):</u> 23.9-34.2%: OR 1.2 (0.6-2.3) 34.3-42.6%: OR 1.2 (0.6-2.4) 42.7-54.0%: OR 1.9 (1.0-3.7) 54.1-66,7%: OR 2.8 (1.5-5.4) 66.8+%: OR 2.7 (1.4-5.4) Estimates adjusted for age, family history of breast cancer, age at first birth, hip BMD, race and BMI. Results for BMD available in the original paper but no significant independent association found between BMD and breast cancer risk.	Limitations ▪ Included *in situ* disease amongst the cases (26% of cases). However, results were similar when excluding *in situ* cases (data not shown in the original paper). ▪ Data not presented for the adjusted effect of breast density based on BI-RADS classification and risk of breast cancer. ▪ Reporting of cancer diagnoses to the SEER programme has been reported to be 94.3% complete. ▪ It appears as though the mammogram side was not randomly selected amongst the control subjects (although the authors note that breast density measurements are highly correlated between sides). ▪ No documentation of blinding of mammography reader to case/control status ▪ Reference category includes relative high breast density potentially underestimating the degree of association between higher breast density categories and risk of breast cancer ▪ Observational study susceptible to residual confounding ▪ Potential for misclassification of breast density Comments ▪ Aimed to determine whether mammographic breast density and bone mineral density of the hip and spine are correlated and independently associated with breast cancer risk. ▪ Craniocaudal view selected as it excludes the pectoralis muscle which has been shown to create artefacts when measuring breast density.

Table 6.1: Evidence tables for primary studies of increased breast density (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Kerlikowske et al. 2005) *Continued*			Data collection Craniocaudal screening examination of the breast that did not have breast cancer was selected in the case subjects. Either side was selected in control subjects. Percentage breast density was estimated after digitisation of mammograms. Breast density was quantified using a computer based threshold method. The BI-RADS system was also used for classification purposes. Participating women also completed a survey at the time of screening. Analysis Multivariable logistic regression used after adjusting for *a priori* co-variates that could act as potential confounders.		Reported conclusions (by authors). Breast density is strongly associated with increased risk of breast cancer, even after taking into account reproductive and hormonal risk factors, whereas BMD, although a possible marker of lifetime exposure to oestrogen is not. Thus a component of breast density that is independent of oestrogen-mediated effects may contribute to breast cancer risk.

Table 6.1: Evidence tables for primary studies of increased breast density (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Maskarinec et al. 2005) USA	Nested, frequency matched, case control study Level III-2.	Study setting. Participants selected from the Hawaii component of the Multiethnic Cohort (MEC) Study. This study used a population based sampling frame and was primarily investigating the role of diet in cancer among 96,810 men and 118,441 women. Sample (all ethnic groups combined) Age at recruitment (years): cases 59.9, controls 57.7, *P*<0.001 BMI (kg/m^2): cases 24.7, controls 25.1, *P*=0.13 Number of mammograms: cases 3.2, controls 2.4, *P*<0.001 Family history of breast cancer in first degree relative (%): cases 17.0, controls 12.1 *P*=0.02 Age at menarche (years): cases 13.0, controls 13.1, *P*=0.32 Parous (%): cases 83.8, controls 89.0, *P*=0.007 Age at first birth (years): cases 24.9, controls 24.8, *P*=0.51 Number of children: cases 2.3, controls 2.6, *P*<0.001 Postmenopausal (%): cases 67.4, controls 70.9, *P*=0.08 Any HRT use (%): cases 71.2, controls 69.2, *P*=0.50	Cases (n=607). All female members of the MEC study diagnosed with a primary breast cancer between study entry (established between 1993-6) were identified as potential cases. Participants were required to be alive at the time of recruitment, sign consent forms and mammogram release forms. Subjects were recruited by mail. Controls (n=667). Participants who were not known to have breast cancer who were on the Hawaii MEC study were potential controls. Controls were randomly selected by ethnic group and age band (± 5 years). Participants were required to be alive at the time of recruitment, sign consent forms and mammogram release forms. Subjects were recruited by mail. Exclusion criteria for cases and controls. Diagnosis or breast cancer, before entry to the cohort study, no mammogram, history of breast augmentation or reduction.	<u>Adjusted odds ratio (95% CI) by percent area of dense tissue as predictor of breast cancer (<10% as reference):</u> 1. Earliest mammogram 10-24.9: OR 1.53 (1.03-2.27) 25-49.9: OR 2.17 (1.46-3.23) 50+: OR 3.14 (2.02-4.88) Per 10%: OR 1.22 (1.14-1.30) 1. Latest mammogram 10-24.9: OR 1.48 (1.02-2.14) 25-49.9: OR 1.74 (1.20-2.53) 50+: OR 2.73 (1.80-4.16) Per 10%: OR 1.16 (1.09-1.23) 2. Mean of all mammograms 10-24.9: OR 1.61 (1.09-2.39) 25-49.9: OR 2.16 (1.45-3.20) 50+: OR 3.59 (2.29-5.62) Per 10%: OR 1.22 (1.14-1.31) <u>Adjusted odds ratio (95% CI) by area cm^2) of dense tissue as predictor of breast cancer (<15 cm^2 as reference):</u> 1. Earliest mammogram 15-29.9: OR 1.34 (0.95-1.88) 30-44.9: OR 2.09 (1.45-3.01) 45+: OR 2.40 (1.66-3.46) Per 10 cm^2: OR 1.17 (1.11-1.24) 2. Latest mammogram 15-29.9: OR 1.30 (0.93-1.81) 30-44.9: OR 1.77 (1.23-2.55) 45+: OR 2.57 (1.80-3.67) Per 10 cm^2: OR 1.16 (1.10-1.23) 1. Mean of all mammograms 15-29.9: OR 1.40 (1.00-1.96) 30-44.9: OR 1.84 (1.27-2.65) 45+: OR 2.91 (2.02-4.21) Per 10 cm^2: OR 1.19 (1.12-1.26)	Limitations ▪ Potential cases 1,587 before applying exclusion criteria. 607 participated. ▪ Overall participation rate was 50.6%. ▪ Values for missing variables were inputted to maximise the number of observations – may have lead to misclassification. ▪ For five cases (0.8%) only the contralateral mammogram at time of diagnosis was available ▪ Observational study susceptible to residual confounding ▪ Potential for misclassification of breast density ▪ Estimated risk varied by ethnicity indicating a potential limitation on generalisability to the New Zealand population. Comments ▪ Well conducted study though limited by the low participation rate. ▪ Primarily investigating the association between breast density and breast cancer in three ethnic groups: Caucasian, Japanese and native Hawaiian women ▪ Mammogram reader blinded to case status ▪ Mean time of 6.3 years between earliest mammogram and diagnosis of breast cancer. ▪ Estimates were similar between the different timings of mammography (although the mean estimates tended to produce the highest of the three odds ratios).

Table 6.1: Evidence tables for primary studies of increased breast density (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Maskarinec et al. 2005) *continued*			Data collection All subjects completed a questionnaire at cohort study entry. Additionally, a 1 page questionnaire was completed by participants in this case control study. Where possible, mammograms were selected that were performed pre-diagnosis. As many mammograms were selected per subject as possible (over a wide timeframe). Computer assisted technology was used to determine breast border and border of dense tissue. Average readings were taken when bilateral mammograms were available and subjects with mammograms on at least 2 dates had 3 variables: earliest, latest and mean mammographic reading. Outcome measures Data on deaths and incident cancer were obtained by annual linkage to the Hawaii Department of Health vital records and the Hawaii Tumour Registry. Analysis Unconditional logistic regression models were fitted.	4. Mean of all mammograms 15-29.9: OR 1.40 (1.00-1.96) 30-44.9: OR 1.84 (1.27-2.65) 45+: OR 2.91 (2.02-4.21) Per 10 cm^2: OR 1.19 (1.12-1.26) All results adjusted for ethnicity, age at mammogram, BMI, age at first live birth, number of children, age at menarche, age at menopause, use of HRT and family history of breast cancer. Results for ethnic specific effects available in the original paper. Estimated risk varied by ethnicity with the strongest level of risk generally being in the group.	Reported conclusions (by authors). Study confirmed the substantial breast cancer risk associated with higher mammographic densities. The magnitudes of risk estimates were similar for percent density and size of the dense area. Although the finding was not statistically significant, the association between breast density and cancer risk appeared weaker in Japanese women than in Caucasian and Native Hawaiian women. This finding suggests that, if breast density were to be added to risk prediction models, it might be necessary to develop different models for ethnic groups whose mammographic features differ substantially from those of Caucasians.

Table 6.1: Evidence tables for primary studies of increased breast density (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Nagata et al. 2005) Japan	Case control study Level III-2.	Study setting. Cases selected for a general hospital in Gifu, Japan. Controls selected from women residing near the same hospital and participating in a breast screening program. Sample 1. Premenopausal women Age (years): cases 43.1, controls 42.7 BMI (kg/m^2): cases 22.0, controls 21.8 Education (years): cases 13.2, controls 12.7 Age at menarche (years): cases 12.7, controls 12.8 Age at first birth (years): cases 26.5, controls 25.3 Parity: cases 1.6, controls 2.2 Ever smoked (%): cases 19.7, controls 14.5 Ever used HRT (%): cases 13.3, controls 11.3 Family history among first degree relatives (%): cases 9.9, controls 4.3 2. Postmenopausal women Age (years): cases 62.2, controls 58.1 BMI (kg/m^2): cases 23.9, controls 23.2 Education (years): cases 11.0, controls 11.4 Age at menarche (years): cases 14.5, controls 14.1 Age at first birth (years): cases 24.8, controls 25.0 Age at menopause (years): cases 48.6, controls 49.2 Parity: cases 2.0, controls 2.3 Ever smoked (%): cases 9.6, controls 7.3 Ever used HRT (%): cases 12.2, controls 10.3 Family history among first degree relatives (%): cases 8.0, controls 3.8	Cases (n=146). Histologically confirmed cases of breast cancer diagnosed between May 2000 and March 2002. Controls (n=659). Selected from screening group between January 2001 and December 2002 and found to be free of breast cancer. Data collection Self-administered questionnaire administered. Exposure histories were recorded up to the date of diagnosis for cases and up to the date of screening for controls. Mammograms of the medio-lateral oblique view were taken. For controls, the mammogram side used was randomly selected and for the cases the side free of cancer was used. Outcome measures Mammographic density assessed by percentage of dense tissue and area of dense tissue. Total breast area was also estimated. Analysis Percent density initially categorised into quintiles though this was reduced to quartiles among postmenopausal women. All analyses stratified by menopausal status. Unconditional logistic regression models were used and included *a priori* co-variates that were potential confounders.	<u>Adjusted odds ratio (95% CI) by percent area of dense tissue as predictor of breast cancer (0% as reference):</u> 2. Premenopausal women 1-24: OR 2.27 (0.64-8.08) 25-49: OR 4.01 (1.16-13.9) 50-75: OR 4.37 (1.24-15.4) 75-100: OR 1.36 (0.31-6.06) *Ptrend* 0.22 3. Postmenopausal women 1-24: OR 1.17 (0.55-2.49) 25-49: OR 3.00 (1.20-7.48) 50-100: OR 4.19 (1.33-13.2) *Ptrend* 0.005 <u>Adjusted odds ratio (95% CI) by area of dense tissue as predictor of breast cancer (0cm^2 as reference):</u> 1. Premenopausal women 0.1-12.0: OR 1.58 (0.41-6.23) 12.1-26.3: OR 4.03 (1.14-14.2) 26.4-44.4: OR 5.14 (1.45-18.3) 44.5+: OR 2.78 (0.77-10.1) *Ptrend* 0.09 2. Postmenopausal women 0.1-9.5: OR 0.83 (0.33-2.12) 9.6-21.3: OR 1.07 (0.41-2.80) 21.4+: OR 4.02 (1.80-8.94) *Ptrend* 0.0002 All estimates for all analyses adjusted for age, BMI, age at menarche, age at first birth, number of full births, use of HRT, history of breast feeding and family history of breast cancer among first degree relatives.	Limitations ▪ Participation rate amongst cases 58%. Participation rate in the screening program (from which the controls were selected) was estimated to be 70%. ▪ Median time between diagnosis of being a case and completing self administered questionnaire was 19 days but 6 didn't complete for 3-12 months. ▪ Controls may not be representative of women who have no breast cancer ▪ Mammograms used were taken at the same time as diagnosis of the case – may be issues with the masking hypothesis which would tend to result in underestimation of the association between breast density and risk of breast cancer. ▪ Observational study susceptible to residual confounding ▪ Potential for misclassification of breast density Comments ▪ Study primarily interested in the association between breast density and breast cancer in Japanese women. Reported conclusions (by authors). Data suggested that mammographic density was associated with the risk of breast cancer in Japanese women as is the case in Caucasian women. However, the associations of the risk of breast cancer with breast size and a high breast density > 75% needs to be confirmed in future studies.

Table 6.1: Evidence tables for primary studies of increased breast density (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Torres-Mejia et al. 2005) UK	Cohort study Level III-2.	Study setting. Part of Guernsey III (GIII) and IV (GIV) cohorts (initiated to investigate the role of endogenous hormones in the aetiology of female breast cancer. Sample (n=3,211) Median age at entry (years): cases 53.2, noncases 51.8 Median age at menarche (years): cases 13, noncases 13 Nulliparity: cases 18.9%, noncases 12.4% Median age at first birth (years): cases 24, noncases 24 Premenopausal at study entry: cases 36.9%, noncases 36.8% Ever used OC: cases 50.9%, noncases 50.8% Ever used HRT: cases 21.6%, noncases 26.7% BMI: cases 23.9, noncases 24.3	Inclusion criteria GIII: all women aged 35+ residents in Guernsey between 1977 and 1985. GIV: volunteers for GIII who participated a few years later (1986-1989). Data collection Detailed, interviewer administered questionnaires completed at entry to GIII and GIV. Only GIV mammograms were considered in this study. Outcome measures Follow up ongoing with information obtained 6-monthly through pathology reports from the sole laboratory in Guernsey, death certificates, and data from the Wessex Cancer Registry. Follow-up interval. Median 15 years (range 0.5-17 years) Analysis Cox proportional hazard models fitted on the age timescale. Follow up time calculated from entry to GIV to the earliest of date of diagnosis of *in situ* or invasive breast cancer, date of death, date of emigration, or 31 October 2003.	<u>Hazard ratio (95% CI) per 1 SD increase in area of dense tissue as predictor of breast cancer:</u> 1.59 (1.29-1.94) <u>Hazard ratio (95% CI) by quartile increase in area of dense tissue (cm^2) as predictor of breast cancer (smallest area as reference):</u> Quartile 2: 2.23 (1.17-4.26) Quartile 3: 3.14 (1.65-5.97) Quartile 4: 3.73 (1.85-7.51) Estimates adjusted for age, age at leaving full time education, social class, job status, parity, height, BMI at GIII, BMI change from GIII to GIV, lacunarity. <u>Hazard ratio (95% CI) by Wolfe grade as predictor of breast cancer (N1 as reference):</u> P1: 2.06 (1.08-3.94) P2: 3.50 (1.98-6.21) DY: 3.90 (1.76-8.62) P for linear trend <0.001.	Limitations • 5,104 (31%) of the target population volunteered for GIII and 75% of these were still alive and lived on Guernsey during GIV (n=3,679). 3,211 accounted for in the analysis (representing 20% of the target population). • Outcome included both *in situ* and invasive breast cancer. • Observational study susceptible to residual confounding • Potential for misclassification of area of density. Most likely to be non-differential resulting in dilution of the study estimates. • Some lack of clarity over entry criteria with discrepancies between methods and results. For example, 29 women were excluded due to being 80+ on entry at GIV but this was not documented as an exclusion in the methods section of the paper. Other reasons for exclusion were unknown menopausal status, history of breast cancer on entry to GIV, breast implants, GIV mammograms no longer available for digitization.

Table 6.1: Evidence tables for primary studies of increased breast density (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Torres-Mejia et al. 2005) *continued*					Comments ▪ Primarily comparing different measures of mammographic features (% breast density, area of dense tissue, area of lucent tissue, area and volume of the breast, fractal dimension, regional skewness, lacunarity, Wolfe classification) as breast cancer risk factors. ▪ Radiologist was blind to the baseline condition of the woman. ▪ Total area of breast density and lacunarity were the two best predictors of breast cancer risk (lacunarity had an inverse risk – results not presented). Reported conclusions (by authors). Findings indicate that breast cancer risk is affected not only by the amount of mammographic density but also by the degree of heterogeneity of the parenchymal pattern and presumably by other features captured by the Wolfe classification.

Table 6.1: Evidence tables for primary studies of increased breast density (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Vacek and Geller 2004) USA	Cohort study Level III-2.	Study setting. Population based cohort study using data from the Vermont Breast Cancer Surveillance System. Sample (n=61,844) Median age (years): 50-54 Family history of breast cancer (%): 18.8 Nulliparity (%): 15.0 Median age at first childbirth (years): 21-30 Postmenopausal (%): 60.8 Ever used HRT (%): 50.4 Median BMI (kg/m^2): 25.0-27.4	Eligibility criteria No prior history of breast cancer ≥1 mammogram with breast density assessment in Vermont between April 1, 1996 and December 31, 2000. Breast cancers diagnosed within a year of the entry date were excluded. Data collection The BI-RADS classification system was used for assigning breast density. Outcome measures Invasive and *in situ* cancers were included. Follow-up interval. Date of entry was defined as the date of their first mammogram with breast density information. Follow up continued until the date of last mammogram (before July 1, 2001) or the date of her last benign biopsy of it occurred after that mammogram. 192,343 person-years follow up with an average of 3.1 years. Analysis Cox regression with age as the time variable was used.	<u>Adjusted relative risk (95% CI) by BI-RADS classification (entirely fat as reference):</u> 1. Premenopausal women Breast density: Scattered: RR 2.50 (0.92-6.82) Heterogeneous: RR 3.62 (1.32-9.92) Extremely dense: RR 4.21 (1.49-11.80) 2. Postmenopausal women Breast density: Scattered: RR 2.06 (1.47-2.89) Heterogeneous: RR 2.75 (1.93-3.92) Extremely dense: RR 3.48 (2.24-5.40) All estimates adjusted for family history of breast cancer, nulliparity, age at first childbirth, postmenopausal hormone use and BMI.	Limitations ▪ From 94,253 women with the requisite mammogram, 3,749 did not want their information used for research. A further 3,243 had a past history of breast cancer. ▪ Invasive and *in situ* cancers were included. ▪ 24,625 were considered as lost to follow up (mainly due to absence of an exit mammogram or biopsy). Women excluded due to insufficient follow up were younger than those in the study. ▪ Short follow-up time may have lead to overestimation of the level of risk ▪ Observational study susceptible to residual confounding ▪ Potential for misclassification of breast density Comments ▪ BI-RADS system is similar to Wolfe classification ▪ BI-RADS classification occurred at enrolment to the study Reported conclusions (by authors). Results correspond well with those from case control studies and suggest that BI-RADS density measurement may be useful in models for assessing breast cancer risk in individual women.

Table 6.1: Evidence tables for primary studies of increased breast density (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Nagao et al. 2003) Japan	Matched case control study Level III-2.	Study setting. Gihoku General Hospital, Gifu, Japan. Sample Mean age (years): cases 52.4, controls 51.2 Mean BMI (kg/m^2): cases 22.8, controls 22.9 Mean age at menarche (years): cases 13.7, controls 13.8 Mean age at first live birth (years): cases 25.8, controls 25.0, *P*=0.002 Number of births: cases 1.9, controls 2.2, *P*= 0.0001 Mean duration of lactation (months): cases 20.2, controls 22.8 Postmenopausal (%): cases 51.5, controls 46.6	Cases (n=237). Histologically verified breast cancer, underwent surgery between Jan 1998 and Dec 1999. Controls (n=742). Randomly selected from breast screening participants and were matched on age (± 1 year) and number of deliveries (± 1). No breast cancer or suspicious lesion on palpation, mammography or ultrasonography. Data collection Mammographic density measured visually using Wolfe's classification and a computer assisted method (three categories: MD fat, MD musc – for muscle, MD mix – for remainder). Medio-lateral oblique view was reviewed for assessment. Analysis Conditional logistic regression model was fitted.	<u>Adjusted hazard ratio (95% CI) by Wolfe grade as predictor of breast cancer (N1 as reference):</u> P1: 1.03 (0.69-1.55) P2: 0.68 (0.36-1.31) DY: 2.20 (1.02-4.77) <u>Adjusted hazard ratio (95% CI) by computer assisted method as predictor of breast cancer (MD fat as reference):</u> MD mix: 1.55 (0.98-2.58) MD musc: 2.83 (1.33-5.98) Both models adjusted for age at first birth and number of births	Limitations ▪ Despite the number of deliveries being matched there were significantly more births among the cases than controls, although this was controlled in the multivariate analysis ▪ Observational study susceptible to residual confounding ▪ No documentation of blinding of mammography readers to case/control status ▪ Potential for misclassification of breast density. This is more likely with Wolfe's classification given its more subjective nature. Given lack of blinding, it is unclear whether such misclassification is likely to be differential or non-differential. ▪ No documentation of participation rate amongst the cases and controls ▪ No documentation of the presence of a significant linear trend ▪ Did not consider area of dense breast tissue ▪ Controls may not be representative of women who have no breast cancer (it was unclear what proportion of women underwent screening) Comments ▪ Same mammography machine used for cases and controls ▪ Wolfe's classification: N1=parenchyma primarily fat, P1=parenchyma chiefly fat with prominent ducts in anterior portion (≤1/4 volume of breast), P2=prominent duct pattern (>1/4 volume of breast), DY=increased density but without a prominent duct pattern as the dominant feature. Reported conclusions (by authors). It is suggested that women with high mammographic densities, classified visually or by computer, have an elevated risk of breast cancer compared with those wit low mammographic densities.

Table 6.1: Evidence tables for primary studies of increased breast density (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Ursin et al. 2003) USA	Case control study Level III-2.	Study setting. Selected from two ongoing breast cancer case control studies conducted at the University of Southern California: the Los Angeles component of the women's CARE study and a study of Asian-American women. Sample Mean age (years): cases 49.3, controls 49.5 Mean BMI (kg/m^2): cases 25.0, controls 25.9, *P*=0.009 Mean age at menarche (years): cases 12.6, controls 12.5 First degree breast cancer family history (%): cases 15.1, controls 9.5, *p*=0.007 Parous (%): cases 78.8, controls 83.5, *P*=0.05 Mean number of full term pregnancies: Cases 2.0, controls 2.2, *P*=0.05 Premenopausal (%): cases 46.8, controls 41.3 Never used HRT (among postmenopausal women): cases 16.9%, controls 13.5%.	Cases (n=662). CARE study. US born white and African-American women resident in Los Angeles County when diagnosed with a first primary invasive breast cancer between June 1994 and August 1998 were eligible as subjects. Asian-American women. Cases diagnosed with a first primary invasive breast cancer between January 1995 and December 1997. Controls (n=443). CARE study. Random digit dialling used amongst residents of LA County. Frequency matched on age and ethnicity. Asian-American women. Frequency matched on age (± 5 years). Potentially eligible controls were identified using a protocol where residences were contacted using an algorithm that defined the initial residence to contacts and then proceeded through a defined sequence of adjacent residences.	<u>Adjusted odds ratio (95% CI) by percent area of dense tissue as predictor of breast cancer (<1% as reference):</u> 1-: OR 1.57 (0.81-3.03) 10-: OR 1.74 (0.91-3.31) 25-: OR 2.30 (1.24-4.28) 50-: OR 3.21 (1.65-6.25) 75+: OR 5.23 (1.70-16.13) *P*trend 0.0001 Adjusted OR for each 10% increase in dense area 1.15 (95% CI 1.07-1.23). Adjusted for age at mammography, BMI, age at menarche, breast cancer family history, number of full term pregnancies, menopausal status and HRT use, and age at FFTP.	Limitations ▪ Participation rates: African-American cases 72%, white cases 75%, Asian-American cases, 60%, African-American controls 71%, white controls 76%, Asian-American controls ▪ Mammograms could be retrieved on 66% of women. ▪ Approximately 90% of eligible breast cancer cases were identified within 2 months of diagnosis. ▪ A further 98 women were excluded due to missing data for specific variables. ▪ Observational study susceptible to residual confounding ▪ Potential for misclassification of breast density Comments ▪ Study focussed on women who were not in a screening program. ▪ One of the aims was to assess if breast density is a risk factor in different ethnic groups: "African Americans, Asian Americans, and whites." Reported conclusions (by authors). Results suggest that mammographic density is a risk factor in all ethnic groups to the same extent. This supports that mammographic density is suitable as a surrogate endpoint for breast cancer in cancer prevention studies

Table 6.1: Evidence tables for primary studies of increased breast density (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Ursin et al. 2003) *Continued*			Data collection Interviewers used structured questionnaires. American study was based on the CARE study questionnaire but had additional questions related to migration and dietary factors. The most recent mammogram was used for assessment of density. Mammograms were digitised. Mammogram read from the contralateral side in cases. For controls, the side read was randomly selected. Density was assessed using two methods: absolute density represents the count of tinted pixels within the region of interest, percent density which is the ratio of absolute density to the total breast area. Outcome measures Cases were identified by reference to the Los Angeles County Surveillance Program. Analysis Unconditional logistic regression models fitted. Pre-set potential confounding variables were included in the model.		

Table 6.1: Evidence tables for primary studies of increased breast density (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Byrne et al. 2001) USA	Nested, matched case control study Level III-2.	Study setting. Participated in the Breast Cancer Detection Demonstration Project. Sample Mean age (years): cases 59.5, controls 59.5 Mean BMI (kg/m^2): cases 24.0, controls 23.9 Mean years of education: cases 13.4, controls 12.8 Premenopausal (%): cases 15.0, controls 13.9 First degree family history of breast cancer (%): cases 30.5, controls 21.5 Nulliparous (%): cases 3.2, controls 3.7 Mean age at first birth (years): cases 24.1, controls 23.5	Cases (n=347). Incident case of breast cancer from participants who had participated in a previous case control study investigating mammographic density. Had a previous surgical biopsy that diagnosed benign breast disease (BBD). Cases diagnosed within one year of the initial mammogram were excluded. Controls (n=410). No history of breast cancer from participants who had participated in a previous case control study investigating mammographic density. Exclusion: had a previous surgical biopsy that diagnosed BBD. Data collection Percentage mammographic density estimated in previous study (based on total area). Analysis Unconditional logistic regression used to estimate odds ratios and 95% confidence intervals. *a priori* confounding variables were incorporated in the model.	<u>Adjusted odds ratio (95% CI) by area of dense tissue as predictor of breast cancer (<10% as reference):</u> 10-49: OR 2.0 (1.2-3.5) 50-74: OR 3.0 (1.7-5.4) ≥ 75: OR 4.4 (2.1-9.0) Adjusted for benign histology, age, race, family history, drinking alcohol, nulliparity and age at first birth, years of education, weight, menopause status, age at menopause, and use of menopausal hormones.	Limitations ▪ Confusing description of methods. ▪ Of the 981 incident cases and 1113 controls, 532 cases and 600 controls had a previous diagnosis of BBD but only 347 cases and 410 controls also had sufficiently detailed histologic information and mammographic density information to include in the study (35% of cases, 37% of controls) ▪ Observational study susceptible to residual confounding ▪ Potential for misclassification of breast density (greater for the visual inspection method). Comments ▪ Considered both benign breast density and mammographic density ▪ Mammographic density estimated prior to determination of case status. Reported conclusions (by authors). Both benign breast disease and the percentage of the breast area with mammographic density were associated with breast cancer risk. However, women with both proliferative benign breast disease and ≥ 75% density were not at as high a risk of breast cancer due to the combination of effects as women with only one of these factors.

Table 6.1: Evidence tables for primary studies of increased breast density (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(van Gils et al. 2000) The Netherlands	Nested case control study Level III-2	Study setting. Participated in Nijmegen breast cancer screening programme for 10 years. Women were aged 35+ years at time of screening Sample	Cases (n=129). Regular screening participants for ~10 years pre diagnosis. Diagnosed with primary breast cancer between 1985 and 1994. Controls (n=517) Four controls randomly selected who were free of breast cancer at the time of the case's diagnosis, had the same year of birth as the case and participated in the same number of screening rounds. Data collection Breast density classified with a fully automated technique on digitized mammograms from screening examinations 10 years before diagnosis. Assessed on the side with the breast cancer (and ipsilateral side in the matching controls). Categorised into proportion of high density mammographic tissue by breast volume. Analysis Conditional logistic regression analysis was used to estimate odds ratios. Parous women with low breast density (<5%) formed the reference category.	<u>Results stratified by parity</u> (reference group 1+ children and breast density <5%), (95% CI) <u>Among group with 1+child:</u> 5-25% density: OR 2.7 (1.3-5.6) >25% density: OR 3.6 (1.7-7.7) <u>Among group with no children:</u> <5% density: OR 1.1(0.2-5.8) 5-25% density: OR 8.5 (3.1-23.0) >25% density: OR 6.6 (2.6-16.5)	Limitations ▪ Observational study susceptible to residual confounding ▪ No documentation of blinding of mammography readers to case/control status ▪ Potential for misclassification of breast density. ▪ No overall estimate supplied for effect of breast density on breast cancer risk ▪ No baseline details comparing cases and controls ▪ No details on response rate ▪ Possible selection bias due to the requirement for regular screening over 10 years. Comments ▪ Primarily examined whether mammographic breast density had an explanatory role in the relationship between parity and breast cancer risk. Reported conclusions (by authors). Since there were few data, no firm conclusions can be drawn. If these findings can be confirmed in a larger study population, however, they may have important implications for the prevention and early detection of breast cancer.

Table 6.1: Evidence tables for primary studies of increased breast density (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Boyd et al. 1999) Canada	Nested, matched case control study Level III-2.	Study setting. Participants of a national mammographic screening study (CNBSS). Participants were selected from the 45,000 women aged 40-59 years who had been randomly allocated to annual mammography Sample Data for ≥1 first degree relative with breast cancer (60 cases, 46 controls): Age (years): cases 49.8, controls 50.7 Age at menarche (years): 12.9, controls 12.6 Number of live births: cases 2.6, controls 2.9 Postmenopausal (%): cases 63.3, controls 65.2.	Cases (n=354). Biopsy verified invasive breast cancer. All women diagnosed with breast cancer within 12 months of entry into the CNBSS were excluded. Controls (n=354). One control randomly selected for each case. Each control had a follow up period at least as long as the corresponding case. Controls were matched on CNBSS centre, year of study entry, age at entry to the study (± 1 year) and time in the study. Both cases and controls had a positive family history according to the following criteria: ≥1 first degree relative with breast cancer, ≥2 first or second degree relative with breast cancer, or ≥1 first or second degree relative with breast cancer Data collection Mammogram at entry to CNBSS was used for measurement. Two methods used to estimate percent occupied by radiologically dense tissue (1) visual inspection, (2) image digitised and thresholds set to define edge of breast and edge of dense breast tissue. Analysis Unconditional logistic regression used with strata of family history criteria.	<u>Estimates below are for adjusted relative risks (95% CI) comparing the most and least extensive categories of percent density.</u> 1. Visual radiologist method ≥1 first degree relative with breast cancer: RR 11.14 (1.54-80.39) ≥2 first or second degree relative with breast cancer: RR 2.57 (0.23-28.22) ≥1 first or second degree relative with breast cancer RR 5.43 (1.85-15.88) 2. Computer assisted method ≥1 first degree relative with breast cancer: RR 4.67 (0.63-34.52) ≥2 first or second degree relative with breast cancer: RR 2.42 (0.16-37.65) ≥1 first or second degree relative with breast cancer RR 6.83 (2.02-23.14) All estimates adjusted for age, age at menarche, menopausal status, number of live births, weight and height.	Limitations ▪ May have included women included in the study cited by (Yaffe et al. 1998) and (Byng et al. 1997) ▪ Observational study susceptible to residual confounding ▪ Potential for misclassification of breast density (greater for the visual inspection method). ▪ Incomplete presentation of baseline details comparing cases and controls. However, authors stated the other two family history strata had similar demographic characteristics to those presented under sample in this table. ▪ Small numbers in each strata ▪ Participation rate unclear Comments ▪ Restricted to women with a family history of breast cancer ▪ Average follow up at time of selection of cases was 7.5 years ▪ Radiologist was blind to the case status of the woman. Reported conclusions (by authors). Results suggest mammographic density may be strongly associated with risk of breast cancer among women with a family history of the disease. Because mammographic densities can be modified by dietary and hormonal interventions, the results suggest potential approaches to the prevention of breast cancer in women with a family history of breast cancer.

Table 6.1: Evidence tables for primary studies of increased breast density (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(van Gils et al. 1998) The Netherlands	Nested, frequency matched case control study Level III-2.	Study setting. Performed within the Nijmejen breast cancer screening programme. Women aged 35+ years were screened biennially in this programme Sample	Study population. The association between breast density and breast cancer risk at time intervals between 0-6 years from initial exam to diagnosis. Mammography technique was updated in 1981-2 after the programme started in 1975. Cases. Regularly screened participants diagnosed with primary breast cancer. 305 cases available before updating mammography and 54 after the update. Cases were divided into four groups corresponding to time of diagnosis in relation to screening round. Controls. Four controls per case. Regularly screening participants with at least as many screens as the case. 776 controls available before updating mammography and 151 after the update. Frequency matched on the first screening round of participation and on age category (35-44 years, 45-54 years, 55+ years). However, had to restrict the analysis to the youngest age category in the latter screening period due to small numbers in the older age groups.	<u>Adjusted odds ratio (95% CI) comparing women with dense versus lucent breasts (≤25% as the reference category) as predictor of breast cancer (all age groups combined):</u> 1. Old mammography technique 0 years between initial examination and diagnosis: OR 1.4 (0.7-2.6) 1-2 years between initial examination and diagnosis: OR 1.2 (0.6-2.3) 3-4 years between initial examination and diagnosis: OR 3.3 (1.5-7.1) 5-6 years between initial examination and diagnosis: OR 1.2 (0.6-2.7) Estimates adjusted for age at first examination, menopausal status, Quetelet index, first degree family history of breast cancer and number of screening examinations. This analysis was restricted to women using the old mammography technique. 2. New mammography technique (Only data for 35-44 age group available) 0 years between initial examination and diagnosis: OR 2.0 (0.3-14.0)	Limitations ▪ Categories of time between density assessment and time of diagnosis subject to misclassification (estimated based on relation with screening round) ▪ Participation rate amongst cases using the old mammographic technique (based on numbers analysed in the "all ages" group) was 81% (note it was 100% when using the new method). Participation rate amongst controls less clear since a person could be a control more than once. ▪ Five controls were excluded because of no mammograms ▪ Had to restrict the analysis to the youngest age category in the latter screening period due to small numbers in the older age groups and no entry questionnaire was completed in this screening period. ▪ Most studies use cranio-caudal views or both cranio-caudal views and medio-lateral obliques views, however, only lateromedial and mediolateral oblique views were available from the screening programme. However, there is a strong correlation in breast density measurement between the different views ▪ Classification of breast density in two categories reduces the degree of contrast between non-exposed and different levels of "exposed" women. ▪ Study had insufficient power to assess the hypothesis across the three pre-assigned age groups. No statistical analysis presented comparing estimates at different time intervals.

Table 6.1: Evidence tables for primary studies of increased breast density (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(van Gils et al. 1998) *Continued*			Data collection Initial mammograms were used to assess breast density. For controls, mammograms of the left breast were used, for cases, mammograms of the affected breast were used. Lateromedial and mediolateral oblique views used for assessment of density. Breast density was classified into two categories based on visual examination. Women completed a questionnaire prior to the first screening round in 1975 but this information was not available in women who were initially screened after the change in mammographic technique. Analysis Odds ratios computed for women with dense breasts compared with lucent breasts at different time intervals and are stratified by the mammography technique used. Multivariate logistic regression used. Adjusted for *a priori* variables that changed the odds ratio for breast density by more than 10%.	1-2 years between initial examination and diagnosis: OR 2.1 (0.5-8.5) 3-4 years between initial examination and diagnosis: OR 1.2 (0.5-3.2) 5-6 years between initial examination and diagnosis: OR 1.2 (0.3-5.2) Estimates adjusted for age at first examination and number of screening examinations	▪ Difficult to compare different mammography techniques due to small numbers, different factors adjusted for, and no direct statistical results presented. ▪ Sample characteristics not documented ▪ Observational study susceptible to residual confounding ▪ Potential for misclassification of breast density Comments ▪ Primarily evaluating the role of "masking bias" in the relationship between breast density and breast cancer. In particular the study tried to evaluate whether change in mammographic technique has changed the role of masking bias and whether there is any difference in the role of masking bias between different age groups. ▪ Would expect an increased risk of breast cancer in the short term after mammography in women with high breast density but this relative risk should return to unity over time if masking bias is the full explanation. ▪ Mammogram reader blinded to case status provided the diagnosis was not made at the initial screening round Reported conclusions (by authors). Due to the small sample size of this study group no firm conclusions could be drawn, but it seems as if masking bias could still play a role with high quality mammography.

Table 6.1: Evidence tables for primary studies of increased breast density (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Yaffe et al. 1998) and (Byng et al. 1997) Canada	Nested, matched, case control study Level III-2.	Study setting. Participants of a national mammographic screening study (CNBSS). Participants were selected from the 45,000 women who had been randomly allocated to annual mammography (from 90,000 who participated in the CNBSS). Follow-up information was available for the first 7 years at the time of defining the study groups for this case-control study. Sample Mean age (years): Cases 49.8, controls 49.8 Mean age at menarche (years): cases 12.8, controls 12.9 Mean age at first live birth (years): cases 25, controls 25 Mean number of live births: Cases 2.3, controls 2.8 Parity (%): cases 78, controls 86, *P*=0.008 Family history of breast carcinoma in first degree relatives (%): Cases 15, controls 12	Cases (n=332). Biopsy verified invasive breast cancer. All women diagnosed with breast cancer within 12 months of entry into the CNBSS were excluded. Controls (n=332). One control randomly selected for each case. Each control had a follow up period at least as long as the corresponding case. Controls were matched on CNBSS centre, year of study entry, age at entry to the study (± 1 year). Data collection Measures of mammographic density included six category subjective classification by a panel of radiologists (SCC), percentage density (PD), regional skewness and fractal dimension. Analysis Proportional hazards model that accounted for matching and adjustment for other risk factors (including age at menarche, menopausal status, number of live births, age at first child, family history of breast cancer, height and weight).	<u>Adjusted relative risk (95% CI) by SCC as predictor of breast cancer (> 75% density compared with no density):</u> RR 6.05 (2.82-12.97) <u>Adjusted relative risk (95% CI) by PD as predictor of breast cancer (> 75% density compared with no density):</u> RR 4.00 (2.12-7.56) <u>Adjusted relative risk (95% CI) by regional skewness as predictor of breast cancer (mean value in highest category versus mean value in lowest category):</u> RR 3.35 (1.57-7.12) <u>Adjusted relative risk (95% CI) by fractal dimension as predictor of breast cancer (mean value in highest category versus mean value in lowest category):</u> RR 2.54 (1.14-5.68) All models adjusted for age at menarche, age at menopause, number of live births, age at first child, family history of breast cancer, height and weight	Limitations ▪ Definition of breast cancer not documented ▪ Observational study susceptible to residual confounding ▪ 354 matched pairs were selected but adequate demographic information was only available on 332 matched pairs. ▪ Potential for misclassification of breast density. ▪ No documentation of participation rate amongst the cases and controls ▪ Incomplete presentation of relative risks for different categories of density ▪ Appear to be duplicate publications – information extracted from both studies under the assumption that the same participants were studied. Comments ▪ Predominantly theoretical study with limited supporting methodology and results ▪ Fractal dimension is a measure of image texture. It is expected that dense breast will yield more sheet like (uniformly dense) terrain and a lower fractal dimension than a fattier breast. ▪ The interactive approach used represents a proportion of breast tissue that is considered dense. ▪ Exclusion of women diagnosed with 12 months of entry to CNBSS was to minimise chance of obtaining prevalent rather than incident breast cancer cases (due to masking of cancer in areas of high density) Reported conclusions (by authors). Measurements of breast density may be helpful in assigning risk groups to women. Such measurements may guide the frequency of mammographic screening, aid the study of breast cancer aetiology, and be useful in monitoring possible risk-modifying interventions.

Appendix 7: Evidence tables for nulliparity

Table 7.1: Evidence tables for secondary studies of nulliparity

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Hunter et al. 1997) North America and Western Europe	Level III-2.	Pooled data from six prospective studies in North America and Western Europe. Information from 322,647 women including 4,827 cases.	Inclusion criteria Prospective study Conducted in North America or Western Europe Dietary fat intake had been estimated and the instrument used had been validated At last 200 incident cases of breast cancer available for analysis Exclusion criteria Subjects whose estimated total energy intake was more than 3 standard deviations above the log transformed mean of the base population. Diagnosed with cancer before baseline (other than non-melanoma skin cancer). Data extraction Methods not documented Analysis Five studies analysed as nested case control studies with a matching ratio of 10 controls per case. Controls sampled without replacement with the same year of birth, who were alive and not known to have out-migrated from the study. Proportional hazards model used. Conditional logistic regression used to fit this model in the studies analysed as nested case-control studies. Random effects model used for pooling.	<u>Pooled multivariate adjusted rate ratio (95% CI) by parity status (no parities as reference):</u> 3+: 0.72 (0.61-0.86) .	Limitations ▪ Methods of identifying eligible studies were not documented (potential publication bias) ▪ Restriction to North America and Western Europe is a potential source of publication bias ▪ Primary studies made use of self report data (potentially resulting in dilution of the measure of effect through non-differential bias) ▪ Methods of data extraction not stated. ▪ Based on observational study susceptible to residual confounding ▪ Incomplete results presented (no information on risk for 1-2 births) Comments ▪ Aimed to assess the relative risks associated with established risk factors for breast cancer, and whether the association between dietary fat and breast cancer risk varies according to levels of these risk factors. Reported conclusions (by authors). Risks for reproductive factors were similar to those observed in case-control studies, relative risks for family history of breast cancer were lower. We found no clear evidence in any subgroups of a major relation between total energy-adjusted fat intake and breast cancer risk.

Table 7.2: Evidence tables for primary studies of nulliparity

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Holmberg et al. 2005) Sweden	Cohort study (record linkage study) Level III-2	Study setting Cohort of all Swedish women born between 1920 and 1959 followed up to 1997 by record linkage. Sample (n=2,041,816)	Inclusion criteria Women born between 1920 and 1959 who were alive and resident in Sweden according to the Census of 1960. Exclusion criteria Incorrect identification numbers Identification number changed since 1960. Not identified in any other register. Data collection Linkage to the following registers: Death Register, Total Population Register, Emigration Register, Cancer Register, Multigeneration Register. Analysis End of follow-up defined as the earliest of first diagnosis of breast cancer, first emigration, death or December 31, 1997. Poisson regression used	<u>Adjusted rate ratio by parity status (nulliparity as reference), (95% CI):</u> Parities: 1: RR 0.93 (0.90-0.95) 2: RR 0.83 (0.81-0.85) 3: RR 0.74 (0.72-0.76) 4: RR 0.62 (0.59-0.64) 5: RR 0.57 (0.53-0.61) 6+: RR 0.43 (0.39-0.48) Adjusted using stratification by age group, calendar period and residence.	Limitations ▪ After applying the exclusion criteria stated 2,041,816 of 2,049,650 women were eligible (99.6%) ▪ Potential limitations of linkage to population registers: relying on accuracy of data in the registers and correct linkage (although risk of incorrect linkage would appear minimal given the use of a unique identifier) ▪ Observational study susceptible to residual confounding Comments ▪ Aim was to analyse the impact of reproductive factors on breast cancer risk among Swedish women by using nationwide population registers. Reported conclusions (by authors). Study shows the feasibility of using population-based registers to retrieve reliable information on reproductive risk factors to eliminate its confounding effect when analysing other risk factors.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Kojo et al. 2005) Finland	Nested, matched case-control study Level III-2	Study setting Study of Finnish cabin attendants. Study sample Age group (years) 38-45: cases 19%, controls 19% 46-55: cases 59%, controls 64% 56-65: cases 19%, controls 16% 66-81: cases 4%, controls 1%	Source population All Finnish female cabin attendants who were born in 1960 or before. Worked as cabin attendants for Finnish flight companies for at least 2 years. Cases (n=27) Breast cancer diagnosis confirmed through the Finnish Cancer Registry. Diagnosed between 1975 and 2000. Controls (n=517) Up to four controls per case, matched on year of birth (±1 year). Data collection Standardised self-administered questionnaire Analysis Conditional logistic regression used.	<u>Adjusted odds ratio by parity status (nulliparity as reference), (95% CI):</u> Parous: OR 1.10 (0.23-4.85) Adjusted for cumulative radiation dose, number of fertile years, family history of breast cancer, alcohol consumption, disruption of sleep rhythm, disruption of menstrual cycle.	Limitations ▪ 544 of 1098 eligible women returned the questionnaire with a participation proportion of 60% for cases and 52% for controls. This low participation may have resulted in selection bias. ▪ Potential information bias related to exposure. Although a nested design was used, exposure data were collected retrospectively so recall bias needs to be considered. Such bias would be expected to overestimate the measure of effect. ▪ Potential information bias related to outcome. No details about histological confirmation of case status or accuracy of the cancer registry used. ▪ Observational study susceptible to residual confounding Comments ▪ Aimed to assess the contribution of occupational versus lifestyle and other factors to breast cancer risk among cabin attendants in Finland ▪ Nested case-control design reduces risk of selection bias when compared with the retrospective, case control designs. Reported conclusions (by authors). Results suggest that breast cancer risk among Finnish cabin attendants is related to well established risk factors of breast cancer, such as family history of breast cancer. There was no clear evidence that the three occupational factors studied affected breast cancer risk among Finnish flight attendants.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Nichols et al. 2005) Vietnam China	Matched, case control study Level III-2	Study setting Cases eligible for a clinical trial of oophorectomy and tamoxifen as treatment for breast cancer. Study sample Mean age (years): cases 41, controls 42. Distribution of cases: Vietnam 93% China 7%. Family history of breast cancer (%) Cases: 1.6, controls 1.8 BMI (kg/m^2) 13.2-18.5: cases 29%, controls 25% 18.6-20.0: cases 23%, controls 25% 20.1-21.6: cases 19%, controls 24% 21.7-40.8: cases 25%, controls 24% Any alcohol (%): cases 16, controls 10	Cases (n=682) Eligibility criteria for clinical trial: Premenopausal women with a new diagnosis of stage IIA, IIB and IIIA breast tumours and a planned mastectomy within 10 weeks. Absence of metastatic cancer and presence of normal chest X-rays, liver function and blood calcium levels within 10 weeks of study entry. Controls (n=649) Non-relative hospital visitors to non-cancer patients matched on age (±1 year) to cases. Data collection Structured in-person interviews. Analysis Unconditional logistic regression used	<u>Adjusted odds ratio by parity status (nulliparous as reference), (95% CI):</u> 1-2 children: OR 0.58 (0.22-1.54) 3-4 children: OR 0.43 (0.16-1.17) >5 children: OR 0.53 (0.18-1.56) *P*trend 0.6 Adjusted for age, hospital, age at first birth, alcohol use and spouse's education	Limitations ▪ Control population may not be representative of the population from which the cases were derived ▪ Participation rate among the cases and controls not stated ▪ Recall bias needs to be considered ▪ Observational study susceptible to residual confounding ▪ Conditional logistic regression would have been appropriate in this individual matched case control study. Comments ▪ Aimed to evaluate associations between reproductive and life style risk factors with breast cancer tumour marker status. Reported conclusions (by authors). Findings support the hypothesis that some breast cancer risk factors differ by breast tumour marker subtypes.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Tamakoshi et al. 2005) Japan	Cohort study Level III-2	Study setting Part of the Japan Collaborative Cohort Study (1988-1990). Enrolled 127,477 people in the study and 110,792 were followed. Of the 64,327 women, 38,720 lived in areas with cancer registries. Study sample (n=38,159)	Study population Japanese women aged 40-79 who responded to a questionnaire on reproductive and other lifestyle factors. Exclusions: history of breast cancer at baseline or within 1 year of follow-up time. Data collection Self-administered questionnaire at baseline. Population Registries were used to determine vital and residential status. Population-based cancer registries used to ascertain the incidence of cancer. Follow up Mean 7.6 years Analysis Follow-up time was from the date of completing the questionnaire to the development of breast cancer, death from any cause, moving out of the study area or end of the study period, whichever occurred first. Cox proportional hazards modelling used	<u>Adjusted rate ratio by parity status (nulliparous as reference), (95% CI):</u> Parous: RR 0.95 (0.38-2.32) Adjusted for age at baseline, study area, smoking status, alcohol consumption, exercise, meat intake, green leafy vegetable intake, family history of breast cancer, BMI at baseline, menopausal status and age at menarche.	Limitations ▪ Missing data provided a potential source of selection bias (e.g. Parity status available on 140 of 151 cases over 267,332 person-years of follow-up) ▪ Potential misclassification of exposure status most likely to be non-differential – diluting any association. ▪ Potential misclassification of outcome but magnitude is likely to be small ▪ Observational study susceptible to residual confounding ▪ No details about characteristics of the study sample Comments ▪ Aimed to evaluate the association between reproductive risk factors and breast cancer risk Reported conclusions (by authors). Study suggests that breast cancer in Japan is similar to that in Western countries, and that reproductive risk factors, particularly the number of parities and age at first delivery, might be important in the aetiology of breast cancer among Japanese women

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Gilani and Kamal 2004) Pakistan	Matched case control study Level III-2	Study setting Cases derived from two cancer hospitals which represent referral centres for rural and urban Punjab, Pakistan. Study sample Age (years): 25-34: cases 29%, controls 29% 35-44: cases 71%, controls 71% Family history of breast cancer (%): cases 11, controls 7 BMI: Normal: cases 35%, controls 64% Overweight: cases 18%, controls 26% Obese: 18%, controls 8% Menopausal status (%): Premenopausal: cases 73, controls 86 Perimenopausal: cases 2, controls 1 Postmenopausal: cases 14, controls 12 Age < 25 at FFTP Cases 47%, controls 74% History of abortions (%): Cases 27%, controls 24%	Cases (n=498) Women younger than 45 years with a first diagnosis of breast cancer (histologically confirmed) between July 1997 and December 1998 at two major cancer hospitals in Lahore. Controls Age matched population based controls (2 controls per case) were selected from two cities and two villages to represent urban and rural areas. Specific areas were randomly selected but individual houses within those areas were selected according to convenience. Data collection Cases interviewed in hospital and controls interviewed at their residence. Analysis Conditional logistic regression used.	<u>Adjusted odds ratio by parity status (parous as reference), (95% CI):</u> Nulliparous: OR 0.66 (0.19-2.30) Adjusted for BMI, family history of breast cancer, consanguineous marriage, menopausal status and age at menarche.	Limitations ▪ Control population may not be representative of the population from which the cases were derived ▪ Participation rates amongst cases and controls unclear ▪ Observational study susceptible to residual confounding ▪ Case control design susceptible to recall bias, potentially overestimating associations with breast cancer risk. Comments ▪ Aim was to determine risk factors for breast cancer among Pakistani women Reported conclusions (by authors). Risk factors identified for Pakistani women below 45 years were similar to those observed in other studies. However, obesity in premenopausal women and late menarche were not protective and consanguinity was identified as a risk.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Oran et al. 2004) Turkey	Matched, case control study Level III-2	Study setting Hospital based case-control study Study sample History of benign breast disease (%): cases 12, controls 8 Ever used OCs (%): cases 25, controls 24 BMI (kg/m^2) >34: cases 1%, controls 1% 30-34: cases 32%, controls 26% 25-29: cases 41%, controls 42% <25: cases 25%, controls 32%	Cases (n=622) Histologically confirmed breast cancer Diagnosed between 1993 and 2000 Controls (n=622) Age matched (±5 years) to cases Admitted to the same hospital as the cases between 1998 and 2000. Exclusions: admission for pregnancy, gynaecological, endocrinological or neoplastic disease. No breast cancer evident on mammography or ultrasonography. Data collection Written questionnaire Analysis Unconditional logistic regression	<u>Adjusted odds ratio by parity status (nulliparous as reference), (95% CI):</u> Parous: OR 0.37 (0.13-1.06) <u>Adjusted odds ratio by full term pregnancy status (no full term pregnancy as reference), (95% CI):</u> Ever had full term pregnancy: OR 0.45 (0.30-0.66) Adjusted for marital status, menopausal status and age at menopause, BMI, smoking, first degree relative with breast cancer, history of benign breast disease.	Limitations ▪ Controls admitted to hospital over a different time period to cases – may have resulted in bias ▪ Control population may not be representative of the population from which the cases were derived (hospital based controls used) ▪ Potential for recall bias ▪ Observational study susceptible to residual confounding ▪ No documentation of participation rates in cases and controls. Comments ▪ Aimed to investigate the association between menstrual, reproductive and life-style factors and breast cancer in Turkish women. Reported conclusions (by authors). Decreased parity, late age at first birth, early menopause, and shorter duration of lactation were the most important determinants of breast cancer risk in Turkish women.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Li et al. 2003b) USA	Case control study Level III-2.	Study setting. Population based case control study set in the Seattle-Puget Sound region. Evaluation of the effect reproductive and anthropometric factors has on the risk of invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC). Sample Age at reference date (%): 65-69 yrs: cases 31, controls 33 70-74 yrs: cases 39, controls 38 75-79 yrs: cases 30, controls 29 First degree family history of breast cancer (%): cases 23, controls 17 Age at menarche (%): 8-11 yrs: cases 19, controls 17 12-13 yrs: cases 54, controls 52 14+ yrs: cases 27, controls 31 Nulliparous (%) Cases 9, controls 9 BMI (kg/m^2) (%) <23.32: cases 22, controls 27 23.33-26.20: cases26, controls 25 26.21-30.11: cases 26, controls 24 30.12+: cases 26, controls 24.	Cases (n=975) Women aged 65-79 years with no previous history of *in situ* or invasive breast cancer who were diagnosed with invasive breast cancer between April 1, 1997 and May 31, 1999. Cases identified from the SEER program. Had to live in one of three stipulated counties and have a Health Care Financing Administration (HCFA) record. Controls (n=1,007) HCFA records used to identify female residents from the same three counties as the cases. Frequency matched to cases on age and county of residence. Data collection Tumour histology obtained from CSS. Subjects interviewed in person. Analysis Unconditional logistic regression used in assessment of all breast cancer cases. Comparison of invasive lobular breast cancer and invasive ductal carcinoma conducted using polytomous logistic regression.	<u>Age adjusted odds ratio by parity status (nulliparous as reference), (95% CI):</u> Parous: OR 1.0 (0.8-1.4)	Limitations ▪ 975 of 1,210 (81%) eligible cases were interviewed. ▪ 1,007 of 1,365 (74%) of eligible controls were interviewed. ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered. ▪ Histology was not independently reviewed which may have resulted in misclassification ▪ Small number of lobular carcinoma cases Comments ▪ Primary aim was to evaluate the association between combined estrogen-progestin HRT breast cancer type (invasive lobular breast carcinoma and invasive ductal carcinoma). Association between anthropometric factors to breast cancer type evaluated here. Reported conclusions (by authors). There were no statistical differences in risk between invasive lobular breast cancer and invasive ductal carcinoma in relation to anthropometric factors. Compared to lower height women, taller women had increased risks in both histologic types. Neither BMI nor weight was strongly related to invasive lobular carcinoma, but higher BMI and weight was related to greater invasive ductal carcinoma risk.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Wrensch et al. 2003) USA	Frequency matched case control study Level III-2	Study setting Residents of Marin County, California including women with breast cancer and controls identified through random digit dialling. Study sample Median age (years): cases 55 years, controls 55 years Family history of breast cancer (%): cases 19, controls 20 Benign biopsy history (%): cases 31, controls 27 Postmenopausal (%): cases 61, controls 66 Ever used Ocs (%): cases 76, controls 85 Highest BMI after age 21 (kg/m^2) <25: cases 65%, controls 49% 25-<30: cases 23%, controls 29% 30+: cases 12%, controls 21%	Cases (n=285) Diagnosis of primary breast cancer between June 1997 and June 1999 if under 50 years and between July 1997 and June 1999 if 50+ years of age. Identified from NCCC cancer registry. Controls (n=286) Identified by random digit dialling and frequency matched to cases by age at diagnosis (±5 years). Data collection Full in-person interviews or abbreviated telephone interviews Analysis Logistic regression used.	<u>Adjusted odds ratio by parity status (no pregnancies as reference), (95% CI):</u> 1 birth: OR 1.0 (0.54-2.0) 2 births: OR 1.1 (0.59-1.9) 3+ births: OR 1.3 (0.68-2.4) Adjusted for age, family history of breast cancer, benign biopsy history, previous radiation treatment, menopause status, reproductive history, OC use, HRT history, highest BMI, number of mammograms, socioeconomic status before age 21, highest degree obtained, religion in which raised, and alcohol and tobacco use.	Limitations ▪ Mixed methods of data collection (brief telephone interview used among women who did not wish to complete the long in-person interview). 5% of controls and 9% of cases completed the short interview ▪ Among the group completing the full interview, complete data were available for 285 cases and 286 controls. The results presented in this table were restricted to these 285 cases and 286 controls. ▪ 50 of 401 eligible cases refused to take part (12%) ▪ 7 of 328 eligible controls refused to take part (2%) ▪ Case interviews conducted between Dec 1999 and Sept 2001 and control interviews between Apr 2000 and Sept 2001. ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered. Comments ▪ Examines recognised breast cancer risk factors and years of residence in Marin County, California, an area with high breast cancer incidence and mortality rates. Reported conclusions (by authors). Despite similar distributions of several known breast cancer risk factors, case control differences in alcohol consumption suggest that risk in this high risk population might be modifiable. Intensive study of this or other areas of similarly high incidence might reveal other important risk factors proximate to diagnosis.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Clavel-Chapelon and Group 2002) France	Cohort study Level III-2	Study setting Used data obtained from the E3N study – a prospective cohort study on cancer risk factors. Restricted to women who replied to a dietary questionnaire from the E3N cohort. Enrolled between 1990 and 1991. Study sample (n=91,260) Age (years): 40-45: 35% 45-50: 24% 50-55: 19% 55-60: 13% 60-65: 8% Number of years of education: <7: 5% 7-11: 8% 12-14: 47% 15-16: 17% 17+: 17%.	Inclusion criteria Part of E3N cohort. Replied to dietary questionnaire Aged 40-65 at baseline. Data collection Self reported questionnaire with follow up questionnaires at approximately two year intervals until April 1997. Deaths detected by notification from family members or insurance company records and cause of death was obtained from the National Service on Causes of Death. Analysis Person time data contributed to time of diagnosis of breast cancer, date of death, date of last questionnaire returned or December 1997, whichever occurred first. Proportional hazard model fitted.	<u>Adjusted rate ratio by number of full term pregnancies (zero as reference), (95% CI):</u> 1: RR 0.76 (0.61-0.95) 2: RR 0.73 (0.60-0.89) 3: RR 0.68 (0.55-0.83) 4+: RR 0.68 (0.53-0.87) Trend (each additional FFTP): RR 0.92 (0.88-0.96), $P < 0.0001$. Adjusted for age at FFTP, age at menarche, number of spontaneous abortions, age, history of benign breast disease, family history of breast cancer, current BMI, ever married, educational level.	Limitations ▪ Potential misclassification of exposure status most likely to be non-differential – diluting any association. However, validation study showed high reproducibility for exposure data including age at menarche and number of live births ▪ Potential misclassification of outcome but magnitude is likely to be small ▪ Reference category of zero births included missing FFTP status for 20 cases ▪ Observational study susceptible to residual confounding Comments ▪ Aim was to obtain a better understanding of the role of hormonal factors in breast cancer risk and to determine whether the effect of reproductive events differs according to age at diagnosis. ▪ Large sample Reported conclusions (by authors). Results suggest that reproductive events have complex effects on the risk of breast cancer.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Gammon et al. 2002) USA	Case control study. Level III-2.	Study setting. Long Island Breast Cancer Study Project. Population based study. Sample Median age group at reference (years): cases 55-64, controls 55-64 Median age at menarche (years): cases 12, controls 12 Nulliparous (%): cases 13, controls 11 Median BMI (kg/m2) at reference: cases 25.2-29.2, controls 22.3-25.1 Never smoked (%): cases 44.8, controls 45.0 Family history of breast cancer (%): cases 19.2, controls 13.0	Cases (n=1,508) Newly diagnosed with a first primary in situ or invasive breast cancer between August 1996 and July 1997, confirmed by physician and medical record who were resident of Nassau and Suffolk, New York at the time of diagnosis. Able to speak English. Controls (n=1,556) Current residents of Nassau and Suffolk Counties who spoke English, who did not have a personal history of breast cancer, and who were frequency matched to the expected distribution of case women by 5 year age group. Random digit dialling used to identify controls. Data collection Self-report, blood and urine sample (collected prior to chemotherapy) and environmental home data (dust, water and soil). Analysis Unconditional logistic regression. Likelihood ratio test used to assist fitting the model.	<u>Age adjusted odds ratio by parity status (nulliparous as reference), (95% CI):</u> Parous: OR 0.78 (0.63-0.98) 1 child: OR 0.97 (0.72-1.32) 2 children: OR 0.83 (0.65-1.05) 3 children: OR 0.78 (0.60-1.00) 4+ children: OR 0.63 (0.48-0.82)	Limitations ▪ 2,271 women with breast cancer were initially identified as potentially eligible, 2,030 of these were identified by the physician as likely to be eligible and consent was obtained in 1,837 (90.5%). The main questionnaire was completed by 1,508 eligible cases (82%). ▪ Response rate to the telephone screener (controls) was 78%. Known response rate among controls under 65 years was 58% (unknown for the 65+ group). The main questionnaire was completed by 1,556 eligible cases (63%). ▪ >97% of residents in the study region are English speaking. ▪ Cases included both invasive and *in situ* disease. ▪ Recall bias needs to be considered. ▪ Observational study susceptible to residual confounding. Results limited to age adjusted estimate.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Kuru et al. 2002) Turkey	Case control study Level III-2	Study setting. Hospital based case control study Sample Mean age (years): cases 49.4, controls 46.4, *P*<0.001 Age <15 yrs at menarche (%): cases 76, controls 65, *P*<0.01 Nulliparous (%): cases 12, controls 5, *P*=0.75 Positive family history (%): cases 6, controls 2, *P*=0.005	Cases (n=504) All women admitted to surgical clinics of Ankara Oncology Education and Research Hospital with histologically proven breast cancer and resident in Ankara or five other regions of Turkey. Controls (n=610) Women residing in the same geographical areas as the cases and admitted to the wards or outpatient clinics of the same hospital during the same interval. Exclusions: women with malignant, endocrine or gynaecological disease. Data collection Collected through questionnaires and interview Analysis Unconditional logistic regression used.	<u>Adjusted odds ratio by parity status (parous as reference), (95% CI):</u> nulliparity: OR 1.18 (0.41-3.35) Adjusted for age, residence, age at menarche, menstrual irregularity, age at first pregnancy, breast feeding, OC use, family history, BMI, education, previous benign breast biopsy, menopausal status and age at menopause.	Limitations ▪ Twelve potential cases and 26 potential controls were excluded due to inability to recall age at menarche/menopause (2% of potential cases, 4% of potential controls). ▪ Recall bias needs to be considered. ▪ Observational study susceptible to residual confounding ▪ Controls may not be representative of the population from which the cases were selected. Hospital based population used. Comments ▪ Study aim was to identify risk factors for breast cancer in Turkey ▪ None of the participants refused interview Reported conclusions (by authors). The results of the present study will lead to a better understanding of the risk factors for breast cancer in a developing country.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Lumachi et al. 2002) Italy	Matched, case control study Level III-2	Study setting Data obtained from a database of information composed of 1184 women who had been referred to a specific breast unit. Study sample Median age 59 years (range 26-89) Family history of breast cancer 10% Abortion 1% Pregnancy 81% Lactation 65% Use of OCs 21% Menopausal patients 70% Mean age at menarche 12.7 years Mean number of births 1.93 Mean months of OCs 30 Mean age at menopause 49	Cases (n=404) "Confirmed" breast cancer who had undergone curative surgery. Controls (n=780) Cases age matched to 389 healthy women and 391 symptomatic non-screened patients without breast cancer. Latter group were excluded from having breast cancer for a median follow up of 68 months (range 28-146 months) Data collection Personal interview at time of first clinical examination. Analysis Logistic regression used.	<u>Adjusted odds ratio by number of pregnancies (1+ pregnancies as reference), (95% CI):</u> No pregnancies: OR 5.25 (3.63-7.58). Adjusted for age, age at first birth, breastfeeding, use of oestrogen replacement therapy and use of oestrogen replacement therapy for more than 40 months.	Limitations ▪ Basis of confirmation of case status was not documented ▪ Accuracy of the data in the database was unclear ▪ Control population may not be representative of the population from which the cases were derived ▪ Control population unlikely to be representative of the total population free from breast cancer leading to biased results. ▪ Case control design susceptible to recall bias, potentially overestimating associations with breast cancer risk. ▪ Observational study susceptible to residual confounding. Comments ▪ Aimed to evaluate risk of breast cancer in self-selected symptomatic women in comparison with the healthy population residing in an urban area of Italy. Reported conclusions (by authors). There were no statistical differences in risk between invasive lobular breast cancer and invasive ductal carcinoma in relation to anthropometric factors. Compared to lower height women, taller women had increased risks in both histologic types. Neither BMI nor weight was strongly related to invasive lobular carcinoma, but higher BMI and weight was related to greater invasive ductal carcinoma risk.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Tryggvadottir et al. 2002) Iceland	Nested, matched case control study Level III-2.	Study setting. Sample selected from a population based cancer registry (80,219 women attending breast and cervical screening during 1979-1995). Women were aged 20-81 years at the time of attending. Termed the CDC cohort. Sample <40years Age at menarche <13 (%): cases 45, controls 32 Nulliparous (%): cases 13, controls 12 Height (%): ≤160cm: cases 13, controls 15 161-169cm: cases 58, controls 56 170+cm: cases 29, controls 29 Weight (%): ≤60kg: cases 42, controls 43 61-79kg: cases 46, controls 48 80+kg: Cases 11, controls 8 40-55 years Age at menarche <13 (%): cases 32, controls 28 Nulliparous (%): cases 8, controls 5 Height (%): ≤160cm: cases 17, controls 20 161-169cm: cases 59, controls 58 170+cm: cases 24, controls 22 Weight (%): ≤60kg: cases 29, controls 28 61-79kg: cases 55, controls 57 80+kg: Cases 16, controls 15	Cases (n=1,120) First invasive breast cancer diagnosed between 1979-1995 identified in the Cancer Registry of Iceland. Controls (n=10,537) Sought 10 controls per case matched on birth year and age when giving information. Alive at least until the diagnosis year of the matched case. Data collection Only answers used before the diagnosis of a first breast cancer were used. Self reported data examining reproductive and menstrual risk factors were included. Analysis Study group stratified according to age of diagnosis of cases (<40, 40-55 and >55 years). Conditional multiple logistic regression was applied.	<u>Adjusted odds ratio by parity status (nulliparous as reference), (95% CI):</u> OR 0.96 (0.74-1.25) Adjusted for age at menarche, age at first birth, number of births, OC use, lactation, height and weight.	Limitations ▪ Record linkage of the Cancer Registry of Iceland and CDC databank identified 85% of those in the CDC databank. ▪ 70% of the 1,601 cases were included in the analysis. ▪ Self reported data may be subject to misclassification. However, this is likely to be small and non-differential, resulting in dilution of relative risk estimates. ▪ Observational study susceptible to residual confounding Comments ▪ Primary aim was to explore the relationship between breast cancer and established risk factors by specific age groups of diagnosis of breast cancer. ▪ Most of the data were collected from women attending cervical screening rather than mammography. ▪ Only answers used before the diagnosis of a first breast cancer were used. Reported conclusions (by authors). The results confirm that age at diagnosis should be taken into account when studying the effects of breast cancer risk factors.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Gomes et al. 2001) Brazil	Case control study Level III-2.	Study setting. Hospital based case control study in Brazil. Sample Median age group (years): 45-54 Education < 12 years (%): 89 Age < 13 years at menarche (%): 33 Age < 45 at menopause (%): 42 Nulliparous (%): 15 Family history of breast cancer (%): 7 Cigarette smoking (%): 23	Cases (n=300) Breast cancer cases aged 25-75 years admitted to Federal University Hospital between January 1978 and December 1987. Controls (n=600) Selected from the same hospital during the same period, free from any cancer, with normal breasts on examination and matched on age (± 2 years) and date of diagnosis (± 6 months) on a 2:1 ratio. Two series of controls used: 1. selected from general outpatient care unit, 2. admitted to gynaecological services. Data collection Medical records used. Analysis Conditional logistic regression used.	<u>Adjusted odds ratio by parity status (6+ parities as reference), (95% CI):</u> 1-5 parities: OR 2.61 (1.72-3.96) Nulliparous: OR 4.56 (2.69-7.73) Adjusted for irregular menstrual cycles, occupation, family history of breast cancer and OC use.	Limitations ▪ 300 of 388 cases were included. Exclusions included presence of distant metastases (n=24), lost biopsy (n=1), nonepithelial tumours (n=9), lack of confirmed biopsy (n=41), male breast carcinoma (n=2), outside age range (n=11), lacking information on menopausal status (n=20). ▪ Data collected from medical records was incomplete leading to exclusion of some variables from the analysis. This may have lead to residual confounding. ▪ Loss of study power resulting from missing data. From the initial study population of 300 cases and 600 controls, complete information was available for 235 matched sets. ▪ The variables included in the final models were not documented. ▪ Controls may not be representative of the population from which the cases were selected ▪ Cases from this hospital based population may not be representative of all cases. ▪ Recall bias needs to be considered in this case control study – likely to overestimate level of risk. ▪ Observational study susceptible to residual confounding Comments ▪ Diagnosis of breast cancer confirmed by second pathologist. Reported conclusions (by authors). The present study indicates that breast cancer diagnosed before and after menopause has a similar risk profile.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Gao et al. 2000) China	Population based, frequency matched, case control study Level III-2	Study setting Data analysed from the Shanghai Breast Cancer Study – a study conducted amongst Chinese women in urban Shanghai. New cases between 1996 and 1998. Study sample Age (years): 25-34: cases 3%, controls 5% 35-44: cases 36%, controls 36% 45-54: cases 39%, controls 33% 55-64: cases 23%, controls 25% Family history of breast cancer (%): cases 4, controls 2 BMI (kg/m^2) ≤20.70: cases 20%, controls 24% 20.71-22.79: cases 24%, controls 25% 22.80-25.20: cases 27%, controls 25% >25.10: cases 29%, controls 25% Ever consumed alcohol (%): cases 4, controls 4 Ever used OC (%): cases 22, controls 21 Ever used HRT (%): cases 3, controls 3	Study population Permanent residents of Shanghai with no past history of cancer. Alive at the time of interview. Cases (n=1,459) Newly diagnosed breast cancer between 25 and 64 years. Cases identified through a rapid case ascertainment system, supplemented by the population based cancer registry. Controls (n=1,556) Randomly selected from the study population and frequency matched to cases by age (5 year intervals). The Shanghai Resident Registry was used as the sampling frame. Data collection Face to face interview by trained interviewers using a structured questionnaire Analysis Unconditional logistic regression	<u>Adjusted odds ratio by nulliparity (parous as reference), (95% CI):</u> OR 1.4 (0.8-2.4) Adjusted for age, education, family history of breast cancer, history of breast fibroadenoma, waist to hip ratio, menarcheal age, menopausal status, menopausal age, and physical activity.	Limitations ▪ 1459 of 1602 eligible cases were interviewed (91%) ▪ 1556 of 1724 eligible controls were interviewed (90%) ▪ Observational study susceptible to residual confounding ▪ Case control design susceptible to recall bias, potentially overestimating associations with breast cancer risk. Comments ▪ Aimed to evaluate the association of menstrual and reproductive risk factors with breast cancer risk. Reported conclusions (by authors). Study suggests that the changes in menstrual and reproductive patterns among women in Shanghai have contributed to the recent increase in breast cancer incidence, particularly among younger women.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Magnusson et al. 1999) Sweden	Case control study Level III-2.	Study setting Population based case-control study Study sample Mean age (years): cases 62.6, controls 63.7 Mean age at menarche (years): cases 13.5, controls 13.6 Mean age at menopause (years): cases 50.5, controls 50.0 Mean parity: cases 1.8, controls 2.1 Mean age at first birth (years): cases 25.3, controls 24.6 Mean recent BMI (kg/m^2): cases 25.7, controls 25.5 Mean BMI at age 18 (kg/m^2): cases 20.6, controls 20.8 Family history of breast cancer (%): cases 16.0, controls 9.2 Benign breast disease (%): cases 13.8, controls 9.6	Cases (n= 3,016) Women aged 50-74 years with invasive breast cancer, without previously diagnosed breast cancer, born in Sweden and resident there between October 1993 and March 1995. Incident cases identified through six regional cancer registries. Women of unknown menopausal status or previous diagnosis of invasive cancer (other than non-melanoma skin cancer) were excluded. Controls (n=3,263) Women frequency matched to the expected age distribution of the cases randomly selected from a continuously updated register of all people residing in Sweden. Women of unknown menopausal status or previous diagnosis of invasive cancer (other than non-melanoma skin cancer) were excluded. Data collection Mailed questionnaires and telephone interviews used. Telephone interviews were restricted to 11% of controls who failed to return the mailed questionnaire Analysis Unconditional logistic regression used.	<u>Adjusted odds ratio by parity status (nulliparous as reference), (95% CI):</u> 1 child: OR 0.69 (0.53-0.90) 2 children: 0.63 (0.49-0.81) 3-4 children: OR 0.50 (0.40-0.64) 5-6 children: OR 0.39 (0.26-0.58) 7+ children: OR 0.06 (0.01-0.26) *P*trend < 0.0001 Estimates adjusted for age, age at menarche, age at first birth, menopausal status, age at menopause, height, BMI one year prior to data collection and use of HRT for at least one year.	Limitations ▪ 16% of eligible cases and 18% of eligible controls did not participate in the study ▪ Mixed methods of data collection, including the use of telephone interviews in a proportion of controls, may have resulted in bias. ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered. Comments ▪ Aimed to examine whether age at menarche is causally involved in breast cancer aetiology or serves as a correlate of other early life exposures. Other aspects of reproductive life, including cycle length and regularity, climacteric symptoms, reproductive history and oral contraceptive use were also examined. ▪ Study restricted to women aged 50 to 74 years. Reported conclusions (by authors). Findings provide some evidence of a role of environmental correlates of early menarche in breast cancer aetiology, and underline the importance of childbirth, especially early in life, in the prevention of breast cancer. Our data are not readily compatible with an important influence of former oral contraceptive use on post-menopausal breast cancer risk.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Tavani et al. 1999) Italy	Case control study Level III-2.	Study setting. Data derived from two case-control studies of breast cancer: 1. greater Milan area between 1983 and 1991 2. six areas of Italy between 1991 and 1994. Hospital based controls used. Less that 4% of cases and controls refused interview, on average. Overall dataset (including women 40+ years) included 5,984 cases and 5,504 controls Sample Age: < 25 years: cases 2%, controls 7% 25-29 years: cases 10%, controls 15% 30-34 years: cases 27%, controls 28% 35-39 years: cases 61%, controls 49% Education < 9 years: cases 43%, controls 52% 9-13 years: cases 37%, controls 35% 13 years: cases 21%, controls 13% Family history of breast cancer: Cases 8%, controls 4% History of benign breast disease: Cases 15%, controls 8%	Cases (n=579) Histologically confirmed incident breast cancer admitted to the major teaching and general hospitals in the areas under surveillance Controls (n=668) Acute hospital admissions (to the same network of hospitals as the cases) for non-neoplastic, non-hormone-related diseases. Data collection Questionnaire administered by centrally trained interviewers. Included information on demographic and lifestyle characteristics. Analysis Unconditional multiple logistic regression used.	<u>Adjusted odds ratio by parity status (nulliparous as reference), (95% CI):</u> 1 child: OR 1.53 (1.09-2.13) 2 children: OR 1.70 (1.21-2.40) 3 children: OR 1.42 (0.86-2.36) 4+ children: OR 1.13 (0.47-2.71) *P*trend 0.05 Adjusted for study, centre, year of recruitment, age, education, BMI, family history of breast cancer, parity and age at first birth.	Limitations ▪ Hospital based controls may not be representative of the population from which the cases were drawn ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered. Comments ▪ Aimed to investigate the relationship between hormonal and lifestyle risk factors and breast cancer risk in women younger than 40 years ▪ Good participation rate in the two case-control studies from which the current dataset were derived. Reported conclusions (by authors). Most risk factors in this large dataset of women aged less than 40 years were similar to those described in breast cancer epidemiology at any age.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Ghadirian et al. 1998) Canada	Frequency matched, case control study Level III-2	Study setting Population based case control study of French Canadians in Montreal. Study sample BMI 1 year ago (kg/m^2): <22.3: Cases 35%, controls 32% 22.3-25.7: cases 32%, controls 34% >25.7: cases 33%, controls 34% Ever smoked cigarettes (%): cases 47, controls 53	Cases (n=414) New cases of histologically diagnosed breast cancer in women aged 35-79 years. Attending physician/surgeon provided permission for inclusion. Controls (n=429) Used modified random digit dialling to identify controls. Frequency matched to cases on age (±5 years) and place of residence. Data collection Face to face interview using standardised questionnaire by trained interviewers. Analysis Unconditional logistic regression used.	<u>Adjusted odds ratio by number of pregnancies (nulliparous as reference), (95% CI):</u> 1: OR 0.78 (0.48-1.27) 2: OR 1.23 (0.80-1.89) 3: OR 0.74 (0.48-1.18) 4: OR 0.89 (0.53-1.50) 5+: OR 0.46 (0.29-0.75) Adjusted for age, marital status, parity, age at FFTP, history of benign breast disease, family history of breast and ovarian cancers, personal income.	Limitations ▪ Participation rate of 77% among the cases ▪ Participation rate amongst the eligible controls 33%. ▪ Observational study susceptible to residual confounding ▪ Case control design susceptible to recall bias, potentially overestimating associations with breast cancer risk. Comments ▪ Investigate the relationship between sociodemographic characteristics, lifestyle, family history of cancer, medical history, and reproductive factors and breast cancer. ▪ Study conducted in parallel with studies of colon and prostate cancer. Reported conclusions (by authors). This study confirms the risk factors of late age at FFTP, nulliparity, late age at menopause, and positive family history of breast cancer in the aetiology of this disease.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(McCredie et al. 1998a) New Zealand	Population based case control study Level III-2	Study setting. Population based case control study Sample Median age group: cases 45-49, controls 40-4. Maori ethnicity (%): cases 7, controls 5 Age at menarche (%) < 12 years: cases 17, controls 16 12-14 years: cases 66, controls 68 15+ years: cases 16, controls 16 Nulliparous (%): cases 11, controls 11 Premenopausal (%): cases 68, controls 77 History of surgery for benign breast disease (%): cases 13, controls 7 Family history of breast cancer in first degree relative (%): cases 11, controls 7.	Study population Selected from women whose names were in a current electoral roll and whose telephone number could be found. Cases (n=891) First diagnosis of breast cancer identified from the National Cancer Registry and the Auckland Breast Cancer Study Group. Women aged 25-54 years Histologically confirmed breast cancer diagnosed between July 1983 and June 1987. Exclusions: previous diagnosis of breast cancer Controls (n=1,864) Random selection from electoral roll. Age 25-54 years. Randomly excluded half the potential controls aged under 35 to approximate more closely the age distribution of the cases. Reference date calculated by subtracting six months from the date of interview. Data collection Telephone interview. Two nurse interviewers were used. Most began with the interviewer being blind to case status but case status was disclosed as the interview progressed.	<u>Adjusted odds ratio by parity status (nulliparity as reference), (95% CI):</u> All parous: OR 0.73 (0.48-1.1) 1: OR 0.86 (0.53-1.4) 2: OR 0.82 (0.54-1.3) 3: OR 0.81 (0.52-1.2) 4+: OR 0.57 (0.37-0.88) *P*trend 0.01 Adjusted for age, ethnicity, age at menarche, age at FFTP, duration of breast feeding, menopausal status, family history and previous surgery for benign breast disease.	Limitations ▪ 891 of 1,126 (79%) eligible cases participated ▪ Participation rate among controls cannot be estimated absolutely due to lack of age data in electoral rolls. However, 15.5% of the group selected from the electoral roll did not participate due to being untraceable, language difficulties, absence overseas, refused participation, illness or death. ▪ Inability to blind interviewers to case status but most interviewers were blind to case status at the beginning of data collection. ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered. Comments ▪ Aimed to assess the influence on breast cancer risk of reproductive factors and the possibility of an interaction with age at diagnosis ▪ Like a nested study set within the total NZ population – which should reduce risk of selection bias. Reported conclusions (by authors). The relationships between reproductive risk factors and age and a women's risk of breast cancer are clearly complex and not yet fully understood. Unravelling these relationships should help to elucidate the pathogenesis of breast cancer. Other investigators could contribute by performing more searching analyses of data that have already been collected as well as by conducting further analyses.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(McCredie et al. 1998a) *continued*			Data collection Telephone interview. Two nurse interviewers were used. Most began with the interviewer being blind to case status but case status was disclosed as the interview progressed. Analysis Logistic regression used.		

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Bleiker et al. 1996) The Netherlands	Nested, matched, case control study Level III-2	Study setting Set within a population based breast screening program. Questionnaire sent to women aged 43 years and older as they were invited to attend screening. Study sample	Cases (n=131) Newly detected breast cancer, diagnosed through 1989-1994. Exclusions: previous diagnosis of breast cancer Controls (n=771) Women free of cancer who had returned the questionnaire. Up to six controls selected for each case with matching on age and moment of screening. Data collection Postal questionnaire – psychological questionnaire sent in 1989-1990. Questionnaire for somatic risk factors sent at each screening round (every 2 years). Analysis Conditional logistic regression	<u>Adjusted odds ratio by parity status (first parity before age 30 as reference), (95% CI)</u> First parity after age 29: OR 1.29 (0.73-2.27) Nulliparity: OR 2.32 (1.39-3.89) Unknown status: OR 0.62 (0.28-1.40) Adjusted for family history of breast cancer and anti-emotionality scale.	Limitations ▪ No data about sample characteristics ▪ 17,159 of 28,940 women invited participated in the screening program (59%). 9,705 returned personality questionnaires (34%). ▪ Selection bias likely due to low participation in screening program and low response to questionnaire. ▪ Excluded controls selected twice and controls who subsequently developed breast cancer (n=15). This was probably unnecessary. ▪ Self-reported exposure data subject to misclassification. Most likely to be non-differential, therefore, diluting any association. ▪ Observational study susceptible to residual confounding. ▪ Did not compare parous with nulliparous women. ▪ Results presented were not based on all 771 controls (key table include 641 controls). Comments ▪ Purpose was to investigate the extent to which personality factors, in addition to somatic factors, may be associated with breast cancer development. ▪ Set in screening program ▪ Nested design excludes possibility of recall bias and reduces risk of selection bias.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Bleiker et al. 1996) *Continued*					Reported conclusions (by authors). With the exception of a weak association between a high score on the anti-emotionality scale and the development of breast cancer, no support was found for the hypothesis that personality traits can differentiate between groups of women with and without breast cancer. We recommend that this study be continued and that other studies be encouraged to explore possible relationships between personality factors and the risk of breast cancer.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Hu et al. 1997) Japan	Case control study Level III-2	Study setting Study conducted in Gifu, Japan. Study sample Mean age: cases 49.6 years, controls 49.4 years Relative height at 12 years: Low: cases 28%, controls 29% Middle: cases 38%, controls 42% Tall: cases 31%, controls 27% Relative weight at 12 years: Light: cases 32%, controls 30% Middle: cases 52%, controls 54% Heavy: cases 11%, controls 9%	Cases (n=157) Histologically confirmed breast cancer between 1989 and 1993. Excluded 3 cases who had no matched controls. Controls (n=369) Age (within 5 years) and residential area (same city/town) matched controls from Gifu, Japan. No breast disease or hormone related cancers. Data collection Self administered questionnaire Analysis Conditional logistic regression	<u>Adjusted odds ratio by number of births (3+ as reference), (95% CI):</u> 1-2 births: OR 1.83 (1.11-2.99) 0 births: OR 6.06 (2.40-15.3) Adjusted for age at menarche, BMI, age at first birth, and duration of breast feeding. Results also presented for number of pregnancies but these were limited to univariate analyses.	Limitations ▪ Self-identified data used. ▪ 157 of 237 cases sent a questionnaire responded and were included (66%) ▪ 369 of 489 eligible controls responded (76%) ▪ Observational study susceptible to residual confounding ▪ Most study variables divided into tertiles based on control population distribution. Such an approach (as opposed to use of continuous data or more strata) increases the possibility of residual confounding. ▪ Small study ▪ Reference category of number of births not ideal (3+ births) when assessing the role of nulliparity. ▪ Case control design susceptible to recall bias, potentially overestimating associations with breast cancer risk. Comments ▪ Aim was to further clarify risk factors for breast cancer in Japanese women Reported conclusions (by authors). No clear conclusions.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Lambe et al. 1996) Sweden	Nested case control study Level III-2	Study setting Case control study nested in a nationwide cohort of Swedish women born between 1925 and 1960. Study sample	Cases (n=12,782) Identified from the Cancer Registry First diagnosis of breast cancer between 1958 and 1984. Identified in the Fertility Registry Aged between 16 and 59 years. Controls (n=54,347) Randomly selected from Fertility registry Matched for year and month of birth. Alive and resident of Sweden at date of diagnosis of the case. No previous history of breast cancer. Data collection Data contained in the Fertility registry Analysis Conditional logistic regression used.	<u>Age adjusted odds ratio by number of live births (nulliparity as reference), (95% CI):</u> 1: OR 0.92 (0.86-0.97) 2: OR 0.84 (0.80-0.97) 3: OR 0.76 (0.71-0.81) 4: OR 0.67 (0.61-0.74) 5: OR 0.53 (0.45-0.63) 6: OR 0.33 (0.24-0.46) 7: OR 0.33 I(0.19-0.57) 8: OR 0.63 (0.33-1.18) 9: OR 0.55 (0.20-1.58)	Limitations ▪ Only 87.8% of the breast cancer cases identified from the Cancer registry were identified in the Fertility Registry – providing a potential selection bias ▪ Relied on use of existing data – limiting the ability to control for potential confounders ▪ Accuracy of the Fertility Registry data was not documented (but is likely to be high) ▪ Observational study susceptible to residual confounding ▪ No details about study sample ▪ Potential misclassification of exposure status most likely to be non-differential – diluting any association. Comments ▪ Investigated the role of parity, age at first birth and age at last birth on breast cancer risk. ▪ Nested case control signs controls recall bas and reduces risk of selection bias ▪ Large study Reported conclusions (by authors). Findings contradict recent claims that age at last birth has a stronger effect than age at first birth on breast cancer. The dominance of age at first birth as risk modulator is likely to reflect the protection afforded by the terminal differentiation of breast cells induced by a first pregnancy.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Minami et al. 1997) Japan	Matched, case control study Level III-2	Study setting Case control study of screen detected breast cancer in Miyagi Prefecture, Japan. 201,363 participants in the breast screening program. Study sample Mean age: cases 52.6 years, controls 52.6 years	Cases (n=204) Diagnosis of breast cancer Controls (n=810) Four controls matched to cases on screening year, age (±2 years) and screening area. Data collection Obtained from medical records taken at screening. Analysis Conditional logistic regression used.	<u>Adjusted odds ratio by parity status (nulliparity as reference), (95% CI):</u> 1 child: OR 0.93 (0.43-1.99) 2 children: OR 0.62 (0.33-1.19) 3+ children: OR 0.56 (0.30-1.06) *P*trend 0.03 Adjusted for age at menarche, history of benign breast disease and family history of breast cancer.	Limitations ▪ Basis of breast cancer diagnosis unclear ▪ Observational study susceptible to residual confounding ▪ Misclassification of exposure information is likely to be small in magnitude and non-differential – leading to dilution of the measure of effect. Comments ▪ Study aimed to investigate the associations between reproductive history and risk of breast cancer among participants of a breast screening program. ▪ Study like a nested case-control design which reduces the risk of selection bias ▪ Prospective collection of data excludes risk of recall bias Reported conclusions (by authors). The results by age group suggest that different mechanisms may exist in breast cancer developing at early and late onset.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Ng et al. 1997) Singapore	Case-control study Level III-2	Study setting Prospective case control study conducted amongst Chinese Singaporeans. Study sample Age 45-49: 34% Age 50-64: 56% Age 65-69: 10% Age at menarche (years): <13: 22% 13-15: 56% >15: 22% Ever pregnant 88% Age at first delivery (years): No births: 12% <22: 25% 22-26: 35% 26-30: 19% >30: 9% Ever used OCs: 36% Ever used HRT: 17% Family history of breast cancer: 4% Stage I disease (cases): 35% Stage II disease (cases): 65%	Cases (n=204) Consecutive Chinese women aged 45-69 years who underwent surgery for Stage I or II breast carcinoma between 1994 and 1996. Controls (n=882) Age matched controls randomly selected from women participating in a population based breast screening program. Data collection Written questionnaire. Analysis Logistic regression used	<u>Odds ratio by parity status (nulliparity as reference), (95% CI):</u> Each additional delivery: OR 0.82 (0.7-0.9) Adjusted for age, menopausal status, age at menarche, pregnant, age at first birth, age at last birth, use of HRT, use of OC, positive family history of breast carcinoma, breast feeding, breast biopsy, smoking, height, weight, BMI and waist to hip ratio.	Limitations ▪ Control population may not be representative of the population from which the cases were derived ▪ 42% of eligible controls receiving an invitation to participate responded. ▪ Observational study susceptible to residual confounding. ▪ Misclassification of exposure information is likely to be small in magnitude and non-differential – leading to dilution of the measure of effect. Comments ▪ Aimed to determine significant factors associated with the risk of breast carcinoma among Chinese women in Singapore aged 45-69 years ▪ Exposure data collected prospectively Reported conclusions (by authors). The risk of breast cancer is strongly associated with changes in lifestyle related to caloric intake and reproductive or menstrual factors. Better and excess nutrition in early and later years of life and fewer births may explain in part the increasing incidence of breast carcinoma occurring in Singapore.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Ramon et al. 1996) Spain	Matched case control study Level III-2	Study setting Case control study using both hospital and community controls. Study sample Age (years) <35: cases 4%, hosp ctrl 3%, comm ctrl 4% 35-45: cases 20%, hosp ctrl 20%, comm ctrl 22% 46-55: cases 13%, hosp ctrl 15%, comm ctrl 13% 56-65: cases 34%, hosp ctrl 33%, comm ctrl 32% 66-75: cases 21%, hosp ctrl 19%, comm ctrl 20% >75: cases 9%, hosp ctrl 10%, comm ctrl 10% Education (years) <7: cases 61%, hosp ctrl 66%, comm ctrl 60% 7-11: cases 29%, hosp ctrl 30%, comm ctrl 34% >11: cases 10%, hosp ctrl 4%, comm ctrl 7%	Cases (n=184) Histologically confirmed incident cases of breast cancer diagnosed between 1989 and 1992. Aged 30+ years No previous history of cancer Cases identified through surgical and pathology records Controls (n=368) Matched by age and residence to cases. 184 hospitalised patients 184 community controls Community controls selected by random digit dialling (selected from the same geographic region as the corresponding case) Hospitalised controls excluded patients with cancer, benign breast disease, and other diseases associated with factors under study. Controls were matched on age (±5 years) and residence. Data collection Face to face interview using a structured questionnaire. Analysis Logistic regression used	<u>Age adjusted odds ratio by number of full term pregnancies (no pregnancies as reference). (95% CI):</u> 1: OR 1.10 (0.55-2.16) 2-3: OR 0.54 (0.30-1.03) >3: OR 0.37 (0.16-0.78)	Limitations ▪ Control population may not be representative of the population from which the cases were derived (mix of hospital based and community controls used). ▪ Potential for recall bias. ▪ Observational study susceptible to residual confounding. Measure of effect only adjusted for age. ▪ No documentation of participation rates in cases and controls. Comments ▪ Carried out to assess associations between parity, lactation and age at FFTP and breast cancer. Reported conclusions (by authors). Study indicates that parity is an independent risk factor associated with breast cancer and that the women with a late age at first full term pregnancy constitute a high risk group.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Talamini et al. 1996) Italy	Case control study Level III-2	Study setting Conducted in six different Italian regions conducted between June 1991 and February 1994. Study sample Median age: cases 55 years, controls 59 years. Education (11+ years of schooling): Cases 25%, controls 16%	Cases (n=2,569) Histologically confirmed incident cases of breast cancer under 80 years of age. Controls (n=2,588) Women resident in the same geographic areas and admitted to the same hospitals as the cases. Admitted for a variety of acute conditions. Exclusions: gynaecological, hormonal or neoplastic disease. Data collection In hospital interview using a structured questionnaire. Analysis Multiple logistic regression	<u>Adjusted odds ratio by parity status (1 parity as reference), (95% CI):</u> Nulliparous: OR 0.8 (0.7-1.0) 2 parities: OR 1.0 (0.8-1.1) 3 parities: OR 0.8 (0.7-0.9) 4 parities: OR 0.7 (0.5-0.9) 5+ parities: OR 0.7 (0.5-0.9) *P*trend < 0.001 Adjusted for area of residence, age, education, and menopausal status.	Limitations ▪ Control population may not be representative of the population from which the cases were derived (hospital based controls used) ▪ Participation rate amongst cases and controls not stated ▪ Recall bias needs to be considered. Such bias may have overestimated degree of association with breast cancer risk. ▪ Non-differential misclassification of age at menarche may also have occurred resulting in dilution of effect. ▪ Observational study susceptible to residual confounding Comments ▪ Aimed to investigate the role of reproductive and menstrual factors in the aetiology of breast cancer, overall and by menopausal status Reported conclusions (by authors). Multiparity, early age at first birth and early age at menopause were the most important determinants of breast cancer risk. The effect of the timing of births was significantly heterogeneous in pre- and postmenopausal women because of the transient adverse effect of such events, evident only in premenopausal women.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Viladiu et al. 1996) Spain	Matched case control study Level III-2	Study setting Population based case control study Study sample Age (years) <50: cases 26%, controls 24% 50-59: cases 27%, controls 22% >59: cases 47%, controls 54% Education No schooling: cases 10%, controls 10% Primary level: cases 80%, controls 73% Higher level: cases 10%, controls 17% Family history of breast cancer (%) Cases 19, controls 9 BMI (Kg/m^2) <24.5: cases 23%, controls 27% 24.5-27.2: cases 25%, controls 26% 27.3-30.2: cases 28%, controls 23% >30.2: cases 25%, controls 25%	Cases (n=330) Diagnosed with histologically or cytologically confirmed or clinically based incident breast cancer between 1986 and 1989 (identified from a gynaecological cancer registry). < 75 years and mentally able to answer the structured questionnaire. Controls (n=346) Random sample of the population matched to the cases by age (±5 years) and county of residence. < 75 years and mentally able to answer the structured questionnaire. Data collection Interviews with trained interviewers using a structured questionnaire. Analysis Unconditional logistic regression used.	<u>Adjusted odds ratio by number of children (nulliparous as reference), (95% CI):</u> 1-3: OR 1.4 (0.7-2.5) 4-5: OR 1.4 (0.7-2.8) 6+: OR 1.6 (0.6-4.2) Adjusted for age, family history of breast cancer, age at first birth and age at menopause.	Limitations ▪ 93.1% of all gynaecological cancers reported in the cancer registry have histological verification (6 cases in this study were based on clinical grounds). ▪ 73% of cases and 84% of controls participated. ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered. Comments ▪ Aimed to explore risk factors for breast cancer with emphasis on the detection of clinical markers of the hormonal imbalance during the perimenarche Reported conclusions (by authors). Hormonal changes in the years following menarche may be relevant to breast cancer risk. The roles of menstrual period length and acne during adolescence should be further explored.

Table 7.2: Evidence tables for primary studies of nulliparity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Wu et al. 1996) USA	Matched, case control study Level III-2	Study setting Population based case control study among Asian-Americans Study sample Mean age at menarche (years): cases 12.9, controls 13.0 Never pregnant (%): cases 19, controls 12 No livebirth (%): cases 24, controls 15	Cases (n=492) Diagnosed with histologically confirmed, incident, primary breast cancer during 1983-1987 Age 20-55 years. Controls (n=768) Selected by random digit dialling in California and from a surveillance program in Hawaii. Matched to cases on age, ethnicity and area of residence (frequency matching in California, individual matching in Hawaii). Data collection Face to face interview Analysis Unconditional logistic regression used.	<u>Adjusted odds ratio by parity status (nulliparous as reference), (95% CI):</u> Parous: OR 0.57 (0.41-0.80) Adjusted for age, area, ethnicity, and migration history.	Limitations ▪ 70% of eligible cases participated in interviews, 58% included in analysis ▪ 75% of eligible controls participated, 60% included in analysis ▪ Mixed methods at different sites – different control selection and matching processes. ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered. Comments ▪ Aimed to quantify breast cancer risk in relation to menstrual and reproductive histories in migrant and US-born Asian-Americans. Reported conclusions (by authors). Menstrual and reproductive factors in Asian-American women are consistent with their breast cancer rates being at least as high as in US whites, and they are. However, the effects of these menstrual and reproductive factors were small and the odds ratios for migration variables changed only slightly after adjustment for these menstrual and reproductive factors. These results suggest that the lower rates of breast cancer in Asians must be largely as a result of other environmental/lifestyle factors.

Appendix 8: Evidence tables for early menarche

Table 8.1: Evidence tables for secondary studies of early menarche

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Hunter et al. 1997) North America and Western Europe	Level III-2.	Pooled data from six prospective studies in North America and Western Europe. Information from 322,647 women including 4,827 cases.	Inclusion criteria Prospective study Conducted in North America or Western Europe Dietary fat intake had been estimated and the instrument used had been validated At last 200 incident cases of breast cancer available for analysis. Exclusion criteria Subjects whose estimated total energy intake was more than 3 standard deviations above the log transformed mean of the base population. Diagnosed with cancer before baseline (other than non-melanoma skin cancer). Data extraction Details not provided. Analysis Five studies analysed as nested case control studies with a matching ratio of 10 controls per case. Controls sampled without replacement with the same year of birth, who were alive and not known to have out-migrated from the study. Proportional hazards model used. Conditional logistic regression used to fit this model in the studies analysed as nested case-control studies. Random effects model used for pooling.	<u>Pooled multivariate adjusted rate ratio (95% CI) by age at menarche (<12 years as reference):</u> ≥15 years: RR 0.72 (0.62-0.82)	Limitations ▪ Methods of identifying eligible studies were not documented (potential publication bias) ▪ Restriction to North America and Western Europe is a potential source of publication bias ▪ Primary studies made use of self report data (potentially resulting in dilution of the measure of effect through non-differential bias) ▪ Methods of data extraction not stated. ▪ Based on observational study susceptible to residual confounding ▪ Incomplete results presented (no information on risk for 12-14 year age group) Comments ▪ Aimed to assess the relative risks associated with established risk factors for breast cancer, and whether the association between dietary fat and breast cancer risk varies according to levels of these risk factors. Reported conclusions (by authors). Risks for reproductive factors were similar to those observed in case-control studies, relative risks for family history of breast cancer were lower. We found no clear evidence in any subgroups of a major relation between total energy-adjusted fat intake and breast cancer risk.

Table 8.2: Evidence tables for primary studies of early menarche

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Nichols et al. 2005) Vietnam China	Matched, case control study Level III-2	Study setting Cases eligible for a clinical trial of oophorectomy and tamoxifen as treatment for breast cancer. Study sample Mean age (years): cases 41, controls 42. Distribution of cases: Vietnam 93% China 7%. Family history of breast cancer (%) Cases: 1.6, controls 1.8 BMI (kg/m^2) 13.2-18.5: cases 29%, controls 25% 18.6-20.0: cases 23%, controls 25% 20.1-21.6: cases 19%, controls 24% 21.7-40.8: cases 25%, controls 24% Any alcohol (%): cases 16, controls 10	Cases (n=682) Eligibility criteria for clinical trial: Premenopausal women with a new diagnosis of stage IIA, IIB and IIIA breast tumours and a planned mastectomy within 10 weeks. Absence of metastatic cancer and presence of normal chest X-rays, liver function and blood calcium levels within 10 weeks of study entry. Controls (n=649) Non-relative hospital visitors to non-cancer patients matched on age (±1 year) to cases. Data collection Structured in-person interviews. Analysis Unconditional logistic regression used	<u>Adjusted odds ratio by age at menarche (<15 years as reference), (95% CI):</u> 15 years: OR 0.74 (0.53-1.04) 16 years: OR 1.11 (0.80-1.53) 17+ years: OR 1.09 (0.82-1.45) *P*trend 0.5 Adjusted for age, hospital, parity, age at first birth, alcohol use and spouse's education	Limitations ▪ Control population may not be representative of the population from which the cases were derived ▪ Participation rate among the cases and controls not stated ▪ Recall bias needs to be considered ▪ Observational study susceptible to residual confounding ▪ Conditional logistic regression would have been appropriate in this individual matched case control study. Comments ▪ Aimed to evaluate associations between reproductive and life style risk factors with breast cancer tumour marker status. Reported conclusions (by authors). Findings support the hypothesis that some breast cancer risk factors differ by breast tumour marker subtypes.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Tamakoshi et al. 2005) Japan	Cohort study Level III-2	Study setting Part of the Japan Collaborative Cohort Study (1988-1990). Enrolled 127,477 people in the study and 110,792 were followed. Of the 64,327 women, 38,720 lived in areas with cancer registries. Study sample (n=38,159)	Study population Japanese women aged 40-79 who responded to a questionnaire on reproductive and other lifestyle factors. Exclusions: history of breast cancer at baseline or within 1 year of follow-up time. Data collection Self-administered questionnaire at baseline. Population registries were used to determine vital and residential status. Population-based cancer registries used to ascertain the incidence of cancer. Follow up Mean 7.6 years Analysis Follow-up time was from the date of completing the questionnaire to the development of breast cancer, death from any cause, moving out of the study area or end of the study period, whichever occurred first. Cox proportional hazards modelling used.	<u>Adjusted rate ratio by age at menarche (≤12 years as reference), (95% CI):</u> 13-14 years: RR 1.05 (0.51-2.15) 15-16 years: RR 1.15 (0.55-2.41) 17+ years: RR 1.27 (0.56-2.85) *P*trend 0.45 Adjusted for age at baseline, study area, smoking status, alcohol consumption, exercise, meat intake, green leafy vegetable intake, family history of breast cancer, BMI at baseline, menopausal status and number of parity.	Limitations ▪ Missing data provided a potential source of selection bias (e.g. Parity status available on 134 of 151 cases over 268,785 person-years of follow-up) ▪ Potential misclassification of exposure status most likely to be non-differential – diluting any association ▪ Potential misclassification of outcome but magnitude is likely to be small ▪ Observational study susceptible to residual confounding ▪ No details about characteristics of the study sample. Comments ▪ Aimed to evaluate the association between reproductive risk factors and breast cancer risk Reported conclusions (by authors). Study suggests that breast cancer in Japan is similar to that in Western countries, and that reproductive risk factors, particularly the number of parities and age at first delivery, might be important in the aetiology of breast cancer among Japanese women.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Gilani and Kamal 2004) Pakistan	Matched case control study Level III-2	Study setting Cases derived from two cancer hospitals which represent referral centres for rural and urban Punjab, Pakistan. Study sample Age (years): 25-34: cases 29%, controls 29% 35-44: cases 71%, controls 71% Family history of breast cancer (%): cases 11, controls 7 BMI: Normal: cases 35%, controls 64% Overweight: cases 18%, controls 26% Obese: 18%, controls 8% Menopausal status: Premenopausal: cases 73%, controls 86% Perimenopausal: cases 2%, controls 1% Postmenopausal: cases 14%, controls 12% Age < 25 at FFTP Cases 47%, controls 74% History of abortions (%): Cases 27, controls 24	Cases (n=498) Women younger than 45 years with a first diagnosis of breast cancer (histologically confirmed) between July 1997 and December 1998 at two major cancer hospitals in Lahore. Controls Age matched population based controls (2 controls per case) were selected from two cities and two villages to represent urban and rural areas. Specific areas were randomly selected but individual houses within those areas were selected according to convenience. Data collection Cases interviewed in hospital and controls interviewed at their residence. Analysis Conditional logistic regression used.	<u>Adjusted odds ratio by age at menarche (≤12 years as reference), (95% CI):</u> 13-14 years: OR 2.02 (1.21-3.38) 15+ years: OR 3.31 (1.63-6.73) Adjusted for BMI, family history of breast cancer, consanguinous marriage, menopausal status and parity.	Limitations ▪ Control population may not be representative of the population from which the cases were derived ▪ Participation rates amongst cases and controls unclear ▪ Observational study susceptible to residual confounding ▪ Case control design susceptible to recall bias, potentially overestimating associations with breast cancer risk. Comments ▪ Aim was to determine risk factors for breast cancer among Pakistani women Reported conclusions (by authors). Risk factors identified for Pakistani women below 45 years were similar to those observed in other studies. However, obesity in premenopausal women and late menarche were not protective and consanguinity was identified as a risk.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Oran et al. 2004) Turkey	Matched, case control study Level III-2	Study setting Hospital based case-control study Study sample History of benign breast disease (%): cases 12, controls 8 Ever used OCs (%): cases 25, controls 24 BMI (kg/m^2) >34: cases 1%, controls 1% 30-34: cases 32%, controls 26% 25-29: cases 41%, controls 42% <25: cases 25%, controls 32%	Cases (n=622) Histologically confirmed breast cancer Diagnosed between 1993 and 2000 Controls (n=622) Age matched (±5 years) to cases Admitted to the same hospital as the cases between 1998 and 2000. Exclusions: admission for pregnancy, gynaecological, endocrinological or neoplastic disease. No breast cancer evident on mammography or ultrasonography. Data collection Written questionnaire Analysis Unconditional logistic regression used	<u>Adjusted odds ratio by age at menarche (<12 years as reference), (95% CI):</u> 12: OR 0.93 (0.71-1.22) 13: OR 1.03 (0.74-1.43) >13: OR 0.76 (0.47-1.23) Adjusted for marital status, menopausal status and age at menopause, history of benign breast disease, first degree relative with breast cancer, OC use and BMI.	Limitations ▪ Controls admitted to hospital over a different time period to cases – may have resulted in bias ▪ Control population may not be representative of the population from which the cases were derived (hospital based controls used) ▪ Potential for recall bias ▪ Observational study susceptible to residual confounding ▪ No documentation of participation rates in cases and controls. Comments ▪ Aimed to investigate the association between menstrual, reproductive and life-style factors and breast cancer in Turkish women. Reported conclusions (by authors). Decreased parity, late age at first birth, early menopause, and shorter duration of lactation were the most important determinants of breast cancer risk in Turkish women.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Beiler et al. 2003) USA	Frequency matched, case control study Level III-2	Study setting Study conducted in three counties of Tennessee. Sample Age group: 20-39 years: cases 11%, controls 11% 40-49 years: cases 35%, controls 34% 50-59 years: cases 35%, controls 36% 60+ years: cases 20%, controls 19%. Education Up to high school: cases 37%, controls 46% Vocational/technical: cases 11%, controls 10% Junior College: cases 26%, controls 25% College: cases 25%, controls 18% Employed: cases 70%, controls 69% Married: cases 53%, controls 69%.	Cases (n=304) African-American women aged 20-64 living in Tennessee, pathologically diagnosed with breast cancer between 1995 and 1998. Physician gave consent to contact patient. Controls (n=305) Selected through random-digit dialling and frequency matched to cases. Frequency matching by five year age groups and county. Data collection Phone interviews by trained interviewers. Analysis Unconditional logistic regression used.	<u>Adjusted odds ratio (95% CI) by age at menarche (>12 years as reference):</u> ≤ 12 years: OR 0.93 (0.60-1.44) <u>Adjusted odds ratio (95% CI) by age at menarche (16+ years as reference):</u> 15 years: OR 1.53 (0.56-4.22) 13-14 years: OR 0.94 (0.44-2.00) ≤ 12 years: OR 1.00 (0.48-2.10) *P*trend not significant Adjusted for marital status, income, education, age, religion, family history of breast cancer, history of benign breast disease, alcohol use, smoking, oral contraceptive use, age at first birth, age at first sexual intercourse, weight status by BMI, daily energy intake, physical activity, electric blanket/mattress use, history of infertility, menarche to regularity, cycle length, length of flow and menopausal status.	Limitations ▪ 670 potentially eligible cases identified (thus participation rate was 45%). Reasons for non-participation included: deceased, lack of physician's consent, could not be located. ▪ 420 households contacted had at least one eligible control. 376 women were contacted in these households. Therefore participation rate was 81%. ▪ Observational study susceptible to residual confounding ▪ Potential for misclassification of exposure status, including potential recall bias, which may lead to overestimation of measure of effect. However, recall bias is less likely for age at menarche since participants were unaware of the study hypothesis. Non-differential bias is therefore likely to have diluted results. ▪ Need to consider whether results are generalisable to other populations. Comments ▪ Primary aim was to assess the relationship between menstrual factors and breast cancer in African-American women. ▪ Cases and controls paid $25 to participate. Reported conclusions (by authors). African-American and Caucasian women may have different risk-factor profiles for breast cancer, based on the research showing that African-American women are more likely to develop breast cancer at a younger age and have more aggressive tumours. Our results suggest an inverse association between menstrual cycle length and post-menopausal breast cancer in African-American women.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Li et al. 2003b) USA	Case control study Level III-2.	Study setting. Population based case control study set in the Seattle-Puget Sound region. Evaluation of the effect of reproductive and anthropometric factors have on the risk of invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC). Sample Age at reference date (%): 65-69 yrs: cases 31, controls 33 70-74 yrs: cases 39, controls 38 75-79 yrs: cases 30, controls 29 First degree family history of breast cancer (%): cases 23, controls 17 Age at menarche (%): 8-11 yrs: cases 19, controls 17 12-13 yrs: cases 54, controls 52 14+ yrs: cases 27, controls 31 Nulliparous (%) cases 9, controls 9 BMI (kg/m^2) (%) <23.32: cases 22, controls 27 23.33-26.20: cases26, controls 25 26.21-30.11: cases 26, controls 24 30.12+: cases 26, controls 24.	Cases (n=975) Women aged 65-79 years with no previous history of *in situ* or invasive breast cancer who were diagnosed with invasive breast cancer between April 1, 1997 and May 31, 1999. Cases identified from the SEER program. Had to live in one of three stipulated counties and have a Health Care Financing Administration (HCFA) record. Controls (n=1,007) HCFA records used to identify female residents from the same three counties as the cases. Frequency matched to cases on age and country of residence. Data collection Tumour histology obtained from CSS. Subjects interviewed in person. Analysis Unconditional logistic regression used in assessment of all breast cancer cases. Comparison of invasive lobular breast cancer and invasive ductal carcinoma conducted using polytomous logistic regression.	<u>Age adjusted odds ratio by age at menarche (8-11 years as reference), (95% CI):</u> 12-13 years: OR 1.0 (0.8-1.2) 14+ years OR 0.8 (0.6-1.0)	Limitations ▪ 975 of 1,210 (81%) eligible cases were interviewed. ▪ 1,007 of 1,365 (74%) of eligible controls were interviewed. ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered. ▪ Histology was not independently reviewed which may have resulted in misclassification ▪ Small number of lobular carcinoma cases Comments ▪ Primary aim was to evaluate the association between combined estrogen-progestin HRT breast cancer type (invasive lobular breast carcinoma and invasive ductal carcinoma). Association between anthropometric factors to breast cancer type evaluated here. Reported conclusions (by authors). There were no statistical differences in risk between invasive lobular breast cancer and invasive ductal carcinoma in relation to anthropometric factors. Compared to lower height women, taller women had increased risks in both histologic types. Neither BMI nor weight was strongly related to invasive lobular carcinoma, but higher BMI and weight was related to greater invasive ductal carcinoma risk.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Wrensch et al. 2003) USA	Frequency matched case control study Level III-2	Study setting Residents of Marin County, California including women with breast cancer and controls identified through random digit dialling. Study sample Median age (years): cases 55 years, controls 55 years Family history of breast cancer (%): cases 19, controls 20 Benign biopsy history (%): cases 31, controls 27 Postmenopausal (%): cases 61, controls 66 Ever used OCs (%): cases 76, controls 85 Highest BMI after age 21 (kg/m^2) <25: cases 65%, controls 49% 25-<30: cases 23%, controls 29% 30+: cases 12%, controls 21%	Cases (n=285) Diagnosis of primary breast cancer between June 1997 and June 1999 if under 50 years and between July 1997 and June 1999 if 50+ years of age. Identified from NCCC cancer registry. Controls (n=286) Identified by random digit dialling and frequency matched to cases by age at diagnosis (±5 years). Data collection Full in-person interviews or abbreviated telephone interviews Analysis Logistic regression used.	<u>Adjusted odds ratio by age at menarche (15+ years as reference), (95% CI):</u> 12-14 years: OR 1.5 (0.74-3.1) ≤11 years: OR 1.2 (0.51-2.6) Adjusted for age, family history of breast cancer, benign biopsy history, previous radiation treatment, menopause status, reproductive history, OC use, HRT history, highest BMI, number of mammograms, socioeconomic status before age 21, highest degree obtained, religion in which raised, and alcohol and tobacco use.	Limitations ▪ Mixed methods of data collection (brief telephone interview used among women who did not wish to complete the long in-person interview). 5% of controls and 9% of cases completed the short interview. ▪ Among the group completing the full interview, complete data were available for 285 cases and 286 controls. The results presented in this table were restricted to these 285 cases and 286 controls. ▪ 50 of 401 eligible cases refused to take part (12%) ▪ 7 of 328 eligible controls refused to take part (2%) ▪ Case interviews conducted between Dec 1999 and Sept 2001 and control interviews between Apr 2000 and Sept 2001. ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered. Comments ▪ Examined recognised breast cancer risk factors and years of residence in Marin County, California, an area with high breast cancer incidence and mortality rates. Reported conclusions (by authors). Despite similar distributions of several known breast cancer risk factors, case control differences in alcohol consumption suggest that risk in this high risk population might be modifiable. Intensive study of this or other areas of similarly high incidence might reveal other important risk factors proximate to diagnosis.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Clavel-Chapelon and Group 2002) France	Cohort study Level III-2	Study setting Used data obtained from the E3N study – a prospective cohort study on cancer risk factors. Restricted to women who replied to a dietary questionnaire from the E3N cohort. Enrolled between 1990 and 1991. Study sample (n=91,260) Age (years): 40-45: 35% 45-50: 24% 50-55: 19% 55-60: 13% 60-65: 8% Number of years of education: <7: 5% 7-11: 8% 12-14: 47% 15-16: 17% 17+: 17%.	Inclusion criteria Part of E3N cohort. Replied to dietary questionnaire Aged 40-65 at baseline. Exclusion criteria Nil documented Data collection Self reported questionnaire with follow up questionnaires at approximately two year intervals until April 1997. Deaths detected by notification from family members or insurance company records and cause of death was obtained from the National Service on Causes of Death. Analysis Person time data contributed to time of diagnosis of breast cancer, date of death, date of last questionnaire returned or December 1997, whichever occurred first. Proportional hazard model fitted.	<u>Adjusted rate ratio by age at menarche (<12 years as reference), (95% CI):</u> 12 years: RR 0.97 (0.85-1.11) 13 years: RR 0.91 (0.79-1.04) 14 years: RR 0.89 (0.77-1.04) 15+ years: RR 0.84 (0.70-1.02) Trend (each additional year at menarche): RR 0.97 (0.93-0.99), $P < 0.05$. Adjusted for age at FFTP, number of full term pregnancies, number of spontaneous abortions, age, history of benign breast disease, family history of breast cancer, current BMI, ever married, educational level.	Limitations ▪ Potential misclassification of exposure status most likely to be non-differential – diluting any association. However, validation study showed high reproducibility for exposure data including age at menarche and number of live births ▪ Potential misclassification of outcome but magnitude is likely to be small ▪ Reference category of zero births included missing age of menarche status for 18 cases ▪ Observational study susceptible to residual confounding Comments ▪ Aim was to obtain a better understanding of the role of hormonal factors in breast cancer risk and to determine whether the effect of reproductive events differs according to age at diagnosis. ▪ Large sample Reported conclusions (by authors). Results suggest that reproductive events have complex effects on the risk of breast cancer.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Gammon et al. 2002) USA	Case control study. Level III-2.	Study setting. Long Island Breast Cancer Study Project. Population based study. Sample Median age group at reference (years): cases 55-64, controls 55-64 Median age at menarche (years): cases 12, controls 12 Nulliparous (%): cases 13, controls 11 Median BMI (kg/m2) at reference: cases 25.2-29.2, controls 22.3-25.1 Never smoked (%): cases 44.8, controls 45.0 Family history of breast cancer (%): cases 19.2, controls 13.0	Cases (n=1,508) Newly diagnosed with a first primary *in situ* or invasive breast cancer between August 1996 and July 1997, confirmed by physician and medical record who were resident of Nassau and Suffolk, New York at the time of diagnosis. Able to speak English. Controls (n=1,556) Current residents of Nassau and Suffolk Counties who spoke English, who did not have a personal history of breast cancer, and who were frequency matched to the expected distribution of case women by 5 year age group. Random digit dialling used to identify controls. Data collection Self-report, blood and urine sample (collected prior to chemotherapy) and environmental home data (dust, water and soil). Analysis Unconditional logistic regression. Likelihood ratio test used to assist fitting the model.	<u>Age adjusted odds ratio by age at menarche (<12 years as reference), (95% CI):</u> 12 years: OR 1.16 (0.95-1.41) 13 years: OR 1.17 (0.96-1.43) 14+ years: OR 0.94 (0.7-1.16)	Limitations ▪ 2,271 women with breast cancer were initially identified as potentially eligible, 2,030 of these were identified by the physician as likely to be eligible and consent was obtained in 1,837 (90.5%). The main questionnaire was completed by 1,508 eligible cases (82%). ▪ Response rate to the telephone screener (controls) was 78%. Known response rate among controls under 65 years was 58% (unknown for the 65+ group). The main questionnaire was completed by 1,556 eligible cases (63%). ▪ >97% of residents in the study region are English speaking. ▪ Cases included both invasive and *in situ* disease. ▪ Recall bias needs to be considered. ▪ Observational study susceptible to residual confounding. Results limited to age adjusted estimate. ▪ Comments ▪ Aim was to determine whether breast cancer risk among women in the counties of Nassau and Suffolk, New York is associated with selected environmental exposures. ▪ Study conducted in the region due to high incidence of breast cancer and concern about effects of environmental contaminants such as DDT. ▪ Lab personnel blinded to case/control status. ▪ Reported conclusions (by authors). ▪ Established risk factors for breast cancer that were found to increase risk among Long Island women include lower parity, late age at first birth, little or no breast feeding and family history of breast cancer. ▪ Other conclusions of less relevance to this review topic were also presented.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Kuru et al. 2002) Turkey	Case control study Level III-2	Study setting. Hospital based case control study Sample Mean age (years): cases 49.4, controls 46.4, *P*<0.001 Age <15 yrs at menarche (%): cases 76, controls 65, *P*<0.01 Nulliparous (%): cases 12, controls 5, *P*=0.75 Positive family history (%): cases 6, controls 2, *P*=0.005	Cases (n=504) All women admitted to surgical clinics of Ankara Oncology Education and Research Hospital with histologically proven breast cancer and resident in Ankara or five other regions of Turkey. Controls (n=610) Women residing in the same geographical areas as the cases and admitted to the wards or outpatient clinics of the same hospital during the same interval. Exclusions: women with malignant, endocrine or gynaecological disease. Data collection Collected through questionnaires and interview Analysis Unconditional logistic regression used.	<u>Adjusted odds ratio by age at menarche (15+ years as reference), (95% CI):</u> <15 years: OR 1.72 (1.30-2.28) Adjusted for age, residence, menstrual irregularity, parity, age at first pregnancy, breast feeding, OC use, family history, BMI, education, previous benign breast biopsy, menopausal status and age at menopause.	Limitations ▪ Twelve potential cases and 26 potential controls were excluded due to inability to recall age at menarche/menopause (2% of potential cases, 4% of potential controls). ▪ Recall bias needs to be considered. ▪ Observational study susceptible to residual confounding. ▪ Controls may not be representative of the population from which the cases were selected. Hospital based population used. Comments ▪ Study aim was to identify risk factors for breast cancer in Turkey ▪ None of the participants refused interview Reported conclusions (by authors). The results of the present study will lead to a better understanding of the risk factors for breast cancer in a developing country.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Tryggvadottir et al. 2002) Iceland	Nested, matched case control study Level III-2.	Study setting. Sample selected from a population based cancer registry (80,219 women attending breast and cervical screening during 1979-1995). Women were aged 20-81 years at the time of attending. Termed the CDC cohort. Sample <40years Age at menarche <13 (%): cases 45, controls 32 Nulliparous (%): cases 13, controls 12 Height (%): ≤160cm: cases 13, controls 15 161-169cm: cases 58, controls 56 170+cm: cases 29, controls 29 Weight (%): ≤60kg: cases 42, controls 43 61-79kg: cases 46, controls 48 80+kg: cases 11, controls 8 40-55 years Age at menarche <13 (%): cases 32, controls 28 Nulliparous (%): cases 8, controls 5 Height (%): ≤160cm: cases 17, controls 20 161-169cm: cases 59, controls 58 170+cm: cases 24, controls 22 Weight (%): ≤60kg: cases 29, controls 28 61-79kg: cases 55, controls 57 80+kg: cases 16, controls 15	Cases (n=1,120) First invasive breast cancer diagnosed between 1979-1995 identified in the Cancer Registry of Iceland. Controls (n=10,537) Sought 10 controls per case matched on birth year and age when giving information. Alive at least until the diagnosis year of the matched case. Data collection Only answers given before the diagnosis of a first breast cancer were used. Self reported data examining reproductive and menstrual risk factors were included. Analysis Study group stratified according to age of diagnosis of cases (<40, 40-55 and >55 years). Conditional multiple logistic regression was applied.	<u>Adjusted odds ratio by age at menarche (per unit change), (95% CI):</u> OR 0.91 (0.87-0.96) Adjusted for parous status, age at first birth, number of births, OC use, lactation, height and weight.	Limitations ▪ Record linkage of the Cancer Registry of Iceland and CDC databank identified 85% of those in the CDC databank. ▪ 70% of the 1,601 cases were included in the analysis. ▪ Self reported data may be subject to misclassification. However, this is likely to be small and non-differential, resulting in dilution of relative risk estimates. ▪ Observational study susceptible to residual confounding. Comments ▪ Primary aim was to explore the relationship between breast cancer and established risk factors by specific age groups of diagnosis of breast cancer. ▪ Most of the data were collected from women attending cervical screening rather than mammography. ▪ Only answers given before the diagnosis of a first breast cancer were used. Reported conclusions (by authors). The results confirm that age at diagnosis should be taken into account when studying the effects of breast cancer risk factors.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Butler et al. 2000) USA	Case control study Level III-2	Study setting Population based study set in Atlanta, Georgia; Seattle, Washington and five counties of New Jersey. Restricted to women aged under 45 years. Study sample Age at menarche (mean years): cases 12.4, controls 12.5 Cycle length (mean days): cases 28.1, controls 28.3 Mean days of flow: cases 5.2, controls 5.1 Regular cycles (%): cases 94.7, controls 91.7	Cases (n=1,647) *in situ* or invasive breast cancer diagnosed between May 1990 and December 1992. Cases identified through frequent monitoring of admission, surgery and pathology records and cancer registries. Controls (n=1,505) Identified through random digit dialling. Controls randomly selected in a manner that ensured frequency matching by geographic area and expected age distribution of cases. Data collection Face to face interviews. Analysis Logistic regression used.	<u>Adjusted odds ratio by age at menarche (15+ years as reference), (95% CI):</u> 14 years: OR 1.2 (0.8-1.7) 13 years: OR 1.4 (1.0-1.5) 12 years: OR 1.5 (1.1-1.9) 11 years: OR 1.1 (0.9-1.5) ≤ 10 years: OR 1.2 (0.9-1.7) Adjusted for age, study site, race, combined age at first full-term pregnancy and parity, and family history of breast cancer.	Limitations ▪ Included *in situ* and invasive disease. ▪ Random digit dialling for control selection: only phoned numbers assumed to be residential. 90.5% response rate to the telephone screener. ▪ Completed interviews obtained from 2,203 of 2,551 eligible cases (86%) and 2,009 of 2,571 eligible controls (78%). Effective control response after allowing for telephone screening non response was 73%. ▪ Controls selected may not be representative of the total control population or of the population from which the cases were selected. ▪ Observational study susceptible to residual confounding ▪ Case control design susceptible to recall bias, potentially overestimating associations with breast cancer risk. Comments ▪ Primary objective was to investigate the effect of menstrual cycle characteristics on risk of breast cancer Reported conclusions (by authors). Findings suggest that future studies should focus on clarifying how the interrelated effects of body size and menstrual factors, such as age at menarche and cycle regularity, contribute to breast cancer aetiology.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Gao et al. 2000) China	Population based, frequency matched, case control study Level III-2	Study setting Data analysed from the Shanghai Breast Cancer Study – a study conducted amongst Chinese women in urban Shanghai. New cases between 1996 and 1998. Study sample Age (years): 25-34: cases 3%, controls 5% 35-44: cases 36%, controls 36% 45-54: cases 39%, controls 33% 55-64: cases 23%, controls 25% Family history of breast cancer (%): cases 4, controls 2 BMI (kg/m^2) ≤20.70: cases 20%, controls 24% 20.71-22.79: cases 24%, controls 25% 22.80-25.20: cases 27%, controls 25% >25.10: cases 29%, controls 25% Ever consumed alcohol (%): cases 4, controls 4 Ever used OC (%): cases 22, controls 21 Ever used HRT (%): cases 3, controls 3	Study population Permanent residents of Shanghai with no past history of cancer. Alive at the time of interview. Cases (n=1,459) Newly diagnosed breast cancer between 25 and 64 years. Cases identified through a rapid case ascertainment system, supplemented by the population based cancer registry. Controls (n=1,556) Randomly selected from the study population and frequency matched to cases by age (5 year intervals). The Shanghai Resident Registry was used as the sampling frame. Data collection Face to face interview by trained interviewers using a structured questionnaire Analysis Unconditional logistic regression	<u>Adjusted odds ratio by age at menarche (≤12 years as reference), (95% CI):</u> 13 years: OR 1.2 (0.9-1.6) 14 years: OR 0.9 (0.7-1.2) 15 years: OR 1.0 (0.7-1.3) 16 years: OR 0.8 (0.6-1.1) 17+ years: OR 0.7 (0.5-0.9) *P*trend < 0.01 Adjusted for age, education, family history of breast cancer, history of breast fibroadenoma, waist to hip ratio, ever having had a live birth, age at first live birth, and physical activity.	Limitations ▪ 1,459 of 1,602 eligible cases were interviewed (91%) ▪ 1,556 of 1,724 eligible controls were interviewed (90%) ▪ Observational study susceptible to residual confounding ▪ Case control design susceptible to recall bias, potentially overestimating associations with breast cancer risk. Comments ▪ Aimed to evaluate the association of menstrual and reproductive risk factors with breast cancer risk. Reported conclusions (by authors). Study suggests that the changes in menstrual and reproductive patterns among women in Shanghai have contributed to the recent increase in breast cancer incidence, particularly among younger women.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Berkey et al. 1999) USA	Cohort study Level III-2	Study setting Participants from the Nurses' Health Study. Study established in 1976 (121,701 participants) with follow-up data collection every 2 years thereafter. This study used data collected through 1992. Sample (n=65,140) Mean age at menarche 12.5 years Mean adult height 64.6 inches Mean age 5 body fat (9 point scale with 9 being most fat): 2.25 Mean age 10 body fat (9 point scale with 9 being most fat): 2.54 Mean age 20 body fat (9 point scale with 9 being most fat): 2.86 Mean peak height velocity 8.28 cm/yr.	Inclusion criteria Participation in Nurses' Health Study. Exclusion criteria Breast cancer diagnosed before 1976. Data collection Data collected from Nurses' Health Study at baseline and the 1988 questionnaire were used. Estimated peak height velocity from a model developed in the Harvard Longitudinal Studies of Child Health and Development. Outcome measures Self-reported breast carcinoma. Analysis Cox proportional hazards model used.	<u>Adjusted rate ratio by age at menarche (≤11 years as reference):</u> 12 years: RR 0.82 13 years: RR 0.85 14 years: RR 0.78 15+years: RR 0.52 (*P* <0.05 compared with reference) *P*trend 0.001 Adjusted for age in1976, adult height, body fatness at ages 5, 10 and 20 years, maternal body fatness, family history, drinking (ages 18-22), adolescent and maternal smoking, family SES, adolescent benign breast disease.	Limitations ▪ Adolescent growth estimated from a model developed in another longitudinal study ▪ Pathology reports obtained in 96% of women with self-reported breast carcinoma, and the reports confirmed the breast cancer in 99.4%. ▪ Final analysis included 65,140 women (54% of original cohort). Losses due to missing data, previous history of breast cancer and race not described as white. ▪ Observational study susceptible to residual confounding. ▪ Potential selection bias due to high non-participation ▪ Potential exposure misclassification given retrospective nature of classification. Most likely to be non-differential given recall before diagnosis of breast cancer, so estimates are likely to have been diluted. Comments ▪ Primary aim was to examine the effect of early life factors on breast cancer risk ▪ The model used for estimating peak height velocity included age at menarche, body fatness at age 10 and adult height. Reported conclusions (by authors). Earlier menarche, extremely lean body mass at age 10 years, and taller adult height were predictive of elevated breast carcinoma risk. The same three factors were also predictive of higher peak growth velocities during adolescence, lending credence to the hypothesis that more rapid adolescent growth may increase the risk of breast carcinoma development.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Magnusson et al. 1999) Sweden	Case control study Level III-2.	Study setting Population based case-control study Study sample Mean age (years): cases 62.6, controls 63.7 Mean age at menarche (years): cases 13.5, controls 13.6 Mean age at menopause (years): cases 50.5, controls 50.0 Mean parity: cases 1.8, controls 2.1 Mean age at first birth (years): cases 25.3, controls 24.6 Mean recent BMI (kg/m^2): cases 25.7, controls 25.5 Mean BMI at age 18 (kg/m^2): cases 20.6, controls 20.8 Family history of breast cancer (%): cases 16.0, controls 9.2 Benign breast disease (%): cases 13.8, controls 9.6	Cases (n= 3,016) Women aged 50-74 years with invasive breast cancer, without previously diagnosed breast cancer, born in Sweden and resident there between October 1993 and March 1995. Incident cases identified through six regional cancer registries. Women of unknown menopausal status or previous diagnosis of invasive cancer (other than non-melanoma skin cancer) were excluded. Controls (n=3,263) Women frequency matched to the expected age distribution of the cases randomly selected from a continuously updated register of all people residing in Sweden. Women of unknown menopausal status or previous diagnosis of invasive cancer (other than non-melanoma skin cancer) were excluded. Data collection Mailed questionnaires and telephone interviews used. Telephone interviews were restricted to 11% of controls who failed to return the mailed questionnaire. Analysis Unconditional logistic regression used.	<u>Adjusted odds ratio by age at menarche (13-14 years as reference), (95% CI):</u> ≤11 years: OR 1.33 (1.06-1.67) 12 years: OR 1.00 (0.86-1.17) 15-16 years: OR 1.00 (0.87-1.15) 17+ years: OR 0.74 (0.54-1.03) *P*trend 0.02 Estimates adjusted for age, parity, age at first birth, menopausal status, age at menopause, height, BMI one year prior to data collection and use of HRT for at least one year.	Limitations ▪ 16% of eligible cases and 18% of eligible controls did not participate in the study ▪ Mixed methods of data collection, including the use of telephone interviews in a proportion of controls, may have resulted in bias ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered ▪ Note reference for age at menarche was 13-14 years rather than the youngest or oldest group. Comments ▪ Aimed to examine whether age at menarche is causally involved in breast cancer aetiology or serves as a correlate of other early life exposures. Other aspects of reproductive life, including cycle length and regularity, climacteric symptoms, reproductive history and oral contraceptive use were also examined. ▪ Study restricted to women aged 50 to 74 years. Reported conclusions (by authors). Findings provide some evidence of a role of environmental correlates of early menarche in breast cancer aetiology, and underline the importance of childbirth, especially early in life, in the prevention of breast cancer. Our data are not readily compatible with an important influence of former oral contraceptive use on post-menopausal breast cancer risk.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Tavani et al. 1999) Italy	Case control study Level III-2.	Study setting. Data derived from two case-control studies of breast cancer: 1. greater Milan area between 1983 and 1991 2. six areas of Italy between 1991 and 1994. Hospital based controls used. Less that 4% of cases and controls refused interview, on average. Overall dataset (including women 40+ years) included 5,984 cases and 5,504 controls Sample Age: < 25 years: cases 2%, controls 7% 25-29 years: cases 10%, controls 15% 30-34 years: cases 27%, controls 28% 35-39 years: cases 61%, controls 49% Education < 9 years: cases 43%, controls 52% 9-13 years: cases 37%, controls 35% 13 years: cases 21%, controls 13% Family history of breast cancer: cases 8%, controls 4% History of benign breast disease: cases 15%, controls 8%	Cases (n=579) Histologically confirmed incident breast cancer admitted to the major teaching and general hospitals in the areas under surveillance Controls (n=668) Acute hospital admissions (to the same network of hospitals as the cases) for non-neoplastic, non-hormone-related diseases. Data collection Questionnaire administered by centrally trained interviewers. Included information on demographic and lifestyle characteristics. Analysis Unconditional multiple logistic regression used.	<u>Adjusted odds ratio by age at menarche (<12 years as reference), (95% CI):</u> 12 years: OR 0.85 (0.61-1.18) 13 years: OR 0.79 (0.56-1.10) 14 years: OR 0.89 (0.61-1.31) 15+ years: OR 0.53 (0.31-0.89) *P*trend 0.06 Adjusted for study, centre, year of recruitment, age, education, BMI, family history of breast cancer, parity and age at first birth.	Limitations ▪ Hospital based controls may not be representative of the population from which the cases were drawn ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered. Comments ▪ Aimed to investigate the relationship between hormonal and lifestyle risk factors and breast cancer risk in women younger than 40 years ▪ Good participation rate in the two case-control studies from which the current dataset were derived. Reported conclusions (by authors). Most risk factors in this large dataset of women aged less than 40 years were similar to those described in breast cancer epidemiology at any age.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Tung et al. 1999) Japan	Case control study Level III-2	Study setting Hospital based case control study Study sample Mean age (years): cases 51.6, controls 54.5 BMI (kg/m^2) ≤20.0: cases 19%, controls 24% 20.1-23.0: cases 30%, controls 25% 23.1-25.0: cases 22%, controls 26% 25.1+: cases 30%, controls 25% Non-smoker (%): cases 82, controls 78 Non-drinker (%): cases 62, controls 65 Family history of breast cancer (%): cases 9, controls 4	Cases (n=376) Newly diagnosed breast cancer between 1990 and 1995. Identified using hospital based cancer registry. Controls (n=430) Admitted during the same period as the cases. No diagnosis of cancer. Data collection Self administered questionnaire. Analysis Logistic regression used.	<u>Adjusted odds ratio by age at menarche (16+ years as reference), (95% CI):</u> 14-15 years: OR 1.75 (1.18-2.70) ≤13 years: OR 1.85 (1.82-2.78) Results for multivariate model but variables included in the model were unclear.	Limitations ▪ 376 of 808 breast cancer patients participated– questionnaire was not delivered due to clerical reasons in some cases and others were not included as the feasibility of the questionnaire was being assessed. A significant selection bias may have resulted. ▪ Hospital based controls may not be representative of the population from which the cases were drawn ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered. Comments ▪ Aimed to evaluate the roles of anthropometric and reproductive factors in the aetiology of breast cancer in Osaka, Japan Reported conclusions (by authors). Results were consistent with findings observed in western countries.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Garland et al. 1998) USA	Cohort study Level III-2	Study setting Part of the Nurses' Health Study II (NHS II). Female registered nurses were aged 25-42 years and living in 14 US states at enrolment in 1989. Study sample (396,299 person-years follow up, 251 cases of breast cancer). Mean age 34 years	Inclusion criteria Enrolled in NHS II Exclusion criteria Cancer at enrolment (not including nonmelanoma skin cancer, hydatidiform mole or cervical cancer). Data collection Postal questionnaire at baseline and every two years. Deaths are reported by family members, the postal service and search of the National Death Index. Analysis Person-time was contributed until the earliest of diagnosis of breast cancer, death, loss to follow-up, or June 1 1993. Proportional hazards model used.	<u>Adjusted rate ratio by age at menarche (<12 years as reference), (95% CI):</u> 12 years: RR 0.79 (0.57-1.10) 13 years: RR 0.74 (0.53-1.03) >13 years: RR 0.66 (0.44-0.99) *P*trend 0.03 Adjusted for age, alcohol intake, history of benign breast disease, family history of breast cancer, quintiles of current BMI, parity, age at FFTP, menopausal status, and duration of OC use.	Limitations ▪ Response rate to questionnaire amongst living participants was 93% in 1991 and 92% in 1993. ▪ Breast cancer confirmation by pathology report check was available in 90% of cases. Confirmation of the self-report was achieved in 98% of these cases. ▪ 28 cases were based on self-report only. Exclusion of these cases led to slight attenuation of the association between age at menarche and breast cancer risk. ▪ Observational study susceptible to residual confounding ▪ Potential misclassification of exposure status most likely to be non-differential – diluting any association. Comments ▪ Primary aim of this report was to examine menstrual cycle characteristics and ovulatory infertility in relation to breast cancer risk. Reported conclusions (by authors). Results are consistent with the hypothesis that reduced exposure to ovulatory menstrual cycles provides a protective effect against breast cancer.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Ghadirian et al. 1998) Canada	Frequency matched, case control study Level III-2	Study setting Population based case control study of French Canadians in Montreal. Study sample BMI 1 year ago (kg/m^2): <22.3: Cases 35%, controls 32% 22.3-25.7: cases 32%, controls 34% >25.7: cases 33%, controls 34% Ever smoked cigarettes (%): cases 47, controls 53	Cases (n=414) New cases of histologically diagnosed breast cancer in women aged 35-79 years. Attending physician/surgeon provided permission for inclusion. Controls (n=429) Used modified random digit dialling to identify controls. Frequency matched to cases on age (±5 years) and place of residence. Data collection Face to face interview using standardised questionnaire by trained interviewers. Analysis Unconditional logistic regression used.	<u>Adjusted odds ratio by age at menarche (<12 years as reference), (95% CI):</u> 12-13: OR 0.93 (0.65-1.33) 13+: OR 0.81 (0.55-1.21) Adjusted for age, marital status, parity, age at FFTP, history of benign breast disease, family history of breast and ovarian cancers, personal income.	Limitations ▪ Participation rate of 77% among the cases ▪ Participation rate amongst the eligible controls 33%. ▪ Observational study susceptible to residual confounding ▪ Case control design susceptible to recall bias, potentially overestimating associations with breast cancer risk. Comments ▪ Investigated the relationship between sociodemographic characteristics, lifestyle, family history of cancer, medical history, and reproductive factors and breast cancer. ▪ Study conducted in parallel with studies of colon and prostate cancer. Reported conclusions (by authors). This study confirms the risk factors of late age at FFTP, nulliparity, late age at menopause, and positive family history of breast cancer in the aetiology of this disease.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(McCredie et al. 1998a) New Zealand	Population based case control study Level III-2	Study setting. Population based case control study Sample Median age group: cases 45-49, controls 40-44. Maori ethnicity (%): cases 7, controls 5 Age at menarche (%) < 12 years: cases 17, controls 16 12-14 years: cases 66, controls 68 15+ years: cases 16, controls 16 Nulliparous (%): cases 11, controls 11 Premenopausal (%): cases 68, controls 77 History of surgery for benign breast disease (%): cases 13, controls 7 Family history of breast cancer in first degree relative (%): cases 11, controls 7.	Study population Selected from women whose names were in a current electoral roll and whose telephone number could be found. Cases (n=891) First diagnosis of breast cancer identified from the National Cancer Registry and the Auckland Breast Cancer Study Group. Women aged 25-54 years Histologically confirmed breast cancer diagnosed between July 1983 and June 1987. Exclusions: previous diagnosis of breast cancer Controls (n=1,864) Random selection from electoral roll. Age 25-54 years. Randomly excluded half the potential controls aged under 35 to approximate more closely the age distribution of the cases. Reference date calculated by subtracting six months from the date of interview. Data collection Telephone interview. Two nurse interviewers were used. Most began with the interviewer being blind to case status but case status was disclosed as the interview progressed. Analysis Logistic regression used.	<u>Adjusted odds ratio by age at menarche (<12 years as reference), (95% CI):</u> 12 years: OR 0.93 (0.7-1.2) 13 years: OR 0.80 (0.6-1.0) 14 years: OR 0.80 (0.6-1.1) 15+ years: OR 0.79 (0.6-1.1) *P*trend 0.06 Adjusted for age, ethnicity, parity, age at FFTP, duration of breast feeding, menopausal status, family history and previous surgery for benign breast disease.	Limitations ▪ 891 of 1,126 (79%) eligible cases participated. ▪ Participation rate among controls cannot be estimated absolutely due to lack of age data in electoral rolls. However, 15.5% of the group selected from the electoral roll did not participate due to being untraceable, language difficulties, absence overseas, refused participation, illness or death. ▪ Inability to blind interviewers to case status but most interviewers were blind to case status at the beginning of data collection. ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered. Comments ▪ Aimed to assess the influence on breast cancer risk of reproductive factors and the possibility of an interaction with age at diagnosis ▪ Like a nested study set within the total NZ population – which should reduce risk of selection bias. Reported conclusions (by authors). The relationships between reproductive risk factors and age and a women's risk of breast cancer are clearly complex and not yet fully understood. Unravelling these relationships should help to elucidate the pathogenesis of breast cancer. Other investigators could contribute by performing more searching analyses of data that have already been collected as well as by conducting further analyses.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Rockhill et al. 1998) USA	Case control Study Level III-2	Study setting Used data from the Carolina Breast Cancer Study, a population based case control study. Study sample Age (years): 20-29: cases 2%, controls 1% 30-39: cases 17%, controls 12% 40-49: cases 41%, controls 40% 50-59: cases 16%, controls 18% 60-69: cases 18%, controls 21% 70-74: cases 7%, controls 9% History of breast cancer in mother/sister (%): cases 15, controls 11 Ever had benign breast biopsy (%): cases 17, controls 17	Study population Women aged 20-74 years residing in central and eastern North Carolina. Cases (n=830) Invasive breast cancer diagnosed between May 1993 and June 1996. Controls (n=758) Sampled from the North Carolina Division of Motor Vehicles Roster of licensed drivers or holders of personal identification cards (<65 years), and from US Health Care Financing Administration files (65-74 years). Randomised recruitment design used that ensured approximately equal numbers across strata of case status, race, and five year age group. Data collection Interviews conducted. Analysis Unconditional logistic regression used	<u>Adjusted odds ratio by age at menarche (14+ years as reference), (95% CI):</u> 13 years: OR 1.3 (1.0-1.7) 12 years: OR 1.2 (0.9-1.6) 11 years: OR 1.3 (1.0-1.9) < 11 years: OR 1.4 (0.9-2.1) Adjusted for 5 year age group, race, family history of breast cancer, history of benign breast biopsy, age at FFTP.	Limitations ▪ 77% of eligible cases and 68% of eligible controls completed interviews. Further exclusions due to incomplete data resulted in final participation rates of 72% (cases) and 61% (controls). ▪ Control population may not be representative of the population from which the cases were derived ▪ Recall bias needs to be considered. Such bias may have overestimated degree of association with breast cancer risk. ▪ Non-differential misclassification of age at menarche may also have occurred resulting in dilution of effect. ▪ Observational study susceptible to residual confounding. Comments ▪ Aimed to evaluate the relationship between risk of breast cancer and both age at menarche and time until onset of regular cycles. Reported conclusions (by authors). Given the inconsistent findings regarding the links between menstrual cycle characteristics and breast cancer, and recent recommendations to delay menarche and alter the patterns of cycles of young women in order to reduce breast cancer risk, this topic calls for further, innovative study.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Goodman et al. 1997) Japan	Prospective cohort study Level III-2	Study setting Set within the Life Span Study (LSS) (Hiroshima and Nagasaki) which analysed the effects of exposure to atomic bomb radiation. Study sample (total cohort 22,200; 161 cases identified during follow up) Age (years): < 50: 30% 50-59: 29% 60-69: 19% 70-79: 16% 80+: 6% Age at time of bombing (years) <15: 32% 15+: 68% Breast dose (Gy) None: 34% <0.061: 35% 0.061-0.300: 18% 0.301+: 13%	Inclusion criteria Within the LSS cohort who were sent a non-radiation questionnaire Exclusion criteria Subjects with unknown A-bomb atomic radiation dose Diagnosed with breast cancer before the survey. Permanent residents outside the catchment area (applied to incident cases). Data collection Completed a mail questionnaire between 1979 and 1981 to study nonradiation risk factors. Primary breast cancer cases were identified from the population based cancer registries. Analysis Average follow up 8.31 years. Follow-up continued to the earliest of diagnosis of first primary breast cancer, death or December 31, 1989.Poisson regression used.	<u>Adjusted rate ratio by age at menarche (16+ years as reference), (95% CI):</u> < 14 years: RR 1.92 (1.20-3.06) 14 years: RR 1.58 (0.99-2.52) 15 years: RR 1.47 (0.90-2.38) *P*trend 0.006 Adjusted for city, attained age, age at time of bombings and radiation dose to the breast.	Limitations ▪ 24,996 of 34,421 women responded to the mail questionnaire (73%). ▪ May have been a selection bias resulting from unclear permanent residence status in the study population that did not develop breast cancer ▪ Potential information bias related to outcome with histological confirmation identified in 98% of cases. ▪ Potential for incorrect classification of follow up time as the date of receipt of questionnaire responses was not recorded (it was assumed all were received on February 1, 1981). ▪ Used self-report data. Potential to result in non-differential misclassification, resulting in dilution of level of effect. ▪ Observational study susceptible to residual confounding Comments ▪ Analysed data from the Life Span cohort to identify nonradiation risk factors for breast cancer and to determine whether these factors were independent of the effects of radiation on breast cancer occurrence Reported conclusions (by authors). Nonradiation risk factors for breast cancer among Japanese atomic bomb survivors were consistent with those identified among other populations of women, although the prevalence of common risk factors was low. Reproductive factors and hormonal use appear to act independently of radiation exposure on the risk of breast cancer among this population.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Minami et al. 1997) Japan	Matched, case control study Level III-2	Study setting Case control study of screen detected breast cancer in Miyagi Prefecture, Japan. 201,363 participants in the breast screening program. Study sample Mean age: cases 52.6 years, controls 52.6 years	Cases (n=204) Diagnosis of breast cancer Controls (n=810) Four controls matched to cases on screening year, age (±2 years) and screening area. Data collection Obtained from medical records taken at screening. Analysis Conditional logistic regression used.	<u>Adjusted odds ratio by age at menarche (≤13 years as reference), (95% CI):</u> 14 years: OR 0.93 (0.59-1.47) 15 years: OR 1.08 (0.67-1.72) 16+ years: OR 0.67 (0.40-1.12) *P*trend 0.21 Adjusted for number of parities, history of benign breast disease and family history of breast cancer	Limitations ▪ Basis of breast cancer diagnosis unclear ▪ Observational study susceptible to residual confounding ▪ Misclassification of exposure information is likely to be small in magnitude and non-differential – leading to dilution of the measure of effect. Comments ▪ Study aimed to investigate the associations between reproductive history and risk of breast cancer among participants of a breast screening program. ▪ Study like a nested case-control design which reduces the risk of selection bias ▪ Prospective collection of data excludes risk of recall bias Reported conclusions (by authors). The results by age group suggest that different mechanisms may exist in breast cancer developing at early and late onset.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Yang et al. 1997) Taiwan	Case control study Level III-2	Study setting Case control study using outpatient attendees as controls (1993-1994). Study sample First degree relative with breast cancer (%): cases 8, controls 2 Previous breast biopsy or operation (%): cases 5, controls 5 Smoking history (%): cases 5, controls 2 Use of OCs (%): cases 27, controls 22 BMI (kg/m^2) < 25: cases 70%, controls 80%	Cases (n=244) Pathologically confirmed breast cancer (age range 20-80 years) Randomly selected from all subjects with breast cancer during the study period. Controls (n=450) Randomly selected from female ophthalmology outpatient attendees Data collection Interview conducted by two experienced nurses using a structured questionnaire Analysis Logistic regression used	<u>Adjusted odds ratio by age at menarche (<13 years as reference), (95% CI):</u> 13+: OR 1.20 (0.87-1.65) Adjusted for menopausal status, family history of breast cancer, previous breast biopsy or operation, smoking history, menses history, regular menstrual cycle, breast feeding, number of full term pregnancies, BMI, age at FFTP, ever use of OCs, history of abortion.	Limitations ▪ Outpatient based controls may not be representative of the population from which the cases were drawn ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered. ▪ 2% refused to participate in the study. ▪ Interviewers were not blinded to case status but multiple efforts were made to minimise interviewer bias (including standardisation of questions and assessment of consistency of responses). Comments ▪ Aimed to investigate risk factors for breast cancer in Taiwan. ▪ Cases selected represented 30% of all women diagnosed with breast cancer during the study period (controls represented 20%). Reported conclusions (by authors). Univariate and multivariate logistic regression suggests that breast cancer in Taiwan is aetiologically similar to breast cancer in moderate to high incidence areas.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Ramon et al. 1996) Spain	Matched case control study Level III-2	Study setting Case control study using both hospital and community controls. Study sample Age (years) <35: cases 4%, hosp ctrl 3%, comm ctrl 4% 35-45: cases 20%, hosp ctrl 20%, comm ctrl 22% 46-55: cases 13%, hosp ctrl 15%, comm ctrl 13% 56-65: cases 34%, hosp ctrl 33%, comm ctrl 32% 66-75: cases 21%, hosp ctrl 19%, comm ctrl 20% >75: cases 9%, hosp ctrl 10%, comm ctrl 10% Education (years) <7: cases 61%, hosp ctrl 66%, comm ctrl 60% 7-11: cases 29%, hosp ctrl 30%, comm ctrl 34% >11: cases 10%, hosp ctrl 4%, comm ctrl 7%	Cases (n=184) Histologically confirmed incident cases of breast cancer diagnosed between 1989 and 1992. Aged 30+ years No previous history of cancer Cases identified through surgical and pathology records Controls (n=368) Matched by age and residence to cases. 184 hospitalised patients 184 community controls Community controls selected by random digit dialling (selected from the same geographic region as the corresponding case) Hospitalised controls excluded patients with cancer, benign breast disease, and other diseases associated with factors under study. Controls were matched on age (±5 years) and residence. Data collection Face to face interview using a structured questionnaire. Analysis Logistic regression used	<u>Age adjusted odds ratio by age at menarche (<12 years as reference), (95% CI):</u> 12-14: OR 0.74 (0.46-1.18) >14: OR 1.07 (0.72-1.62)	Limitations ▪ Control population may not be representative of the population from which the cases were derived (mix of hospital based and community controls used) ▪ Potential for recall bias. ▪ Observational study susceptible to residual confounding. Measure of effect only adjusted for age. ▪ No documentation of participation rates in cases and controls. Comments ▪ Carried out to assess associations between parity, lactation and age at FFTP and breast cancer Reported conclusions (by authors). Study indicates that parity is an independent risk factor associated to breast cancer and that the women with a late age at first full term pregnancy constitute a high risk group.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Suh et al. 1996) Korea	Case control study Level III-2	Study setting Case control study utilising both hospital and community based controls. Study sample Age at interview (years) 30-34: all three groups 5% 35-39: all three groups 14% 40-44: all three groups 24% 45-49: all three groups 22% 50-54: all three groups 13% 55-59: all three groups 12% 60-64: all three groups 7% 65+: all three groups 3% Occupation: Housewife: cases 72%, hosp controls 77%, comm. controls 53% Educational attainment below high school: cases 71%, hosp controls 85%, comm. controls 85% BMI (kg/m^2) <20.0: cases 15%, hosp controls 15 %, comm. controls 10 % 20.0-22.4: cases 29%, hosp controls 30%, comm. controls 20% 22.5-24.9: cases 26%, hosp controls 30%, comm. controls 26 25.0+: cases 30%, hosp controls 25%, comm. controls 44%	Cases (n=190) Histologically diagnosed incident breast cancer between Jan 1993 and June 1994. Controls (n=380) Two groups of controls were used: (1) 190 cancer free women undergoing gynaecological examination at the same hospital as the cases, (2) 190 women recruited for a diabetes prevalence survey from the community. Both control groups were frequency matched on age (5 year intervals). Exclusions from control groups: history of malignancy, TB, thyroid disease, diabetes, history of hysterectomy or oophorectomy, postmenopausal due to surgical or drug induced reason and women with missing information. Data collection Face to face interview by trained interviewers. Analysis Unconditional logistic regression used.	<u>Adjusted odds ratio by age at menarche (≤14 years as reference), (95% CI):</u> 1. Hospital controls 15-16 years: OR 0.83 (0.49-1.38) 17+ years: OR 0.61 (0.33-1.11) *P*trend > 0.05 2. Community controls 15-16 years: OR 0.31 (0.17-0.56) 17+ years: OR 0.16 (0.08-0.31) Ptrend <0.01 Results adjusted for age at interview, occupation, educational attainments, family history of breast cancer, past history of benign breast disease, BMI, history of ever had a full term pregnancy.	Limitations ▪ Control population may not be representative of the population from which the cases were derived (mixture of hospital and community based controls used) ▪ Participation rate amongst cases and controls not stated ▪ Recall bias needs to be considered. Such bias may have overestimated degree of association with breast cancer risk. ▪ Non-differential misclassification of age at menarche may also have occurred resulting in dilution of effect. ▪ Observational study susceptible to residual confounding ▪ A different questionnaire was used in the community sample to that used in the other two groups ▪ Measures of effect were different between the two control groups. Comments ▪ Aimed to evaluate the relationship between menstrual and reproductive risk factors and the risk of breast cancer in Korea Reported conclusions (by authors). Findings support the hypothesis that the longer exposure to ovarian hormones during the reproductive years, the higher the risk of breast cancer.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Talamini et al. 1996) Italy	Case control study Level III-2	Study setting Conducted in six different Italian regions between June 1991 and February 1994. Study sample Median age: cases 55 years, controls 59 years. Education (11+ years of schooling): Cases 25%, controls 16%	Cases (n=2,569) Histologically confirmed incident cases of breast cancer under 80 years of age. Controls (n=2,588) Women resident in the same geographic areas and admitted to the same hospitals as the cases. Admitted for a variety of acute conditions. Exclusions: gynaecological, hormonal or neoplastic disease. Data collection In hospital interview using a structured questionnaire. Analysis Multiple logistic regression	<u>Adjusted odds ratio by age at menarche (<12 years as reference), (95% CI):</u> 12 years: OR 1.1 (0.9-1.3) 13 years: OR 1.1 (0.9-1.3) 14 years: OR 1.0 (0.8-1.2) 15+ years: OR 0.8-1.2) *P*trend 0.56 Adjusted for area of residence, age, education, and menopausal status.	Limitations ▪ Control population may not be representative of the population from which the cases were derived (hospital based controls used) ▪ Participation rate amongst cases and controls not stated ▪ Recall bias needs to be considered. Such bias may have overestimated degree of association with breast cancer risk. ▪ Non-differential misclassification of age at menarche may also have occurred resulting in dilution of effect. ▪ Observational study susceptible to residual confounding Comments ▪ Aimed to investigate the role of reproductive and menstrual factors in the aetiology of breast cancer, overall and by menopausal status Reported conclusions (by authors). Multiparity, early age at first birth and early age at menopause were the most important determinants of breast cancer risk. The effect of the timing of birth was significantly heterogeneous in pre- and postmenopausal women because of the transient adverse effect of such events, evident only in premenopausal women.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Viladiu et al. 1996) Spain	Matched case control study Level III-2	Study setting Population based case control study Study sample Age (years) <50: cases 26%, controls 24% 50-59: cases 27%, controls 22% >59: cases 47%, controls 54% Education No schooling: cases 10%, controls 10% Primary level: cases 80%, controls 73% Higher level: cases 10%, controls 17% Family history of breast cancer (%) Cases 19, controls 9 BMI (Kg/m^2) <24.5: cases 23%, controls 27% 24.5-27.2: cases 25%, controls 26% 27.3-30.2: cases 28%, controls 23% >30.2: cases 25%, controls 25%	Cases (n=330) Diagnosed with histologically or cytologically confirmed or clinically based incident breast cancer between 1986 and 1989 (identified from a gynaecological cancer registry). < 75 years and mentally able to answer the structured questionnaire. Controls (n=346) Random sample of the population matched to the cases by age (±5 years) and county of residence. < 75 years and mentally able to answer the structured questionnaire. Data collection Interviews with trained interviewers using a structured questionnaire. Analysis Unconditional logistic regression used.	<u>Adjusted odds ratio by age at menarche (12-14 years as reference), (95% CI):</u> <12 years: OR 0.9 (0.6-1.3) >14 years: OR 1.4 (0.9-2.2) Adjusted for age, family history of breast cancer and age at first birth.	Limitations ▪ 93.1% of all gynaecological cancers reported in the cancer registry have histological verification (6 cases in this study were based on clinical grounds). ▪ 73% of cases and 84% of controls participated. ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered. Comments ▪ Aimed to explore risk factors for breast cancer with emphasis on the detection of clinical markers of the hormonal imbalance during the perimenarche Reported conclusions (by authors). Hormonal changes in the years following menarche may be relevant to breast cancer risk. The roles of menstrual period length and acne during adolescence should be further explored.

Table 8.2: Evidence tables for primary studies of early menarche (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Wu et al. 1996) USA	Matched, case control study Level III-2	Study setting Population based case control study among Asian-Americans Study sample Mean age at menarche (years): cases 12.9, controls 13.0 Never pregnant (%): cases 19, controls 12 No livebirth (%): cases 24, controls 15	Cases (n=492) Diagnosed with histologically confirmed, incident, primary breast cancer during 1983-1987 Age 20-55 years. Controls (n=768) Selected by random digit dialling in California and from a surveillance program in Hawaii. Matched to cases on age, ethnicity and area of residence (frequency matching in California, individual matching in Hawaii). Data collection Face to face interview. Analysis Unconditional logistic regression used.	<u>Adjusted odds ratio by age at menarche (≤12 years as reference), (95% CI):</u> 13-14: OR 0.87 (0.67-1.14) 15+: OR 0.69 (0.48-1.00) Per year: OR 0.94 (0.86-1.03) Adjusted for age, area, ethnicity, and migration history.	Limitations ▪ 70% of eligible cases participated in interviews, 58% included in analysis ▪ 75% of eligible controls participated, 60% included in analysis ▪ Mixed methods at different sites – different control selection and matching processes. ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered. Comments ▪ Aimed to quantify breast cancer risk in relation to menstrual and reproductive histories in migrant and US-born Asian-Americans. Reported conclusions (by authors). Menstrual and reproductive factors in Asian-American women are consistent with their breast cancer rates being at least as high as in US whites, and they are. However, the effects of these menstrual and reproductive factors were small and the odds ratios for migration variables changed only slightly after adjustment for these menstrual and reproductive factors. These results suggest that the lower rates of breast cancer in Asians must be largely as a result of other environmental/lifestyle factors.

Appendix 9: Evidence tables for post menopausal obesity

Table 9.1: Evidence tables for secondary studies of post menopausal obesity

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Harvie et al. 2003)	Level III-2.	Cochrane Library (2001 issue 2) MEDLINE (1966-Ocotber 2002) Embase (1980-October 2002) Cancer Lit (1975-October 2002). Bibliographies of included studies and proceedings from the meetings of the American Society of Clinical Oncology, Conference on Diet Nutrition and Cancer and the European Conference on Nutrition and Cancer held in 2001 and 2002. Experts were contacted.	Inclusion criteria Cohort and case-control studies provided separate analyses of the relationship between waist and breast cancer risk in pre- and/or post-menopausal women. Case-control studies were only included if waist and hip measurement had been made before commencing treatment for breast cancer. Sufficient information needed to be provided to estimate odds ratio or relative risk based on quantiles for waist or WHR. Data extraction Inclusion and data extraction was assessed independently by two reviewers. Data extracted included study design, participant data, study location, timing of waist/WHR measurement, definitions of quantiles, numbers of cases and women or person years in each quantile, relative risk/odds ratio with 95% confidence intervals for most adjusted data and most adjusted data without adjustment for BMI or weight. Characteristics of study quality were assessed using pre-specified criteria. Data analysis Unadjusted relative risks and adjusted relative risks were calculated (comparing highest with lowest quantiles) by two reviewers independently. Differences in outcomes between smallest waist/WHR and largest waist/WHR quantiles were combined across studies using relative risks in random effects meta-analyses. Effects were assessed separately in cohort and case-control studies.	<u>Pooled relative risk: breast cancer by waist measurement (Lowest versus highest) in postmenopausal women</u> Adjusted RR (no adjustment for BMI): cohort studies: 0.61 (95% CI 0.52-0.73) Adjusted RR (with adjustment for BMI): cohort studies: 0.95 (95% CI 0.62-1.43) Case-control data RR 1.1 (95% CI 0.66-1.83) <u>Pooled relative risk: breast cancer by WHR (Lowest versus highest) in postmenopausal women</u> Adjusted RR (no adjustment for BMI): cohort studies: 0.76 (95% CI 0.67-0.86) Adjusted RR (with adjustment for BMI): cohort studies: 0.89 (95% CI 0.73-1.08) Case-control data RR 0.55 (95% CI 0.26-1.17)	Limitations and comments ▪ Well conducted study with use of independent reviewers to select, extract and appraise studies ▪ Thorough search (search strategy for MEDLINE presented in study) ▪ Overcomes limitation of Connolly et al regarding timing of measurement of WHR - given weight increase cannot have occurred resulting from breast cancer treatment ▪ Study is limited to consideration of central obesity and selection criteria are restrictive ▪ Publication bias present – a number of studies stated they measured both WHR and waist circumference but only presented WHR data ▪ Variation in the method of measuring waist and hip circumference between studies ▪ Lack of knowledge on the transition from premenopausal to post-menopausal status in cohort studies limits the interpretation of these analyses ▪ Lack of consideration of intermediate WHR categories – no assessment of trend possible ▪ Potential lack of control of important confounding with the use of observational studies in the meta-analysis ▪ Presented data separately for pre and post menopausal women ▪ 8 papers identified for inclusion (5 cohort studies and 3 case-control studies). Reported conclusions (by authors). The relationship between a smaller measurement of waist or WHR and lower risk of post-menopausal breast cancer appears to result from the associated correlation with BMI.

Table 9.1: Evidence tables for secondary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Connolly et al. 2002)	Level III-2.	PubMed and MEDLINE for the period January 1966-August 2002. Search terms: abdominal fat, WHR, waist circumference, hip circumference combined with breast cancer and risk. Cited references of publications obtained from the search were also reviewed for relevant articles.	Inclusion criteria Study contained a specific estimate of breast cancer risk associated with waist to hip ratio (WHR) and/or mean WHR values for breast cancer cases and noncases separately. When there was more than one version of the study, the version selected had the longer follow up and/or larger number of study participants. Exclusion criteria Nil stated Data extraction Data extracted by two authors independently. Pre-specified criteria extracted. Data was only extracted between extreme categories (i.e. highest and lowest WHR categories) Data analysis Random effects model employed and additional subgroup and regression analyses performed to investigate observed differences between studies.	<u>Pooled odds ratio: breast cancer by WHR in postmenopausal women, case control studies</u> OR 1.75 (95% CI 1.07-2.87) 7 studies <u>Pooled odds ratio: breast cancer by WHR in postmenopausal women, cohort studies</u> OR 1.21 (95% CI 0.99-1.48) 6 studies	Limitations and comments ▪ Restricted to studies reporting WHR ▪ Lack of consideration of intermediate WHR categories – no assessment of trend possible ▪ Potential variability in cut points for WHR across included studies – therefore some lack of comparability is possible. A random effects model was appropriately used. ▪ 19 studies included with 12,437 cases of breast cancer and 120,556 controls/noncases. Only 13 reported results for postmenopausal women separately. ▪ Potential lack of control of important confounding with the use of observational studies in the meta-analysis. ▪ Four included studies did not present results for postmenopausal women alone. ▪ 8 of the 13 relevant studies adjusted for BMI and 11 of the 14 relevant studies adjusted for age. In both cases the risk estimate was lower in the studies that adjusted for these factors. ▪ WHR measured post breast cancer diagnosis (up to 1 year post diagnosis) in some studies – may be associated with overestimation of risk in these studies due to weight gain during this time. ▪ Time of assessment of menopausal status varied between studies – probably only had a minor effect on the results. ▪ Variation in the method of measuring waist and hip circumference between studies. Reported conclusions (by authors). Greater WHR is associated with increased risk of breast cancer and suggests that the avoidance of abdominal obesity may reduce risk of the disease.

Table 9.1: Evidence tables for secondary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Bergstrom et al. 2001)	Level III-2.	MEDLINE List of references in the selected studies.	Inclusion criteria Published between 1966 and 1997. Prospective studies: ≥ 100 cases Population based case-control studies: ≥ 200 cases Exclusion criteria Nil stated Data extraction Abstracted BMI, major potential confounders, adjusted RRs and their confidence intervals, number of cases number of controls/person-years. Data analysis BMI was summarised as follows: used midpoint of closed ranges and added 10% to the cut point of open intervals. Performed a co-variance analysis of the log relative risk on body mass with terms for study, BMI and their interaction. Checked assumption of linearity. Once a log-linear dose response was accepted, estimated a relationship between each selected study. Individual slopes were combined using the inverse of their variances as weights. Fixed and random effects were calculated for the common regression slope. Three meta-analyses performed for each site: (1) included all eligible studies suitable for meta-analysis, (2) restricted to studies with incident cases, (3) also accounted for major confounders.	<u>Risk of breast cancer: Post menopausal women</u> Controlling for major confounders: RR 1.03 per unit increase in BMI (Fixed effect 95% CI 1.02-1.04, random effect 95% CI 0.75-1.27) RR for obese women (BMI ≥ 30): 1.25 RR for overweight women (25≤BMI<30): 1.12	Limitations and comments ▪ Aim of the study was to estimate the impact overweight has on avoidable causes of cancer in Europe. ▪ Examined six cancers, including breast cancer. ▪ Selected *a priori* desirable characteristics for design, study size and period of publication, and when possible only included studies with these characteristics. However, the characteristics were not defined. ▪ Possible misclassification of open ended BMI categories. ▪ Analysis controlling for major confounders only included three studies, meta-analysis of all eligible studies included 13 studies and estimated RR was 1.02. ▪ Unclear if there was heterogeneity between included studies. ▪ Confidence intervals not presented for categorisation into overweight and obese categories. ▪ Search terms or strategy not presented. ▪ Model controlling for important confounders included age, reproductive factors, alcohol and diet – potential for confounding by other variables. ▪ Few studies included all desirable information Reported conclusions (by authors). No conclusion specific to breast cancer. Some 36 000 cases could be avoided by halving the prevalence of overweight and obese people in Europe.

Table 9.2: Evidence tables for primary studies of post menopausal obesity

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Lukanova et al. 2006) Sweden	Prospective cohort study Level III-2.	Study setting Population based study in one county, the Northern Sweden Health and Disease Cohort (NSHDC) study. Overall study aim was to screen for CVD and diabetes and to promote healthy lifestyle. This study assessed the effect of BMI on cancer risk (common cancers) in men and women. Sample All persons residing in Vasterbotten County invited to participate, study began in 1985 and is on-going. A total of 35,362 women (91.8%) available for analysis. Mean age at entry 46.1 years. Mean BMI at baseline 25.3. Total cancer cases identified 1,440 of which 422 breast cancer cases in women 49 years and over.	Data collection Self-administered questionnaire at baseline to collect demographic data, medical examination and counselling session on healthy lifestyle. Health exam, new blood sample and since 1994 an update of questionnaire information every 10 years. Cohort linked to national registries: Swedish Person Register for deaths up to the end of 2001 and Northern Sweden Region Person Register for deaths in 2002-03. Invasive cancers identified via linkage to Swedish Cancer Registry. Person-years of follow-up assessed from entry date until diagnosis, death emigration, or end of period at 31 October 2003. Analysis BMI quartile cut-offs in women ≥ 49 years and WHO specified categories. Obesity and morbid obesity classes were combined because few participants were morbidly obese.	Mean follow-up period 8.2 years <u>Breast cancer rates and RR in women 49 years and over</u> BMI kg/m^2 RR (95% CI) quartiles 18.5-22.7 1 reference 22.8-24.9 0.99 (0.76-1.3) 25.0-27.8 0.90 (0.68-1.18) ≥27.9 1.04 (0.80-1.36) *P*trend = 0.83 <u>Breast cancer in women 49 years and over</u> BMI kg/m^2 WHO RR (95% CI) 18.5-24.9 1 reference 25.0-29.9 0.92 (0.74-1.14) ≥30.0 1.09 (0.83-1.43) *P*trend = 0.70	Limitations ▪ Postmenopausal status subject to misclassification as it was based on an age cut-off of 49 years. ▪ Self reported health and socio-demographic data, weight and height updated every 10 years by trained nurse. Height and weight measured more than once in subset of cohort. Agreement was high with r=0.81 between repeated weight/height measures at 10 years post baseline in ~10,000 male and female subjects. ▪ Residual confounding likely in this observational study both with known confounders (e.g. reproductive factors, HRT use not adjusted for) and unknown confounders. Comments ▪ No individual data available on age at menopause but mean age from other nested studies of the NSHDC study reported to show mean age of menopause in this population to be 49-50 years. ▪ Population based scope of study may minimize selection bias. ▪ Small differences in health status and socio-demographic factors between participants and non-participants reported.

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Lukanova et al. 2006) *continued*			Site specific cancer incidences, standardised incidence ratios (SIRs) based on annual observed over expected number of cases based on age and gender. BMI averages estimated every ten years. Directly standardised cancer rates (rate/10,000 person years) were calculated across BMI quartiles using age distribution of entire population. Relative risks and 95% CI (likelihood ratios) were calculated using Poisson models, adjusted for age, calendar year and smoking status. Tests for linear trend were calculated using the median BMI of each category as a score and entering this as a continuous term in the regression model.		Reported conclusions (by authors). There was a positive association between BMI and overall risk of cancer. The effects of obesity on sex-steroid metabolism was seen to underlie the differential effect of increasing body weight on breast cancer before and after menopause. An inverse association of BMI with breast cancer was seen in women diagnosed before age 49. There was a lack of clear association between BMI and breast cancer risk for women 49 years and over which may be due to non-adjustment for HRT and other reproductive factors.

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Tehard and Clavel-Chapelon 2006) France	Prospective cohort study Level III-2.	Study setting. The E3N study based on a cohort of French women examining the relationship between pre and postmenopausal breast cancer over a five year period and a range of anthropometric variables. Sample The cohort consists of 98,997 women aged 40-65 years at inclusion (1990-1991), insured in a national health insurance scheme and were enrolled after replying to a dietary questionnaire in 1993. This study is based on the fourth questionnaire (1995) where women were asked to report on anthropometric variables. Based on follow-up sample of 69,116 women, 1,135 who developed breast cancer (275 premenopausal and 860 postmenopausal).	Participants were followed up at 2-year intervals by self-administered questionnaires. Data collection: A total of n=69,150 women answered this questionnaire. Mean follow-up time was 4.7 years for post-menopausal group. Participants were asked to measure anthropometric circumferences wearing no shoes and in underclothes. Menopausal status was recorded with detailed questions related to date, symptoms and type of menopause. Post-menopause was defined as the cessation of periods for natural reasons or due to radiation, chemotherapy, or surgery. All women were asked about breast cancer diagnosis which was confirmed through contact with primary physician. Deaths were confirmed via the insurance scheme database and cause of death information from the National Service on Causes of Deaths. Women with undefined status or who had never menstruated, or other basal cell carcinoma reported were excluded.	<u>Relative risks in post-menopausal women n=860 cases and non-cases 41,497 (multivariate RRs)</u> BMI RR (95% CI) < 20.7 1 reference 20.7-22.3 1.16 (0.91-1.48) 22.3-24.4 1.10 (0.87-1.40) ≥24.4 1.21 (0.96-1.52) *P*trend = NS BMI (WHO) RR (95% CI) < 18.5 0.49 18.5-24.9 1 reference 25.0-29.9 1.07 (0.89-1.30) ≥30.0 1.44 (1.04-1.99) *P*trend = NS All BMI adjusted RRs for thorax, breast, waist, hip, and WHR circumference were NS *P* values for trend tests. There were no significant *P* values for trend tests by HRT user status for weight and BMI classes	Limitations ▪ Residual confounding likely in this observational study both with known confounders not adjusted for and unknown confounders. ▪ Short-term follow-up (4.7 years) using fourth questionnaire data may lead to overestimate of level of risk. ▪ Likely selection bias as insurance scheme based cohort largely consisted of women who were teachers, considered to be health conscious, and were on average slimmer than French women in general. Comments ▪ No significant differences in anthropometric characteristics between post-menopausal cases and non-cases derived from the fourth questionnaire. ▪ Validation exercise found no difference in the E3N cohort of self-reported anthropometric measurements compared with those measured by technicians. ▪ Primarily evaluating the association between various anthropometric measures as risk factors for breast cancer. Reported conclusions (by authors). Menopause is a turning point in the relationship between anthropometric measurements and breast cancer risk. Weight, BMI, thorax and waist circumference, and WHR were negatively related to breast cancer risk in premenopausal women.

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Tehard and Clavel-Chapelon 2006) *continued*			Analysis: Variables adjusted for were: History of breast cancer in first degree relatives, age at menarche, age at first birth, parity, history of benign breast cancer, alcohol consumption, years of education, marital status, physical activity, BMI adjustments Cox proportional hazards model, age as time scale.		Among post-menopausal women thorax and waist circumference were positively related to breast cancer risk. Many relationships were explained by BMI which when adjusted for moved RRs towards unity. There was no observed effect-modification from HRT use.

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Chow et al. 2005) Hong Kong	Case control study Level III-2.	Study setting. Breast clinic at Queen Mary Hospital, Hong Kong. To analyse the association between BMI and breast cancer risk among Chinese women in Hong Kong. Sample A total of 247 eligible cases, 353 controls, mean age 47.2 versus 43.6 years. Cases diagnosed with primary breast cancer by triple assessment between 1995 and 2002. Controls had a diagnosis of benign breast disease and excluded by triple assessment between 1995 and 2002.	Cases (n=198): identified from medical records, newly diagnosed, specialist, radiologically, histologically confirmed breast cancer cases, aged 24-85 years. Chinese women only. All patients had undergone breast cancer treatment. Excluded patients with documented malignancy at other sites. Controls (n= 353) had a diagnosis of benign breast disease and excluded by triple assessment. Data collection Face to face interviews conducted by trained interviewers using a structured questionnaire. Questions about body weight and height at diagnosis, 5 years before and other risk factors for breast cancer. Analysis Quartile distributions were used to categorise BMI. Odds ratios were calculated to measure association between BMI and breast cancer risk using logistic regression. The cut-off age for menopause was 51 at time of diagnosis based on previous research. Analysis adjusted for age differences (p<001) between cases and controls but not other factors due to no significant differences in demographic factors and family history, smoking and alcohol consumption.	<u>Postmenopausal women n=121 cases and n=131 controls</u> At diagnosis BMI OR (95% CI) < 19 19-23 1.78 (0.79-4.04) 23-27 1.73 (1.04-2.86) 27-31 2.06 (1.08-3.93) > 31 3.82 (1.03-14.27) *P*trend *p*< 0.001 Present BMI OR (95% CI) < 19 19-23 2.03 (0.65-6.32) 23-27 1.51 (0.83-2.77) 27-31 1.47 (0.66-3.00) > 31 1.22 (0.30-5.05) *P*trend *p*= 0.06 <u>Five years before diagnosis</u> BMI OR (95% CI) < 19 19-23 0.97 (0.34-2.74) 23-27 1.33 (0.69-2.55) 27-31 1.64 (0.76-3.57) > 31 2.18 (0.63-7.60) *P*trend *p*= 0.12	Limitations ▪ Residual confounding likely in this observational study both with known confounders not adjusted for and unknown confounders. ▪ Significant differences in baseline details comparing cases and controls for age, regular alcohol user. ▪ Likely recall bias in recalling parameters for BMI 5 years previously. ▪ Possible selection bias due to single hospital source for cases and controls. ▪ Reliability and validity of structured questionnaire not established. ▪ Menopause defined as an age cut-off of 51 years, may be subject to misclassification bias. Comments ▪ Only age adjusted. ▪ Participation rate was 80% of eligible cases and controls. Reported conclusions (by authors). High BMI at diagnosis was positively associated with an increased risk of breast cancer in post-menopausal Chinese women living in Hong Kong. Present BMI and BMI at five years before breast cancer diagnosis was poorly associated with breast cancer risk in both pre- and post -menopausal women.

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Silvera et al. 2005) Canada	Prospective cohort study Level III-2.	Study setting. Conducted from amongst participants in the Canadian National Breast Screening Study (NBSS). An RCT of screening for breast cancer. To examine the independent and combined associations of physical activity, energy intake, and BMI with risk of subsequent breast cancer. Sample A total of 89,835 women aged 40-59 years with no history of breast cancer were recruited into the trial between 1980 and 1985. A total of 49,613 women returned questionnaires on dietary data.	After exclusions of women with extreme energy intake and physical activity, missing BMI and physical activity information there were 40,318 women for the analysis including 1,673 incident cases of breast cancer. Mean age in non-cases was 48.5 and in cases 49.5. Data collection At recruitment a self-administered questionnaire on demographic information and height, weight etc was completed and a dietary (food frequency) questionnaire was administered to women visiting screening centres. BMI derived from baseline measurements of height/weight undertaken by nurses at time of randomisation. Data from these questionnaires was used to calculate daily energy intake. Breast cancer cases were ascertained using linkage to the Canadian Cancer Database. Deaths were ascertained from linkage to the National Mortality Database.	<u>Post-menopausal women n=662 cases and person-years 2,244,616</u> <u>Adjusted hazard ratios Model A</u> BMI <25 1.00 reference 25-29 1.12 (0.91-1.38) ≥ 30 1.26 (0.95-1.67) *P*trend *p*= 0.08 *P* for interaction *p*=0.38 no significant interaction effect between menopausal status and BMI.	▪ Limitations ▪ Residual confounding likely in this observational study both with known confounders not adjusted for and unknown confounders. ▪ Questionnaire validated in a pilot version but against an interviewer-administered diet history questionnaire. Vigorous physical activity was measured only in terms of average time spent per day in the last month. Inclusion of house work may have contributed to high duration of physical activity. ▪ Approximately 22% of study subjects and 30% of breast cancer cases were missing information on physical activity. Although it was reported there was little difference between these subjects and those with the information. ▪ The minimum age at baseline was 40 years and average follow-up was 16.4 years so many premenopausal women at enrolment would have become post-menopausal. Misclassification bias as the results for premenopausal women therefore reflect a mix of breast cancers diagnosed pre- and post-menopause. ▪ Different dates for ascertainment of breast cancer cases and deaths linked to 31 December 2000 (for Ontario), 1998 Quebec, 1999 for the rest of Canada. ▪ The use of baseline anthropometric measurements as a risk predictor of disease occurrence a number of years later. Weight and BMI can change over time and was not re-assessed over the long follow-up period.

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Silvera et al. 2005) *continued*			Analysis Cox proportional hazards model (using age as time scale). Association between breast cancer risk and participation in vigorous physical activity, energy intake, BMI. Participants considered at risk from enrolment until date of diagnosis, follow-up termination or death, whichever occurred earliest. Multivariate model A included age, alcohol, smoking history, use of oral contraceptives, HRT, parity, age at menarche, age at first live birth, family history, history of breast disease, menopausal status at baseline, study centre, and randomisation group. Model B included model A plus adjustment for energy intake, participation in physical activity and BMI. Trend test using median values of categories and regression model coefficients were tested using Wald test. Tests for interaction were based on likelihood ratio tests.		Comments ▪ Other stratified breakdowns for vigorous physical activity and energy intake by menopausal status and BMI category. ▪ No significant differences reported at baseline between cases and controls in reproductive factors, BMI, smoking, alcohol consumption and menopausal status. Reported conclusions (by authors). Breast cancer risk may vary according to various combinations of energy intake and expenditure by BMI and menopausal status. Obese postmenopausal women with high calorific intake may be at increased risk of breast cancer.

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Zhu et al. 2005) U.S.A	Matched case control study Level III-2.	Study setting Residents of Davidson, Shelby or Hamilton Counties Tennessee with telephone contact. Study to examine the association between BMI and breast cancer risk among African American women Sample A total of 670 eligible African American female cases aged between 20 to 64 years with diagnosis between 1995 and 1998. Matched controls from a total of 5,970 households were potentially eligible of which 420 eligible women were identified. Mean BMI at baseline for included subjects 28.4 for cases, 27.8 for controls. Mean BMI at 18 21.2 for cases and 21.6 for controls.	After exclusions Cases (n=304) African-American women newly diagnosed with breast cancer. Controls (n=305) population based controls from African American women without a history of breast cancer frequency matched to cases by 5-year age range and county. Data collection Cases identified from the Tennessee Cancer Reporting System (TCRS). Patient Physician identified and approached for consent and 74% of these patients agreed to participate and were interviewed. Controls were randomly chosen via one-step random-digit telephone dialling (RDD) conducted immediately after the corresponding cases were interviewed. Controls were interviewed in the same way as for cases. Face to face interviews by trained interviewers on history of exposure to range of risk factors, 1-3 years following cancer diagnosis for cases using a reference date to benchmark information. For cases this was date of diagnosis and controls the year of diagnosis of the matched cases. Information was collected based on or before reference date.	<u>Post-menopausal women</u> <u>Adjusted odds ratios of breast cancer for BMI at reference date</u> BMI at age 18 <25 1.00 reference 25-< 30 1.50 (0.70-3.21) ≥ 30 2.32 (1.04-5.19) *P*trend *p*= 0.039 <u>Post-menopausal women</u> <u>Adjusted odds ratios of breast cancer for BMI at age 18</u> BMI at age 18 <25 1.00 reference 25-< 30 0.99 (0.40-2.48) ≥ 30 1.35 (0.20-9.15) *P*trend *p*= 0.856 <u>Post-menopausal women</u> <u>Adjusted odds ratios of breast cancer for change per year in BMI</u> Annual BMI change Quartile 0.104 1 reference 0.104 to < 0.202 2.50 (1.08-5.82) 0.202 to < 0.364 3.25 (1.32-8.02) ≥ 0.364 0.97 (0.34-2.78) *P*trend *p*= 0.498	Limitations ▪ Only subjects with telephone contact were included. ▪ Cancer registry system reportedly ascertains approximately 80% of cases during period. ▪ Recall bias due to interviews 1-3 years after diagnosis for cases and BMI at age 18. ▪ No statistical tests of baseline characteristics to gauge level of difference between cases and controls. ▪ Participants were paid $25 for a completed interview and an additional $10 for agreeing to release their tumour tissue specimens. ▪ Only 45% of eligible cases and 7% of eligible controls were included in analysis. Possible selection bias. ▪ Residual confounding likely in this observational study both with known confounders not adjusted for and unknown confounders. Comments ▪ Post-menopause was defined as no periods during the 3-months before the reference date (except pregnancy). Reported conclusions (by authors). Increased BMI at reference date is associated with increased risk of breast cancer in African American women for post-menopausal tumours. BMI at age 18 was not associated with increased risk of breast cancer. An increased average BMI per year change was more strongly associated with increased risk than the lowest quartile of change. However no obvious linear trend was apparent and the increase in risk may not be a linear function of BMI change.

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Zhu et al. 2005) *continued*			Analysis BMI was defined at age 18 and at reference date. BMI change per year between the two time points was computed. WHO BMI categories were used and since few women were in the underweight category this was combined with the normal weight category. Logistic regression was used to calculate odds ratios and 95% confidence intervals. Adjustment was performed for demographic variables and potential lyimportant confounders.		

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Lahmann et al. 2004) European Union	Prospective cohort study Level III-2.	Study setting. EPIC a multi-centre study to investigate the association between nutrition and cancer risk. Subjects were recruited in 23 administrative centres in 10 European countries during 1992-2000, usually those residing in these areas. Sample This study was based on data from 336,053 female participants aged 25-70 years. This was further restricted only to 235,486 women with measured or predicted anthropometric measurements (not self-reported measurements). Mean age of post-menopausal women included in analysis: 64 years.	After exclusions 176,886 women from 9 countries of whom 103,344 were naturally post-menopausal. Median age of post-menopausal women 64 years, 1,405 cases of malignant primary breast cancer. Exclusions: peri-menopausal status, surgical menopause, uncertain status, missing data of hormone use or OC use and women > 80 years at baseline. Data collection Food-related, lifestyle and medical history questionnaires were completed by participants who had given consent. Anthropometric measurements and a blood sample were obtained by a visit to a centre at enrolment. Women were classified according to menopausal status at enrolment based on an algorithm using information on menstrual status/history, type of menopause, use of OCs and menopausal hormones. Incident breast cancer cases were identified from population cancer registries or by active follow-up.	Pooled country specific multivariate RR adjusted for age, education, smoking status, alcohol consumption, parity, age at first pregnancy, age at menarche <u>Post-menopausal Non-HRT user BMI (n=79,030)</u> RR <25 1.00 reference 25-< 29.9 1.30 (1.12-1.51) > 30 1.31 (1.08-1.59) *P*trend *p*= 0.0012 <u>Post-menopausal HRT user BMI (n=24,314)</u> RR <25 1.00 reference 25-< 29.9 0.94 (0.76-1.15) > 30 0.66 (0.45-0.98) *P*trend *p*= 0.064 <u>Post-menopausal Non-HRT user BMI (n=79,030)</u> Quintiles RR <21.5 1.00 reference 21.6-23.5 1.02 (0.78-1.33) 23.6-25.6 1.35 (1.06-1.73) 25.7-28.7 1.38 (1.08-1.76) ≥ 28.8 1.36 (1.06-1.75) *P*trend *p*= 0.002	Limitations ▪ Incident cases based on data from follow-up between 31st December 1999 and 31st December 2000 in most centres. ▪ Some variation between centres in measurement of waist and hip circumference. Some protocol differences in the wearing of clothes during measurements. As a result body weight, and waist and hip circumferences were adjusted to reduce heterogeneity. A sensitivity analysis was reported that no effect was observed by body measure. ▪ Other confounding factors such as family history or dietary intake not controlled for. Residual confounding likely in this observational study both with known confounders not adjusted for and unknown confounders. ▪ Limited duration of follow-up (median 4.7 years). ▪ Relative risk of breast cancer incidence and BMI was not available irrespective of HRT use status. Comments ▪ Post-menopausal women who did not use hormones at baseline had an elevated risk of breast cancer with increasing weight, BMI and hip circumference, with weight being the strongest predictor. Among current HRT users this association tended to be inversely related.

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Lahmann et al. 2004) *continued*			Follow-up was only from study entry (1992-2000) until first breast cancer diagnosis, death, emigration or end of follow-up period. Analysis Cox proportional hazards model used. Age was the underlying time variable, age (in days) at enrolment, and exit time age (in days). Multivariate models were stratified by age at recruitment, and by study centre and simultaneously adjusted for established breast cancer risk factors. Missing covariate data adjusted for. Trend tests using quintile scores and a random effects model was used to estimate overall effect across countries. Interaction terms for HRT use were tested.	Post-menopausal HRT user BMI (n=24,314) Quintiles RR <21.5 1.00 reference 21.6-23.5 0.90 (0.69-1.17) 23.6-25.6 0.91 (0.70-1.19) 25.7-28.7 0.85 (0.64-1.13) ≥ 28.8 0.71 (0.50-1.01) *P*trend *p*= 0.073 Data on family history was not available, energy intake data was available but reported to not affect risk estimates of any body measures.	Reported conclusions (by authors). Height was positively associated with breast cancer in the entire cohort in post-menopausal women. HRT use was a modifier of the association between body weight, BMI waist, and hip circumference and post-menopausal breast cancer. Hip circumference was a strong predictor of breast cancer after adjusting for BMI in post-menopausal women.

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Lahmann et al. 2004) France	Prospective cohort study Level III-2.	Study setting. The E3N study based on a cohort of French women examining the relationship between pre and postmenopausal breast cancer over a five year period and a range of anthropometric variables. Sample The cohort consists of 98,997 women aged 40-65 years at inclusion (1990-1991), insured in a national health insurance scheme and were enrolled after replying to a dietary questionnaire in 1993. This study analysed anthropometric data from the first five questionnaires (baseline until June 2000 when 6th questionnaire sent out).	Participants were followed up at 2-year intervals by self-administered questionnaire. Data collection: Based on follow-up sample of 94,805 women, 2,308 who developed breast cancer (786 premenopausal and 1,522 postmenopausal). Mean follow-up time was 9.7 years for all women. Participants were asked to measure anthropometric circumferences wearing no shoes and in underclothes. Menopausal status was recorded with detailed questions related to date, symptoms and type of menopause All women were asked about breast cancer diagnosis which was confirmed through contact with primary physician. Deaths were confirmed via the insurance scheme database and cause of death information from the National Service on Causes of Deaths. Women with undefined status or who had never menstruated, or other basal cell carcinoma reported were excluded. Analysis: Variables adjusted for were: History of breast cancer in first degree relatives, age at menarche, age at first birth, parity, history of benign breast cancer, alcohol consumption, years of education, marital status, physical activity, BMI adjustments Cox proportional hazards model, age as time scale.	<u>Post-menopausal women</u> Weight (kg) RR (95% CI) < 53 1 reference 53-58 0.95 (0.82-1.10) 58-64 1.02 (0.88-1.18) > 64 1. 06 (0.91-1.21) 64-68 0.99 (0.82-1.19) > 68 1.10 (0.93-1.29) *P*trend = 1.05 (1.02-.08) BMI RR (95% CI) ≤ 20.6 1 reference 20.6-22.2 0.91 (0.79-1.07) 22.2-24.2 0.95 (0.81-1.08) > 24.4 1.06 (0.93-1.21) 24.2-26.2 0.97 (0.81-1.14) > 26.2 1.15 (1.00-1.34) *P*trend = 1.06 (1.02-.09) BMI (WHO) RR (95% CI) < 18.5 0.72 (0.51-1.00) 18.5-25 1 reference 25.0-30 1.05 (0.92-1.20) ≥30.0 1.23 (1.00-1.59) *P*trend = 1.06 (1.02-1.09) Estimates adjusted for history of breast cancer in first degree relatives, age at menarche, age at first birth, parity, history of benign breast cancer, alcohol consumption, years of education, marital status, physical activity, BMI adjustments	Limitations ▪ The use of baseline anthropometric measurements as a risk predictor of disease occurrence a number of years later. To address this, study was updated every two years using self-reported weight/BMI changes over time. ▪ Change in menopausal status over time was accounted for with 24,910 women changing their menopausal status between baseline and the year 2000, during which 350 cases of post-menopausal breast cancer occurred. The estimate of RR using their weight and BMI recorded pre-menopause would have been misclassification error. ▪ Residual confounding likely in this observational study both with known confounders not adjusted for and unknown confounders. ▪ Likely selection bias as insurance scheme based cohort largely consisted of women who were teachers, considered to be health conscious, and were on average slimmer than French women in general. Comments ▪ Validation exercise found no difference in the E3N cohort of self-reported anthropometric measurements compared with those measured by technicians. ▪ Primarily evaluating the association between various anthropometric measures as risk factors for breast cancer ▪ Reported conclusions (by authors). ▪ The risk of premenopausal breast cancer decreased with increasing weight or BMI while the risk of post-menopausal breast cancer increased with increasing weight and BMI and was similar in HRT users and those never using HRT.

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(MacInnis et al. 2004) Australia	Prospective cohort study Level III-2.	Study setting. The Melbourne Cohort Study. Assessment of association between body size and composition and the risk of invasive breast cancer in post-menopausal women. Sample A total of 41,528 people (24,479 women) aged 27-75, 99.3% of whom were ages 40-49 at baseline. Recruitment between 1990 and 1994. Southern European migrants were deliberately over sampled to increase the range of exposures and genetic variation.	A total of 13,598 post-menopausal women (at baseline) were included in analysis after exclusions for pre-existing breast cancer and invalid measurements. Recruitment via electoral roles (compulsory registration in Australia), media advertising, telephone directories (particularly for immigrants). Data collection Height, weight, waist and hip circumference measured at baseline. Also blood samples taken to measure hormones of a sub-cohort of women not using HRT at baseline. Interview asked questions about conventional risk factors and HRT and OC use. Passive follow-up via record linkage to electoral rolls, electronic phone book, and Victorian Cancer Registry. Deaths until 30 June 2002. Cases were identified via notification to the Victorian Cancer Registry. *In situ* were not included as cases. Analysis Cox proportional hazards. Person time from baseline ended at date of diagnosis of breast cancer, diagnosis of unknown primary site, date of death or leaving Victoria.	There were 357 histologically verified incident cases of breast cancer. Average follow-up 9.1 years. <u>Breast cancer risk in relation to anthropometric measurements</u> <u>Hazard ratio (95% CI) designated increase of measure</u> BMI (per 5 kg/m2) 1.14 (1.02-1.27)* WHR (per 0.1 unit) 1.10 (0.94-1.29) Fat mass (per 10 kg) 1.18 (1.06-1.31)** Percent fat (per 10%) 1.21 (1.03-1.42)* *p<0.05; **p<0.01; Models adjusted for age at attendance, country of birth, education, physical activity and HRT use. An additional analysis showed no association of breast cancer risk before 15 years menopause. After 5 years menopause risk increased significantly and remained constant. The obesity-breast cancer relationship may be stronger for tumours that are either ER-positive or of high grade but it was not evident that the effect of increased body size differed by tumour stage.	Limitations ▪ Residual confounding likely in this observational study both with known confounders not adjusted for and unknown confounders. ▪ Unclear whether questionnaire was reliable and validated. ▪ No breakdown of baseline socio-demographic, medical, risk factor data for women included in this analysis. ▪ The use of baseline anthropometric measurements as a risk predictor of disease occurrence a number of years later. Comments ▪ Primarily evaluating the association between various anthropometric measures as risk factors for breast cancer. Reported conclusions (by authors). Body size was positively associated with the risk of breast cancer in postmenopausal women and this relationship was only evident for women who were 15 or more years post-menopause. It is possible that women could reduce their risk of breast cancer by maintaining ideal body weight through increased physical activity and decreases in dietary intake after menopause.

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Pan et al. 2004) Canada	Matched case control study Level III-2.	Study setting. A population based study using the National Enhanced Cancer Surveillance System to assess the association between obesity and overall and site specific cancer risk. Sample Data from 21,022 people with one of nineteen types of cancers and 5,039 controls between 1994 and 1997 in eight out of the 10 Canadian provinces. Mean age for cases 58.3 years, controls 55.8 years. Frequency matching to case group with similar age and sex distributions in the selection of population controls. Variable sampling strategy for control selection in each province depending on data availability, data quality, and confidentiality restrictions.	Total female cases (n=9,522): newly diagnosed, histologically confirmed cancer cases. Controls (n= 2,492) population based controls matched for sex, age (5 year age-group), cancer site, and province. Data collection Provincial cancer registries identified people with incident cases of histologically confirmed primary cancer, newly diagnosed between 1994 and 1997. Questionnaires were sent out and completed and returned (or via interview) representing 68.8% of cases eligible and 75.4% of those cases contacted. The same questionnaires were sent out and completed and returned by controls. Reference date defined as 2-years before interview. Analysis Odds ratios, 95% CIs, and unconditional logistic regression.	Post-menopausal women 1,449 cases. <u>Breast cancer site ICD-O/2 and ICD-9 coded C50, 174/175</u> BMI OR (95% CI) < 25 1.00 reference 25-<30 1.17 (1.00-1.39) ≥30 1.66 (1.33-2.06) ORs adjusted for 5-year age group, province of residence, education, pack-years of smoking, alcohol consumption, total caloric intake, vegetable intake, dietary fibre intake, recreational physical activity, menopausal status, number of live births, age at menarche, age at end of first pregnancy.	Limitations ▪ No statistical tests of baseline characteristics to gauge level of difference between cases and controls. Specific socio-demographic details for breast cancer cases and matched controls unknown. ▪ Selection of controls varied by province. Possible selection bias. ▪ Residual confounding likely in this observational study both with known confounders not adjusted for and unknown confounders. ▪ Classification method for menopausal status not specified. ▪ Misclassification bias due to underreporting of weight as self-reported data from questionnaires. ▪ Interval between reference date and diagnosis date two years some pre-existing diseases may have already affected weight ▪ A total of 68.8% of cases eligible and 75.4% of those cases contacted were included. A total of 66.8% of controls eligible and 62.1% of those controls contacted were included. Comments Explored the association of obesity with cancer risk for 19 different cancers. Diet questionnaire validated. Pilot questionnaires tested in seven provinces in 1993. Reported conclusions (by authors). Study adds evidence to previously established associations between obesity and risk of breast cancer in post-menopausal women.

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Sweeney et al. 2004) U.S.A.	Prospective cohort study Level III-2.	Study setting. Iowa Women's Health Study (IWHS) initiated in 1986 to examine the association between body fat and its distribution and cancer incidence in post-menopausal women. Sample A random sample of women between the ages of 55 and 69 years who held Iowa drivers licences were mailed a questionnaire in January 1986. After exclusions there were 36,658 women with a median age of 61 years at baseline.	During the 16 year follow-up 2,286 post-menopausal women aged 56-84 years were identified with incident breast cancer. Data collection Self-reported information on medical, reproductive histories, diet, anthropometric, sociodemographic and lifestyle factors. Incident breast cancer cases were identified through annual linkage to the National Cancer Institute's Surveillance Epidemiology and End Results Program. . Person years of follow-up were calculated from date of the baseline questionnaire until date of breast cancer diagnosis, date of move from Iowa, or date of death or at end of follow-up at 31 December 2001 when there were 29,687 surviving participants. Analysis Cox proportional hazards regression with age as time scale and 95% CIs and hazard ratios calculated or three age intervals 55-64, 65-74, and 75-84 years. Control for potential confounders using a range of co-variates considered to be risk factors according to previous breast cancer studies.	Cases 428 in women aged 55-64, 1,297 in women aged 65-74 and 561 in women aged 75-84 years. Age at diagnosis 55-64 years Hazard ratio (95%CI) BMI <23.5 1 reference 23.5-26 0.86 (0.64-1.16) >26-29.5 1.26 (0.96-1.64) >29.5 1.34 (1.03-1.75) *P*trend =0.004 Age at diagnosis 65-74 years Hazard ratio (95%CI) BMI <23.5 1 reference 23.5-26 1.21 (1.03-1.42) >26-29.5 1.26 (1.08-1.49) >29.5 1.48 (1.26-1.73) *P*trend <0.0001 Age at diagnosis 75-84 years Hazard ratio (95%CI) BMI <23.5 1 reference 23.5-26 1.19 (0.92-1.53) >26-29.5 1.45 (1.14-1.85) >29.5 1.44 (1.12-1.84) *P*trend =0.001 Significant trends were evident for Waist/hip ratios for each of the three age groups *P*trends =0.01, =0.0004, =0.002 Significant trends were evident for weight change, age 18 to baseline for each of the three age groups *P*trends =0.001, <0.0001, <0.0001	Limitations ▪ Residual confounding likely in this observational study both with known confounders not adjusted for and unknown confounders. ▪ Self-reported measures were reported to be shown to be reliable and valid. ▪ Possible recall bias due to estimates of BMI at age 18. ▪ The use of baseline anthropometric measurements as a risk predictor of disease occurrence a number of years later. Weight (BMI) can change over time and was not re-assessed over the long follow-up period. ▪ A total of 43% of women returned the questionnaire Comments ▪ Study primarily evaluating the association between various anthropometric measures as risk factors for breast cancer with increasing age in elderly women. ▪ No differences reported between responders and non-responders to questionnaire Reported conclusions (by authors). High BMI a modifiable risk factor was consistently associated with increased breast cancer risk for all age-groups in this cohort of post-menopausal women.

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Adebamowo et al. 2003) Nigeria	Case control study Level III-2.	Study setting. Breast cancer cases seen at the University College Hospital, Ibadan, Nigeria. Hospital serves a catchment of 3 million people and is a referral centre for other hospitals. To study the association between breast cancer, BMI and height in an urbanised African population. Sample Consecutive cases presenting and confirmed histologically from March 1998 to August 2000. A total of 312 cases but 73 lived outside area, and 5 refused leaving 234 cases for the study. Mean BMI 25.1 for cases and 24.2 for controls.	Cases (n=234): newly diagnosed, histologically confirmed breast cancer cases, both pre- and post-menopausal women, mean age 45.5 years. Controls (n=273): both pre- and post-menopausal women, mean age 42.3 years. A community adjoining the hospital was randomly selected by ballot. Names were randomly selected from the community register and people were invited to the study clinic set up in the community. Recruitment inclusion criteria were females, above 18 years, absence of any type of cancer, urban residence for most of their lives. Data collection Cases and controls interviewed by trained nurse practitioner. Analysis Univariate and multivariate logistic regression models using a stepwise process to determine confounders by any >10% variation in coefficients from the addition of a new variable and tests for association with breast cancer incidence outcome. Removed variables reintroduced to test for any joint association with included variables and automated models rerun and compared with purposeful models	Post-menopausal women, cases n=104 mean age 53.6 years, control n=89 mean age 58.4 years. Model A OR (95% CI) BMI < 30 1 reference ≥ 30.0 1.82 (0.78-4.31) Continuous model BMI 1.04 (0.98-1.11) (units/kg/m^2) Model adjusted for age, age of onset of menarche, later age at first full-term pregnancy, regularity of periods.	Limitations ▪ Significant differences between cases and controls in age, age of menarche, height, weight, obesity, irregularity of period, social status. ▪ Determination of pre- post-menopausal status non-defined. ▪ Residual confounding likely in this observational study both with known confounders not adjusted for and unknown confounders. ▪ Self-reported demographic, obstetric, and gynaecological history. ▪ Of eligible cases, 75% participated in the study whereas 98% of eligible controls participated. Comments ▪ Study on the association between breast cancer, BMI and height in an urbanised African population. Reported conclusions (by authors). The study failed to find any association between breast cancer risk and obesity but height was positively associated with breast cancer risk in urbanised Nigerian women.

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Carpenter et al. 2003) U.S.A	Nested matched case control study Level III-2.	Study setting. Population based study in Los Angeles County to examine effects of obesity and lifetime exercise patterns on post-menopausal breast cancer risk according to family history. Sample Socioeconomic data not provided.	Cases (n=1,883): Three groups of post-menopausal women diagnosed with breast cancer between March 1987 and April 1996, aged between 55 and 72 years, U.S. born (plus European born in first group of women), Caucasian (including Hispanic) or African American. Controls (n= 1,628): Individual matching of one control subject to each breast cancer case by age (within 3 years), ethnic origin, neighbourhood of residence. Neighbourhood controls based on predetermined walk patterns for neighbourhoods where case patients lived at the time of diagnosis. Matching strategy used from previous study, reanalysis of data. Exclusions Exclusions for unknown menopause, hysterectomy without oophorectomy, menstruating women, last period before 35th birthday and missing covariate data, controls outside age range of cases. Data collection Re-analysis of data from previous study (group 1 patients) plus new cases (groups 2 and 3) and re-matched to controls. Populations from Cancer Surveillance Program (CSP) county cancer registry. Interviews for each case-control pair were usually conducted by same interviewer. Analysis Conditional logistic regression used.	BMI at ref date OR <21.7 1.00 reference 21.7-23.6 1.02 (0.88-1.37) 23.7-27.0 1.35 (0.95-1.46) ≥ 27.1 1.34 (1.09-1.66) *P*trend *p*= 0.005 Additionally adjusted for average MET hours/week of lifetime physical activity. BMI at age 18 OR <18.9 1.00 reference 19.0-20.29 1.02 (0.88-1.37) 20.3-22.16 1.35 (0.95-1.46) ≥ 22.17 1.34 (1.09-1.66) *P*trend *p*= 0.74	Limitations ▪ Socio-demographic data not provided for cases or controls ▪ Restriction to women with known age of menopause may have introduced selection bias. ▪ Residual confounding likely in this observational study both with known confounders not adjusted for and unknown confounders. ▪ Self-reported height and weight at reference period and possible recall bias due to estimates of BMI at age 18. ▪ Use of a range of baseline anthropometric measurements as a risk predictor of disease occurrence a number of years later. ▪ First degree relative with breast cancer incidence significantly different between cases and controls. ▪ Of eligible cases 66% interviews were completed within 1 year of diagnosis. Comments ▪ Evaluation of simultaneously effects of BMI, adult weight change, and exercise by HRT status did not produce very different risk estimates, HRT therefore not included. Reported conclusions (by authors). BMI and exercise activity, both modifiable risk factors for breast cancer have differential effects depending on a woman's family history of breast cancer and may impact through different biological processes.

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Lahmann et al. 2003) Sweden	Prospective cohort study Level III-2.	Study setting. The Malmo Diet and Cancer Study, based in Sweden, a part of the EPIC multi-centre cohort study. To investigate the association between various adiposity measures and weight change during adulthood and breast cancer risk. Sample This study was based on data from 13,375 post-menopausal women aged 50-73 years resident in Malmo. Total female cohort consisted of 17,035 women born between 1923 and 1950 with completed data on all study parts. mean age: cases 58.9 years, non cases 59.9 years.	Post-menopausal women, cases: n=246 of breast cancer (invasive n=211, *in situ* n=35), non-cases: 11,913. Exclusions: women with clinically confirmed prevalent cancer and cervical cancer *in situ*. Data collection Baseline measurements performed during 1991-1996, median follow-up period 5.7 years from enrolment to 31 December 1999. Baseline anthropometric measurements and body composition examination. Body composition was estimated using a electronic analyser. Data on recalled weight at age 20 years. Various reproductive, socio-demographic and lifestyle characteristics were obtained from a standardised health questionnaire at study entry. Incident breast cancer cases were identified via record linkage and active follow-up from the Swedish National Death Registry and the National Tax Board. Follow-up was from study entry (1991-1996) until first breast cancer diagnosis, death, emigration or end of follow-up period. Analysis Cox proportional hazards model used.	Post-menopausal women n=12,159 <u>Multi-variate adjusted*</u> <u>BMI</u> Quintiles RR 95% CI <22.0 1.00 reference 22.0-23.8 1.05 (0.67-1.62) 23.9-25.7 1.20 (0.78-1.85) 25.8-28.5 1.31 (0.86-2.01) > 28.5 1.54 (1.01-2.35) *P*trend *p*= 0.023 <u>Multi-variate adjusted*</u> <u>% Body Fat</u> Quintiles RR 95% CI <27.0 1.00 reference 27.0-29.9 1.37 (0.86-2.18) 30.0-32.9 1.45 (0.93-2.28) 32.0-36.0 1.34 (0.84-2.15) > 36 .0 2.01 (1.26-3.21) *P*trend *p*= 0.010 *adjusted for age, height, (% BF model), occupation marital status, smoking status, alcohol consumption, parity/age at first pregnancy, age at menarche and current HRT. There was no significant *P*trend for age-adjusted and multivariate adjusted WHR or waist circumference.	Limitations ▪ Likely recall bias on self-reported weight at age 20 years. This was only available for 87% of women in the cohort (198 cases, 10,511 non-cases). ▪ Residual confounding likely in this observational study both with known confounders (family history and dietary factors) not adjusted for and unknown confounders. ▪ Invasive and *in situ* cancers were included. ▪ Limited duration of follow-up (median 5.7 years). ▪ Age defined cut-off for menopause at age 50 years ▪ Participation rate was 43% amongst women, possible selection bias in cohort. Comments ▪ Validated and reliable health, diet and questionnaires. Body composition method validated in middle-aged and elderly adults. ▪ Primarily evaluating the association between various anthropometric measures as risk factors for breast cancer. Reported conclusions (by authors). The risk of breast cancer was positively associated with height, weight, BMI, %BF and adult weight gain. These trends were statistically significant. Fat distribution, expressed as either WHR or waist circumference was not associated with elevated risk.

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Lahmann et al. 2003) *continued*				Age adjusted Weight change (kg) Quintiles RR 95% CI < 5.0 1.05 (0.65-1.68) 5.0-9.9 1.00 reference 10.0-13.9 1.25 (0.68-1.79) 14.0-21.0 1.08 (0.76-1.85) > 21 .0 1.43 (1.02-2.45) *P*trend *p*= 0.039 Multi-variate adjusted* Weight change (kg) < 5.0 1.12 (0.77-1.89) 5.0-9.9 1.00 reference 10.0-13.9 1.17 (0.71-1.93) 14.0-21.0 1.25 (0.78-1.99) > 21 .0 1.75 (1.11-2.77) *P*trend *p*= 0.028	

Table 9.2: Evidence tables for primary studies of post menopausal obesity (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Li et al. 2003b) USA	Case control study Level III-2.	Study setting. Population based case control study set in the Seattle-Puget Sound region. Evaluation of the effect of reproductive and anthropometric factors on the risk of invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC). Sample Age at reference date (%): 65-69 yrs: cases 31, controls 33 70-74 yrs: cases 39, controls 38 75-79 yrs: cases 30, controls 29 First degree family history of breast cancer (%): cases 23, controls 17 Age at menarche (%): 8-11 yrs: cases 19, controls 17 12-13 yrs: cases 54, controls 52 14+ yrs: cases 27, controls 31 Nulliparous (%) Cases 9, controls 9 BMI (kg/m^2) (%) <23.32: cases 22, controls 27 23.33-26.20: cases26, controls 25 26.21-30.11: cases 26, controls 24 30.12+: cases 26, controls 24.	Cases (n=975) Women aged 65-79 years with no previous history of *in situ* or invasive breast cancer who were diagnosed with invasive breast cancer between April 1, 1997 and May 31, 1999. Cases identified from the SEER program. Had to live in one of three stipulated counties and have a Health Care Financing Administration HCFA) record. Controls (n=1,007) HCFA records used to identify female residents from the same three counties as the cases. Frequency matched to cases on age and country of residence. Data collection Tumour histology obtained from CSS. Subjects interviewed in person. Analysis Unconditional logistic regression used in assessment of all breast cancer cases. Comparison of invasive lobular breast cancer and invasive ductal carcinoma conducted using polytomous logistic regression.	Overall cases and controls BMI Quartiles OR (95% CI) < 23.3 1 reference 23.3-26.2 1.3 (1.0-1.7) 26.2-30.1 1.4 (1.1-1.9)* ≥ 30.1 1.4 (1.0-1.8)* * p value < 0.05 No significant differences between carcinoma types with stratified analysis	Limitations ▪ 975 of 1,210 (81%) eligible cases were interviewed ▪ 1,007 of 1,365 (74%) of eligible controls were interviewed ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered. ▪ Histology was not independently reviewed which may have resulted in misclassification ▪ Small number of lobular carcinoma cases Comments ▪ Primary aim was to evaluate the association between combined estrogen-progestin HRT breast cancer type (invasive lobular breast carcinoma and invasive ductal carcinoma). Reported conclusions (by authors). There were no statistical differences in risk between invasive lobular breast cancer and invasive ductal carcinoma in relation to anthropometric factors. Compared to lower height women, taller women had increased risks in both histologic types. Neither BMI nor weight was strongly related to invasive lobular carcinoma, but higher BMI and weight was related to greater invasive ductal carcinoma risk

Appendix 10: Evidence tables for hormone replacement therapy

Table 10.1: Evidence tables for secondary studies of hormone replacement therapy

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Greiser et al. 2005)	Level III-2	Medline Cochrane Controlled Trials Register Recent systematic reviews and reference lists of pertinent articles, topic specific reviews, editorials, supplements, conference proceedings and abstract books used to identify other relevant studies. Period: 1989-August 2004	Inclusion criteria Cohort studies, case control studies and randomised controlled trials if information on unopposed oestrogen (ET) or oestrogen-progestin therapy (EPT) was provided. In studies with multiple publications from the same population, only data from the most recent publication were included. In the case of double publication, datasets were only included from the first publication. Exclusion criteria 1989 publications that were included in a previous meta-analysis (published in 1991). Data extraction Data were abstracted and statistical analyses performed independently using two different approaches.	<u>Effect of HRT on breast cancer</u> Case control study, pre 1992: OR/RR 1.18 (95% CI 1.09-1.29) Case control study, 1992 onwards: OR/RR 1.34 (95% CI 1.25-1.43) Cohort/RCT study, pre 1992: OR/RR 1.13 (95% CI 1.00-1.29) Cohort study/RCT, 1992 onwards: OR/RR 1.70 (95% CI 1.62-1.78) <u>Effect of EPT on breast cancer</u> Case control study, pre 1992: OR/RR 0.99 (95% CI 0.84-1.17) Case control study, 1992 onwards: OR/RR 1.48 (95% CI 1.33-1.65) Cohort/RCT study, pre 1992: OR/RR 1.33 (95% CI 1.14-1.54) Cohort/RCT study, 1992 onwards: OR/RR 1.95 (95% CI 1.87-2.04) <u>Increase of breast cancer risk per year of EPT use</u> Case control study, pre 1992: OR/RR 0.98 (95% CI 0.96-1.01) Case control study, 1992 onwards: OR/RR 1.05 (95% CI 1.03-1.06) Cohort/RCT study, pre 1992: OR/RR 1.08 (95% CI 1.04-1.12) Cohort/RCT study, 1992 onwards: OR/RR 1.09 (95% CI 1.09-1.10)	Limitations and comments ▪ Examined a range of research questions ▪ Limited databases examined ▪ Clear description of methodology ▪ Assumptions made were clearly defined but may have been associated with misclassification (e.g. when durations were reported as "greater than" 20% was added to the duration). ▪ Six RCTs, 15 cohort studies and 21 case control studies were included. ▪ Possibility of important confounding – for example, no adjustment by time since menopause. ▪ No estimates for effect of current use of HRT. Reported conclusions (by authors). There is evidence that relative risks for breast cancer risks for HRT, in particular EPT, have been increasing in recent years. Given the widespread use of HRT, and often long duration, more detailed knowledge about differential breast cancer risks of both oestrogen's and progestin's are necessary to minimise breast cancer risk in symptomatic women who consider HRT.

Table 10.1: Evidence tables for secondary studies of hormone replacement therapy (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Greiser et al. 2005) *continued*			Data analysis Major outcomes were ▪ the association between specified groups of hormone regimens and lifetime risk of breast cancer ▪ magnitude of time-dependent risk. ▪ Effects of menopausal hormonal therapy on breast cancer summarised using a fixed effects model applying the general variance method. ▪ Cochrane's Q used to examine heterogeneity ▪ Analyses stratified by type of study, type of hormone therapy and midterm of year of case ascertainment.	<u>Effect of unopposed oestrogen use on breast cancer</u> Case control study, pre 1992: OR/RR 1.02 (95% CI 0.93-1.11) Case control study, 1992 onwards: OR/RR 1.18 (95% CI 1.08-1.30) Cohort/RCT study, pre 1992: OR/RR 1.19 (95% CI 1.10-1.28) Cohort/RCT study, 1992 onwards: OR/RR 1.27 (95% CI 1.19-1.35) <u>Increase of breast cancer risk per year of unopposed oestrogen use</u> Case control study, pre 1992: OR/RR 0.998 (95% CI 0.990-1.007) Case control study, 1992 onwards: OR/RR 1.009 (95% CI 1.003-1.016) Cohort/RCT study, pre 1992: OR/RR 1.010 (95% CI 1.002-1.018) Cohort/RCT study, 1992 onwards: OR/RR 1.031 (95% CI 1.023-1.039)	

Table 10.1: Evidence tables for secondary studies of hormone replacement therapy (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Lee et al. 2005b)	Level III-2.	Medline database for studies subsequent to the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) report. CGHFBC studies.	Inclusion criteria Examined effect of oestrogen-progestin therapy (EPT) on incident breast cancer risk Exclusion criteria Studies restricted to oestrogen therapy alone or only evaluated breast cancer mortality. Studies that did not adjust for age at menopause. Studies that did not have information on risk by duration of use of EPT. Duplicate data Results restricted to continuous combined use of EPT. Data extraction Methods not stated Data analysis Log-odds ratios per year of use were calculated for each study using the meta-analytic methods described by Greenland. Fixed effects and random effects estimates calculated by standard methods.	<u>EPT and breast cancer risk</u> EPT increased risk of breast cancer by 7.6% (95% CI 7.0-8.2%) for every year of use. Sequential EPT use associated with lower risk than continuous-combined EPT use (difference in OR 0.015, 95% CI 0.000-0.030).	Limitations ▪ Focussed research questions. ▪ Clear description of methods including the MeSH terms used. ▪ Validity of included studies not explicitly considered in the key estimates presented. ▪ Considered 10 recent studies plus the pooled CGHFBC analysis. ▪ Weak evidence of heterogeneity (p=0.07). No evidence of publication bias based on funnel plot. ▪ Included the Women's Health Initiative trial. Comments ▪ Meta-analysis of results reported by the CGHFBC and subsequent studies (through March 2004) examining effect of EPT on breast cancer including how it is affected by schedule of progestin administration and histologic subtype. Reported conclusions (by authors). 7.6% increase in breast cancer risk per year of use. Higher risk for continuous combined than sequential EPT use.

Table 10.1: Evidence tables for secondary studies of hormone replacement therapy (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Shah et al. 2005)	Level III-2.	MEDLINE (1966 through Sept 2003) CancerLit (1975 through Sept 2003) Reference lists of prior meta-analyses Search terms included: Hormone replacement therapy Estrogen replacement Cancer Neoplasm	Inclusion criteria Postmenopausal women English language Reported data on cancer incidence, mortality, pathology or stage Study included a comparison group Incorporated longitudinal ascertainment of exposure and outcome Study reported data on rates of cancer in at last two groups (never and current users) or a summary estimate with CIs/P value was presented Distinguished between non-contraceptive and contraceptive oestrogen use Reports for meta-analyses had to provide estimates of risk for women using ERT or HRT at study inception In datasets presented in multiple publications, studies were selected with the most up to date results, longest follow up or most relevant outcomes. Exclusion criteria Editorials, letters and non-systematic reviews Data extraction Two investigators reviewed all titles and studies included in the meta-analyses. Relevant data initially abstracted by one reviewer and compared with results found by AHRQ reviewers where available, and independently abstracted by another reviewer. Discrepancies were resolved by consensus. Data analysis Both fixed and random effects models were performed but results presented were restricted to random effects model. US Preventive Service Task Force quality criteria were used. Publication bias assessed with "trim and fill" method.	<u>Effect of unopposed oestrogen use on breast cancer</u> OR 1.16 (95% CI 1.06-1.28) < 5 years use: OR 1.16 (95% CI 1.02-1.32) ≥ 5 years use: OR 1.20 (95% CI 1.06-1.37) RCT evidence (1 study): adjusted HR 0.77 (95% CI 0.57-1.06) <u>Effect of combined oestrogen-progestogen use on breast cancer</u> OR 1.39 (95% CI 1.12-1.72) < 5 years use: OR 1.35 (95% CI 1.16-1.57) ≥ 5 years use: OR 1.63 (95% CI 1.22-2.18) RCT evidence (2 studies):HR (HERS study) 1.30 (95% CI 0.77-2.19) adjusted HR (WHI study) 1.26 (95% CI 0.83-1.92)	Limitations and comments ▪ Search strategy presented. ▪ Comprehensively reported methodology. ▪ made use of two reviewers. ▪ Did not pursue unpublished data since other meta-analyses found this step added little to their analyses. ▪ 15 studies included in the meta-analysis. Identified 10 meta-analyses, 56 case control studies, 41 cohort studies and 4 RCTs (exclusions were due to duplicate data or did not provide data on current use). ▪ Heterogeneity between studies included in meta-analyses, therefore random effects model most appropriate. Meta-regression did not reveal variables responsible for the heterogeneity. ▪ Conflicting data between RCTs and observational studies for the effect of unopposed oestrogen. ▪ This meta-analysis represents an advance on earlier meta-analyses in that it is the most comprehensive and it specifically excludes studies that included women taking oral contraceptives. Reported conclusions (by authors). Current use of oestrogen alone and combined HRT are associated with increased but different risks of breast cancer. Conclusions differ from earlier reports because studies confounded by premenopausal oral contraceptive use were excluded.

Table 10.1: Evidence tables for secondary studies of hormone replacement therapy (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Garbe et al. 2004)	Level III-2.	All 63 studies included in the pooled re-analysis by the Oxford Collaborative Group were considered.	Inclusion criteria Included in the pooled re-analysis by the Oxford Collaborative Group Exclusion criteria Unpublished studies Data restricted to association with fatal breast cancer Lack of results examining the association between HRT and breast cancer. Data extraction Study design, study period, country study was conducted, primary study objective, number of breast cancer cases, matching or otherwise of controls, response rate, presence of adjustment for reproductive risk factors, age at menopause, type of menopause or BMI, whether the study was included in pooled re-analysis, whether breast cancer surveillance was taken into account in the study design/analysis, risk of breast cancer for ever use of HRT. Data analysis All rate ratios were converted by logarithmic transformation to obtain more symmetrical distributions. Multiple linear regression, weighted by the inverse of the logarithm of the rate ratio was used in all analyses. All factors were included in the regression using a backward stepwise approach. A study design index was formed by counting the number of desirable features among six characteristics (was the HRT association the primary objective of the study, was the exposure recorded at personal interview and/or examination of medical record, whether the study included a surveillance component, whether the design included matching or tight adjustment for age, whether the risk was adjusted for age at menopause, and whether the risk was adjusted for reproductive risk factors).	<u>Key result with all six desirable properties present</u> Rate ratio 0.98 (95% CI 0.83-1.15) Note when none of the six properties were present the RR was 1.14 (95% CI 1.00-1.29)	Limitations and comments ▪ Well focussed study question. ▪ Limitations regarding the selection process that are described in the Collaborative re-analysis. ▪ Appropriate statistical methodology. ▪ Used meta-regression to explore whether design features explained heterogeneity between studies examining the effect of HRT on risk of breast cancer. ▪ Suggested the approach used in the Collaborative re-analysis is problematic given the lack of control over design features – especially given the inclusion of observational study results. It was also noted that the collaborative re-analysis relied heavily on unopposed and often high dose oestrogen. ▪ There were alternative desirable properties that could have been employed – may have resulted in a different RR estimate. ▪ Excluded a significant number of studies that had been considered in the Collaborative re-analysis – might have led to publication bias. ▪ From the 39 studies included, 27 had been included in the Collaborative re-analysis. ▪ Two studies excluded in analysing the design characteristics due to their extreme outlier weights. Reported conclusions (by authors). Design factors of epidemiological studies could be an alternative explanation for the reported 14% increase in the risk of breast cancer associated with the use of HRT.

Table 10.1: Evidence tables for secondary studies of hormone replacement therapy (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Warren 2004)	Level III-2.	Not stated. Comparison of results from the Women's Health Initiative (WHI) with other RCTs and observational studies published during 1987-2002 and meta-analyses and reviews that may have included literature pre 1987.	Inclusion criteria Study designs as indicated under data sources. Where possible, studies were restricted to those that used HRT rather than oestrogen replacement therapy (ERT) or a combination of ERT and HRT. When this was not possible, the review noted this point. Data extraction The WHI findings were noted and then compared with similar outcomes from the other selected studies. Data analysis Systematic review with no meta-analysis.	<u>Key WHI findings</u> HRT effect on incidence of invasive breast cancer: HR 1.26 (nominal 95% CI 1.00-1.59). Increase emerged after 4 years follow up. <u>HR by duration of previous use:</u> <5 years: 2.13 5-10 years: 4.61 >10 years: 1.81 <u>1997 Collaborative re-analysis</u> ERT/HRT effect on breast cancer: RR 1.14 (P<0.0001) RR of breast cancer with HRT or progestin alone with < 5 years use 1.15. <u>Magnusson et al (Sweden)</u> HRT (medium potency estrogens) effect on breast cancer OR 1.63 (95% CI 1.37-1.94) Increased risk per year of use OR 1.14 <u>Persson et al (Sweden)</u> HRT (medium potency estrogens) effect on breast cancer Adjusted RR: 1-6 years use: 1.4 (95% CI 0.9-2.3) ≥ 6 years 1.7 (95% CI 1.1-2.6) <u>Olsson et al (Sweden)</u> HRT (continuous combined) effect on breast cancer, adjusted HR: 4.60 (95% CI 2.39-8.84)	Limitations and comments ▪ No search strategy or search source described. ▪ Inclusion criteria lacked clarity. ▪ Details of data extraction and analysis not stated. ▪ Primarily assessing whether the findings of WHI, which examined the effect of conjugated equine estrogens combined with medroxyprogesterone acetate could be extended to other HRT preparations. ▪ Persson et al adjusted for age, follow up time, age at first pregnancy, BMI, education and menopause age/status. Other estimates presented were not adjusted for potentially important confounders. ▪ Considered a wide range of outcomes. This review has restricted the results presentation to breast cancer. ▪ Author is a consultant for Wyeth, Solvay and Merck Pharmaceuticals and has research support from Ortho, Berlex, Pfizer and Merck Pharmaceuticals. Reported conclusions (by authors). Findings of the WHI (longer duration combined conjugated equine estrogens plus medroxyprogesterone acetate is associated with increased RR of breast cancer) are consistent with other studies that used similar products. Reviewer conclusions. Lack of adequate description of study methods makes it difficult to draw conclusions from this review. However, there is consistency in the key findings across included studies (as outlined under authors conclusions). Relative risk for current use in most studies ranged between 1.1 and 1.4.

Table 10.1: Evidence tables for secondary studies of hormone replacement therapy (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Warren 2004) *Continued*				Ross et al (USA) OR per 5 years of use 1.24 (95% CI 1.07-1.45) Schairer et al (USA) Current use: RR 1.4 (95% CI 1.1-1.9) RR increased by 0.08 for each year of use. Newcomb et al (USA) Ever use: RR 1.43 (95% CI 1.18-1.74) Weiss et al (USA) ≥ 5 years HRT use: OR 1.37 (95% CI 1.06-1.77) < 2 years use: no increased risk.	

Table 10.1: Evidence tables for secondary studies of hormone replacement therapy (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Humphrey 2002)	Level III-2.	Medline database from 1992-2000 and all previously published meta-analyses. Reference lists of key articles, letters and editorials were also reviewed.	Inclusion criteria English language articles. Studies that evaluated breast cancer incidence or mortality in association with HRT. Published between 1992 and 2000. Studies evaluating the effect of HRT on breast density were also reviewed. Data extraction 8 meta-analyses (from 1988-1997), 1 nested case-control study, 14 case control studies and 15 cohort studies evaluating breast cancer incidence, mortality or both met the inclusion criteria. Data were extracted to prepared forms. When more than one study from the same population was reported, data from the most recent publication were reviewed. Data analysis Description of key findings – no meta-analysis was performed.	<u>Ever or short term use of oestrogen (ERT)</u> No overall increase in risk. Increased risk noted in the Collaborative re-analysis meta-analysis but 7 other meta-analyses found no such increase in risk. 6 of 7 cohort studies found no association. The majority of case-control studies including the best quality studies showed no association. <u>Long term use of ERT/HRT</u> Conflicting results. 12 of 19 original studies showed no increased risk of breast cancer. 5 meta-analyses showed increased risk with duration of use over 5 years (RR 1.23-1.51) and 2 cohort studies of good quality also showed increased risk (RR 1.46-1.5). 8 of the 12 case control studies, including the 2 of highest quality showed no increased risk. <u>Combined oestrogen/progestin (EPT) use</u> Among the 3 cohort studies, none showed statistically significant increases in risk associated with ever or short term use. 1 of 2 cohort studies evaluating duration of HRT use found increased risk for duration over 4 years among lean women (RR 2.0). 2 of 3 case control studies showed increased risk with increasing duration of use, however, the best quality study showed no association. <u>Current use of ERT/EPT</u> All 3 meta-analyses showed increased risk (RR 1.21-1.40). 3 good quality cohort studies showed elevated risk in association with current HRT, ERT and EPT. Findings were inconsistent across the 4 case control studies. The best one showed no association.	Limitations and comments ▪ Focus of review was broad (including effect of HRT on breast density and breast cancer mortality, as well as incidence) ▪ Restricted to English language articles ▪ Included studies published outside the period specified for this review (ie. pre 1996) ▪ Medline was the only database searched – may have missed some eligible studies ▪ Likely selection bias – exacerbated by the lack of RCTs – as women taking HRT are different to women who do not take HRT ▪ Search strategy provided ▪ 2 reviewers independently selected studies Reported conclusions (by authors). Association of short term HRT with the development of breast cancer is uncertain based on multiple studies with inconsistent findings. Increased risk is largely confined to current and long-term use (>5-10 years) and the risk is relatively small (RR 1.2-1.5). The addition of progesterone to oestrogen and current, as well as long term use, may be associated with breast cancer risk above oestrogen itself. Data is limited by the observational designs and RCTs are needed to validly evaluate the relationship.

Table 10.1: Evidence tables for secondary studies of hormone replacement therapy (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Bush et al. 2001)	Level III-2.	Keywords estrogen, estrogen replacement therapy, or hormone replacement therapy and breast cancer or breast neoplasm were used to search for articles published between 1975 and 2000 in MEDLINE and Dialogweb. Reference lists from identified original articles, previous reviews and meta-analyses were also searched.	Inclusion criteria All published papers with original data. Exclusion criteria Where there were multiple publications from one study population, the risk estimate from the most recent publication that assessed information from the entire population was presented. Data extraction Unadjusted or age adjusted risk estimates for breast cancer incidence and mortality rate among ever users or oestrogen compared with never users was abstracted from the publication (or calculated by the authors). All cohort studies were reviewed to assess if duration of hormone use had been presented. Data analysis For case control studies odds ratios (with 95% confidence intervals) were presented and for cohort studies relative risks (with 95% confidence intervals) were presented.	<u>ERT and breast cancer risk</u> 20% of studies reported risk estimates less than 0.9, 33% reported risk estimates greater than 1.1, 47% reported risk estimates between 0.9 and 1.1. <u>HRT and breast cancer risk</u> 4 of 20 found statistically significant results, 2 with increased risk and 2 with decreased risk	Limitations and comments ▪ Each co-author conducted their own search using combinations of keywords and the results were compared between co-authors. ▪ Compared ever users with never users for two key outcomes: breast cancer incidence and mortality. ▪ Search strategy not clear with variation between co-authors. It is not possible to assess how systematic the search was likely to be. ▪ 45 studies identified that assessed the association between ERT and breast cancer and 20 that assessed the association between HRT and breast cancer. ▪ No control for potentially strong confounders such as time since menopause. ▪ No assessment of current users. Reported conclusions (by authors). The evidence did not support the hypotheses that oestrogen use increases the risk of breast cancer and that combined hormone therapy increases the risk more than oestrogen alone.

Table 10.1: Evidence tables for secondary studies of hormone replacement therapy (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Collaborative Group on Hormonal Factors in Breast Cancer 1997)	Level III-2.	Studies were identified from review articles, literature searches and discussions with colleagues. All collaborators (196 collaborators were listed on the original HRT publication in 1997) were sent a list of studies and key references and asked if they knew of additional studies (published or unpublished).	Inclusion criteria Case-control and nested case-control studies Included ≥100 women with incident, invasive breast cancer. Prospective studies were included using a nested case-control design in which four controls were randomly selected for each woman with breast cancer. Data extraction Data were sought on the use of HRT, sociodemographic factors, family history of breast cancer, height, weight, age at menarche, reproductive history, use of hormonal contraceptives, gynaecological surgery, whether menstrual periods had ceased and, if so, age at cessation and the reason for cessation. Data analysis Data from different studies combined using Mantel-Haenszel techniques, estimating odds ratios, confidence intervals and P values. Results were routinely stratified by study, centre within study, age group and parity. Where appropriate, results were also stratified by age at first birth and smoking history. Key estimates summarised with 95% confidence intervals, all other estimates were accompanied with 99% confidence intervals.	<u>Current HRT users</u> RR increased by 1.023 (95% CI 1.011-1.036) for each year of use. RR for at least 5 years use 1.35 (95% CI 1.21-1.49) Five or more years after cessation of HRT, no significant excess risk of breast cancer	Limitations and Comments ▪ Estimated that the studies incorporated over 80% of the worldwide information on the topic (63 published and two unpublished studies). However, original data were contributed by 51 studies. ▪ Made use of individual patient data ▪ Well defined data variables. ▪ Inconsistent, implausible and missing data clarified by correspondence with the original authors where possible. ▪ Potential misclassification error related to variables collected (e.g. Current use of HRT defined as use within 12 months of diagnosis, women who stopped menstruating during the year of diagnosis were classified as premenopausal) ▪ Information collected on 52,705 cases and 108,411 controls. Main analyses restricted to 17,949 cases and 35,916 controls (with known age at menopause and known use of HRT). ▪ Possible surveillance bias with women on HRT being more likely to be assessed for breast cancer. ▪ The databases searched and search strategy used was not described. ▪ Made use of self-reported data. ▪ Adequately controlled for potentially strong confounding related to timing of menopause and BMI. Also controlled for confounding by other variables through use of conditional logistic regression model. ▪ Most women had used predominantly oestrogen alone preparations. Reported conclusions (by authors). Risk of breast cancer increases in women using HRT and increases with increasing duration of use. Effect is reduced after cessation of HRT and has largely disappeared after about five years.

Appendix 11: Evidence tables for hormonal contraceptives

Table 11.1: Evidence tables for secondary studies of hormonal contraceptives

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Collaborative Group on Hormonal Factors in Breast Cancer 1996)	Level III-2.	Studies were identified from review articles, literature searches and discussions with colleagues. All collaborators (196 collaborators were listed on the original HRT publication in 1997) were sent a list of studies and key references and asked if they knew of additional studies (published or unpublished).	Inclusion criteria Case-control and cohort studies Included ≥100 women with incident, invasive breast cancer Recorded information on reproductive factors and use of hormonal therapies Exclusion criteria Nil stated Data extraction Data for individual women were collated centrally OCs were grouped into 3 categories (low oestrogen, <50μg; medium oestrogen, 50μg; high oestrogen >50μg). Data analysis Data analysis was conducted centrally. Data from different studies combined using Mantel-Haenszel techniques, estimating odds ratios, confidence intervals and P values. Results were routinely stratified by study, centre within study, age group, parity. Where appropriate, results were also stratified by age at first birth and smoking history.	<u>Relative risk of breast cancer in OC users</u> Current users: RR 1.24 (95% CI 1.15-1.33) 1-4 years after stopping: RR 1.16 (95% CI 1.08-1.23) 5-9 years after stopping: RR 1.07 (95% CI 1.02-1.13) ≥ 10 years after stopping: RR 1.01 (95% CI 0.96-1.05). Cancers diagnosed were less advanced in ever users compared with never users. RR for tumours that had spread beyond the breast (ever users versus never users) 0.88 (95% CI 0.81-0.95).	Limitations and comments ▪ Included individual data from 54 studies (53,297 women with breast cancer and 100,239 women without breast cancer). ▪ Prospective studies were included by use of a nested case-control design with four randomly matched controls per case. ▪ Clear description of data collection and statistical analysis. ▪ Analyses included 350 cases and 1096 controls with unknown use of OC. ▪ Differential reporting of OC use may be present – potentially overestimating the effect of OC use on breast cancer. ▪ Evidence of statistical heterogeneity between studies and between study designs raising questions of whether results should have been combined. However, after recency of use was controlled, variability between studies was reduced. ▪ The databases searched and search strategy was not described. Reported conclusions (by authors). There is a small increase in the risk of breast cancer while taking oral contraceptives and during the 10 years thereafter. The older women are at last use, the larger the number of excess cancers diagnosed during this period is likely to be, although the additional cancers diagnosed are mainly localised to the breast.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Jernstrom et al. 2005) Sweden	Matched case control study Level III-2.	Study setting. South Swedish Health Care Region (population based series) Sample Age at menarche (years): cases 12.7, controls 13.0 Parous (%): cases 80, controls 85 Parity (number): cases 1.84, controls 1.86 Age at FFTP (years): cases 24.6, controls 24.7 First degree relative with breast cancer (%): cases 15, controls 6	Cases (n=222) Diagnosed with a first invasive breast cancer at age ≤40 years between 1990 and 1995 in the South Swedish Health Care region. Controls (n=735) Controls selected from a prospective population based cohort. Every eighth woman in the region between ages 25 and 65 was invited to participate. Three control women matched on age (±5 years) per case and were at least as old as the case at the time of diagnosis. Controls were randomly selected. Exclusions: missing data regarding ever OC use or had developed breast cancer. Data collection Combination of written questionnaire and patient charts (when questionnaires not available) were used for data collection Analysis Conditional logistic regression used. Multivariate models adjusted for *a priori* risk factors.	<u>Relative risk of breast cancer by timing of oral contraceptive use (Reference: never use): adjusted OR (95% CI)</u> 1. Per year of OC use prior to age 20 years OR 1.17 (1.03-1.33) 2. Per year of OC use age 20 years or older OR 1.02 (0.98-1.07) Above estimates adjusted for age at menarche, parity, first degree family history of breast cancer and having ever smoked. <u>Relative risk of breast cancer by ever use of oral contraceptives (Reference: never use): OR (95% CI)</u> OR 1.65 (0.95-2.87) <u>Relative risk of breast cancer by timing of oral contraceptive use in relation to first child: OR (95% CI)</u> 1. OC use before the first child (reference: no use before first child) OR 1.63 (1.02-2.62) 2. OC use after the first child (reference: no use after first child) OR 1.03 (0.66-1.61)	Limitations ▪ 245 of 259 eligible cases agreed to participate (95%). However, 23 further cases excluded due to lack of information resulting in inclusion of 222 cases (86% of eligible cases). ▪ Overall participation rate amongst the prospective population based cohort was 75%. ▪ Mixed methods of data collection among the cases, which may produce variable levels of misclassification. Method of data collection appeared to be related to severity of illness. However, the authors stated "in general, the information provided by the two sources was internally consistent for each woman". ▪ Data collection in the controls was based on questionnaire alone. Although the same questions were included on OC use and reproductive risk factors among the cases and controls, the questionnaire for controls was more extensive than that for cases. ▪ Differential misclassification may occur due to the different types of data collection tool and the possibility of recall bias (although recall bias is unlikely to explain the non-significant findings). ▪ Mean interval between diagnosis and questionnaire completion was 42 months ▪ Observational study susceptible to residual confounding

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Jernstrom et al. 2005) *continued*				Relative risk of breast cancer by timing of oral contraceptive use in relation to age 20 years: OR (95% CI) 1. OC use before age 20 (reference: no use before 20) OR 2.10 (1.32-3.33) 2. OC use 20+ years (reference: no use after 20+ years) OR 1.02 (0.63-1.64)	Comments ▪ Aimed to evaluate the combined effects of OC use and genetic/familial factors in a population tested for BRCA1/2 mutations in early onset breast cancers ▪ Cases verified by data from the Swedish Cancer Registry Reported conclusions (by authors). Each year of OC use prior to age 20 years conferred a significantly increased risk for early-onset breast cancer, while there was no risk associated with use after age 20 years.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Norsa'adah et al. 2005) Malaysia	Matched case control study Level III-2.	Study setting. Hospital based study Sample Parous (%): cases 85, controls 99, *P*<0.0001 Age at menarche (median years): 12-16 in cases and controls Premenopausal (%): cases 72.8, controls 73.5 BMI (kg/m^2): Underweight (<18.5): cases 12.2%, controls 6.1% Normal (18.5-24.9): cases 38.1%, controls 53.7% Overweight/obese (25.0+): cases 49.7%, controls 40.1% *P*=0.02 Family history of breast cancer in first degree relative (%): cases 6.1, controls 0.7, *P*=0.002 Ever used HRT (%): cases 1.4, controls 4.1	Cases (n=147) Histologically confirmed primary breast cancer. Recruited from inpatients and outpatients in two referral hospitals. Diagnosed between 1991 and 2000. Exclusions for cases: male patient, cognitive problems. Controls (n=147) Matched on age (± 5 years) and ethnicity. They were patients attending the same hospital. Exclusions for controls: known malignant, hormonal, gynaecological or endocrine diseases. Data collection Standardised, structured questionnaires were used. Analysis Conditional logistic regression used.	<u>Relative risk of breast cancer by ever use of oral contraceptives (Reference: never use): adjusted</u> RR (95% CI) RR 2.5 (1.3-4.8) Adjusted for number of children, family history and BMI at diagnosis.	Limitations ▪ Controls may not be representative of the population from which the cases were selected ▪ Cases from this hospital based population may not be representative of all cases (tended towards more severe disease). ▪ Participation rate not stated among cases, controls or overall ▪ Potential for recall bias which would tend to result in overestimation of the relative risk. However, use of hospital based controls may reduce the risk of recall bias. ▪ Potential for misclassification of the variables collected which could result in residual confounding ▪ Observational study susceptible to residual confounding Comments ▪ Aim was to identify risk factors for breast cancer in women in Malaysia ▪ Clear definitions provided for variables collected Reported conclusions (by authors). Study reconfirmed that similar risk factors identified in Western populations were responsible for the occurrence of breast cancer in Kelantan. It also supported the theory that breast cancer occurrence was related to oestrogen exposure and familial factors. It suggested the importance of having children, maintaining ideal body weight and caution for oral contraceptive users and women with a family history of breast cancer.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Yavari et al. 2005) Iran	Matched case control study Level III-2.	Study setting. Hospital based (teaching hospital) case control study Sample Mean age (years): cases 48.7, controls 50.2. Education level (%): Primary or lower: cases 51, controls 61 Middle school: cases 14, controls 15 High School: cases 23, controls 19 College/University: cases 12, controls 4 Ever married (%): cases 95, controls 99 Post menopausal (%): cases 77, controls 53 Nulliparous (%): cases 7, controls 4 Family history of breast cancer (%): cases 15, controls 8	Cases (n=303) Female patients with histopathologically confirmed breast cancer identified through the oncology and surgery departments of a University based teaching hospital in Tehran. Controls (n=303) Controls collected from other wards or outpatients clinics in the same hospital as the cases. Matched to cases on age (± 2 years). No current or past history of breast cancer. Data collection In person interview using a constructed questionnaire. Analysis Logistic regression used.	Relative risk of breast cancer by use of oral contraceptives (Reference: never use): adjusted OR (95% CI) Ever use: OR 1.95 (1.32-2.87)	Limitations ▪ Unclear whether conditional or unconditional logistic regression was used ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered ▪ Participation rate in cases and controls not documented ▪ Co-variates included in the final logistic regression model were not clear ▪ Hospital based controls may not be representative of the population from which the cases were drawn Comments ▪ Study aimed to determine roles of reproductive factors for breast cancer among women in Iran. Reported conclusions (by authors). "The lack of significant association of some variables such as family history and the risk of developing breast cancer in final model may be related to power of study to estimate the risk. Also we should be aware of the limitation of the case control study, including case and control ascertainment and representation."

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Dumeaux et al. 2004) Norway	Prospective, cohort study Level III-2.	Study setting. Part of the Norwegian Women and Cancer Study (NOWAC), a large prospective follow-up study. Between January 1991 and January 1997, 179,388 women for the general population of Norway, aged 30-70 years were invited to participate in NOWAC. Sample (n=87,084) Mean age at inclusion (years): 43 Mean age at menarche (years): 13 Mean age at first birth (years): 22 Mean parity (number): 2.3 Mean BMI (kg/m^2): 22.6 Family history of breast cancer (%): 4.4 Postmenopausal (%): 27.1 Ever used HRT (%): 33.2	Eligibility criteria Inclusion criteria Women were sampled according to birth year from the national population register (Statistics Norway). Exclusion criteria Incomplete alcohol or OC data Prevalent cancer Data collection Follow up information collected by linkage to the national cancer registry and to death certificates. Information collected by postal questionnaire. Analysis Cox proportional hazard model fitted. *a priori* confounders were included in the model.	<u>Relative risk of breast cancer by duration of OC use (reference: no use): adjusted RR (95% CI)</u> 0-4 yrs use: RR 1.19 (1.03-1.38) 5-9 yrs use: RR 1.16 (0.95-1.41) 10+ yrs use: RR 1.29 (1.05-1.60) *P*trend 0.01 <u>Relative risk of breast cancer by oestrogen dose (reference: never user): adjusted RR (95% CI)</u> 0.1-49.9 mg: RR 1.26 (1.05-1.52) 50.0-99.9 mg: RR 1.21 (0.96-1.54) 100.0+ mg: RR 1.28 (1.00-1.64) *P*trend 0.01 <u>Results of OC use stratified by alcohol intake: adjusted RR (95% CI)</u> 1. No alcohol intake OC use never: 1 (reference) OC use 0-9 yrs: 1.15 (0.87-1.51) OC use 10+ yrs: 1.99 (1.27-3.10) *Ptrend* 0.02 2. 0.1-4.9 g alcohol/day OC use never: 1.19 (0.96-1.47) OC use 0-9 yrs: 1.56 (1.27-1.93) OC use 10+ yrs: 1.73 (1.28-2.35) *Ptrend* 0.0009 3. 5.0-9.9g alcohol/day OC use never: 1.72 (1.30-2.28) OC use 0-9 yrs: 1.54 (1.18-2.01) OC use 10+ yrs: 1.17 (0.71-1.95) *Ptrend* 0.18 4. 10.0+g alcohol/day OC use never: 1.89 (.26-2.82) OC use 0-9 yrs: 2.02 (1.46-2.79) OC use 10+ yrs: 1.97 (1.13-3.43) *Ptrend* 0.88	Limitations ▪ 102,443 of the 179,388 (57%) women invited to participate were included in NOWAC. 10 were excluded from follow-up, 5,933 women recruited in 1997 were excluded due to lack of questions about alcohol intake in that cohort, 2,785 were excluded due to prevalent cancer and 2,609 due to missing values for OC use. Finally included 86,948 women in the analysis (48% of the eligible population) ▪ Information collected by postal questionnaire – susceptible to misclassification, which is likely to be non-differential given the prospective collection, leading to dilution of risk estimates. However, accuracy of OC data improved by use of a photo booklet of all OCs sold and marketing period. Alcohol intake estimates were reproducible over time (1991/2 compared with 1998 when a sub-sample of participants received a validation questionnaire). ▪ Observational study susceptible to residual confounding Comments ▪ Aim was to examine how the use of oral contraceptives interact with alcohol on breast cancer risk. ▪ National population register includes all residents who stay in Norway > 6 months ▪ The national cancer registry is "estimated to be almost complete"

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Dumeaux et al. 2004) *continued*				RR adjusted for effects of age, invitation to do breast screening, age at menarche, age at first birth and parity, family history of breast cancer in mother, menopausal status, HRT use and BMI. Results imply competitive responders may be present between OC use and alcohol intake.	Reported conclusions (by authors). Findings in conjunction with biological data imply that alcohol and OCs have antagonistic effects on breast cancer risk through a common pathway. Whether the interactive effect differs according to menopausal status remains unclear and needs further investigation.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Strom et al. 2004) USA	Case control study Level III-2.	Study setting. Part of the Women's Contraceptive and Reproductive Experiences Study, a population based, multi-centre case control study. Sample Mean age (years): cases 49.4, Controls 49.7 Education (%): < High School: cases 9.5, controls 8.8 High School: cases 28.8, controls 29.2 Some College: cases 32.0, controls 32.5 College degree: cases 29.7, controls 29.7 Age at menarche (years): cases 12.4, controls 12.4 Nulliparous (%): cases 17.2, controls 19.4 Family history of breast cancer (%): 9.7, controls 17.0 BMI 5 years before reference date (kg/m^2) < 21.5: cases 23.7, controls 24.9 21.5-28.5: cases 51.7, controls 53.0 28.5+: cases 24.6, controls 22.2	General exclusions: Previous or current diagnosis of breast cancer (*in situ* or invasive disease) Cases (n=4,575) Randomly sampled cases with histologically confirmed, first primary, invasive breast cancer diagnosed between 1994 and 1998. Younger women and blacks were over sampled. Controls (n=4,682) Identified using random digit dialling. Frequency matched to the age and race distribution of the cases. Data collection In person interviews using a structured questionnaire. Analysis Conditional logistic regression used.	<u>Relative risk of breast cancer by ever use of contraceptive injection (Reference: never used contraceptive injection): OR (95% CI)</u> OR 0.87 (0.66-1.15) <u>Relative risk of breast cancer by recency of use of contraceptive injection (Reference: never used contraceptive injection): OR (95% CI)</u> ≤ 1 year: OR 0.67 (0.35-1.30) >1 years: OR 0.67 (0.68-1.26) <u>Relative risk of breast cancer by duration of use of contraceptive injection (Reference: never used contraceptive injection): OR (95% CI)</u> < 6 mths: OR 0.60 (0.37-0.98) 6 - < 12 mths: OR 0.89 (0.50-1.57) 12-<24 mths: OR 0.94 (0.50-1.77) 24+mths: OR 1.38 (0.77-2.47) <u>Relative risk of breast cancer by ever use of contraceptive implant (Reference: never used contraceptive implant): OR (95% CI)</u> OR 0.67 (0.21-2.13) Presentation of results restricted to unadjusted estimates as adjustment for confounders had no effect on the results other than to increase variability.	Limitations ▪ Response rates: 76.5% for cases and 64.5 % for controls ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered ▪ Small sample size for use of implantable contraceptives Comments ▪ Investigated the relationship between breast cancer and use of injectable and implantable progestin-only contraceptives. Reported conclusions (by authors). This study does not support an increased risk of breast cancer associated with the use of injectable or implantable progestin-only contraceptives in women aged 35 to 64.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Althuis et al. 2003) USA	Case control study Level III-2.	Study setting. Population based case control study Sample	Study population Women < 45 years Exclusions: no residential phone, previous diagnosis of breast cancer, used solely progestin only pills. Cases (n=1,640) Newly diagnosed with *in situ* or invasive breast cancer during 1990-1992. Patients aged 20-54 years. Controls (n=1,429) Ascertained through random digit dialling. Data collection In person interviews. Outcome measures Hospital records abstracted to document clinical and pathologic characteristics of the breast cancers. Analysis Assessments made in relation to OC use within 5 and 10 years of diagnosis. Logistic regression used.	<u>Relative risk of breast cancer by ever use of oral contraceptives (Reference: never used): adjusted RR (95% CI)</u> RR 1.24 (1.0-1.5) <u>Relative risk of breast cancer by recency of use of oral contraceptives (Reference: never used): adjusted RR (95% CI)</u> < 5 years: RR 1.47 (1.2-1.9) 6-10 years: RR 1.33 (1.0-1.7) >10 yrs: RR 1.13 (0.9-1.4) <u>Relative risk of breast cancer by oral contraceptive potency and type (Reference: never used): adjusted RR (95% CI)</u> Multiple results were presented, statistically significant results are reproduced here. Ethinyl estradiol > 35 μg: RR 1.99 (1.2-3.2) Progestin low potency: RR 1.40 (1.1-1.8) Oestrogen low potency: RR 1.38 (1.1-1.8) All estimates adjusted for age, site, race, menopausal status, combination variable for age at first birth and number of births, age at menarche, family history of breast cancer, BMI and mammography use.	Limitations ▪ Cases included *in situ* disease ▪ Interviews obtained for 86% of eligible cases. ▪ Telephone screening for controls had a 90.5% screening response rate. Interviews obtained for 78% of eligible controls giving an effective response rate of 71%. ▪ Lack of sample characteristics presented. ▪ Observational study susceptible to residual confounding. ▪ Recall bias needs to be considered. Recall of pill type has been shown to be problematic in previous research. Comments ▪ Investigated whether recent OC use is associated with an excess risk of breast cancer across all or specific OC types Reported conclusions (by authors). Findings suggest that newer low-potency/low oestrogen dose OCs may impart a lower risk of breast cancer than that associated with earlier high-potency/high-dose preparations.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Li et al. 2003b) USA	Case control study Level III-2.	Study setting. Population based case control study set in the Seattle-Puget Sound region. Sample Age at reference date (%): 65-69 yrs: cases 31, controls 33 70-74 yrs: cases 39, controls 38 75-79 yrs: cases 30, controls 29 First degree family history of breast cancer (%): cases 23, controls 17 Age at menarche (%): 8-11 yrs: cases 19, controls 17 12-13 yrs: cases 54, controls 52 14+ yrs: cases 27, controls 31 Nulliparous (%) Cases 9, controls 9 BMI (kg/m^2) (%) <23.32: cases 22, controls 27 23.33-26.20: cases26, controls 25 26.21-30.11: cases 26, controls 24 30.12+: cases 26, controls 24.	Cases (n=975) Women aged 65-79 years with no previous history of *in situ* or invasive breast cancer who were diagnosed with invasive breast cancer between April 1, 1997 and May 31, 1999. Cases identified from the SEER program. Had to live in one of three stipulated counties and have a Health Care Financing Administration (HCFA) record. Controls (n=1,007) HCFA records used to identify female residents from the same three counties as the cases. Frequency matched to cases on age and country of residence. Data collection Tumour histology obtained from CSS. Subjects interviewed in person. Analysis Unconditional logistic regression used in assessment of all breast cancer cases. Comparison of invasive lobular breast cancer and invasive ductal carcinoma conducted using polytomous logistic regression.	<u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: never use): adjusted OR (95% CI)</u> < 5 years: OR 0.9 (0.7-1.2) 5+ years: OR 1.1 (0.8-1.5) Adjusted for age <u>Relative risk of ductal carcinoma by duration of oral contraceptive use (Reference: never use): adjusted OR (95% CI)</u> < 5 years: OR 0.8 (0.6-1.1) 5+ years: OR 1.0 (0.7-1.4) <u>Relative risk of lobular carcinoma by duration of oral contraceptive use (Reference: never use): adjusted OR (95% CI)</u> < 5 years: OR 1.1 (0.7-1.6) 5+ years: OR 1.6 (1.0-2.6)	Limitations ▪ 975 of 1,210 (81%) eligible cases were interviewed. ▪ 1,007 of 1,365 (74%) of eligible controls were interviewed. ▪ Observational study susceptible to residual confounding. ▪ Recall bias needs to be considered. ▪ Histology was not independently reviewed which may have resulted in misclassification. ▪ Small number of lobular carcinoma cases. Comments ▪ Primary aim was to evaluate the association between combined estrogen-progestin HRT by breast cancer type (invasive lobular breast carcinoma and invasive ductal carcnoma). Reported conclusions (by authors). Pattern of results observed suggest that factors influencing endogenous hormones and duration of ovarian function may be more strongly associated with ductal carcinoma risk, while exogenous hormones may be more strongly associated with lobular carcinoma risk.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Suter et al. 2003) USA	Case control study Level III-2.	Study setting. Population based case control study among women aged under 45 years. Sample Age <35 years at reference (%): cases 13.2, controls 17.1 Positive family history (%): cases 37.9, controls 24.6 Age at menarche 8-12 years: cases 52.9, controls 51.0 13-15 years: cases 44.7, controls 45.8 16+ years: cases 2.5, controls 3.3 No history of live birth (%): cases 27.5, controls 19.9 BMI (kg/m^2): 15.7-<21.2: cases 24.9, controls 26.0 21.2-<23.6: cases 30.8, controls 24.9 23.6-<27.0: cases 22.9, controls 24.5 27.0-57.2: cases 21.4, controls 24.5	Cases (n=524) Women diagnosed with incident, first primary breast cancer before age 45 years from May 1990 to December 1992. Cases identified through the Cancer Surveillance System of Western Washington. Controls (n=461) Identified through random digit dialling and frequency matched to cases on 5 year age group and reference year. Data collection In person interview using a structured questionnaire. Details provided on molecular methods - the reader is referred to the original paper if this information is required. Analysis Logistic regression used.	<u>Relative risk of breast cancer by ever use of oral contraceptives (Reference: never used): adjusted OR (95% CI)</u> OR 1.3 (0.9-1.8) <u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: never used): adjusted OR (95% CI)</u> < 5 years: OR 1.3 (0.9-1.8) 5-<10 years: OR 1.4 (0.9-2.1) 10+ years: OR 1.2 (0.7-1.8) <u>Relative risk of breast cancer by recency of use of OC (Reference: never used): OR (95% CI)</u> 10+ years ago: OR 1.3 (0.9-1.8) 5-<10 years ago: OR 1.2 (0.8-1.9) < 5years/current: OR 1.4 (0.9-2.1) Estimates adjusted for age at reference and reference year.	Limitations ▪ Participation rate: cases 69%, controls 56% ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered ▪ OC use was not part of the primary aim of the study Comments ▪ Primarily investigating the relationship between the androgen receptor repeat variation and breast cancer in young women from the general population. Reported conclusions (by authors). No OC related conclusions presented.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Gammon et al. 2002) USA	Case control study. Level III-2.	Study setting. Long Island Breast Cancer Study Project. Population based study. Sample Median age group at reference (years): cases 55-64, controls 55-64 Median age at menarche (years): cases 12, controls 12 Nulliparous (%): cases 13, controls 11 Median BMI (kg/m^2) at reference: cases 25.2-29.2, controls 22.3-25.1 Never smoked (%): cases 44.8, controls 45.0 Family history of breast cancer (%): cases 19.2, controls 13.0	Cases (n=1,508) Newly diagnosed with a first primary *in situ* or invasive breast cancer between August 1996 and July 1997, confirmed by physician and medical record, who were resident of Nassau and Suffolk, New York at the time of diagnosis. Able to speak English. Controls (n=1,556) Current residents of Nassau and Suffolk Counties who spoke English, who did not have a personal history of breast cancer, and who were frequency matched to the expected distribution of case women by 5 year age group. Random digit dialling used to identify controls. Data collection Self-report, blood and urine sample (collected prior to chemotherapy) and environmental home data (dust, water and soil). Analysis Unconditional logistic regression. Likelihood ratio test used to assist fitting the model.	<u>Relative risk of breast cancer by ever use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> OR 1.21 (0.99-1.49) Adjusted for age at reference, race, cigarette smoking, alcohol use, use of HRT, lactation and mammography	Limitations ▪ 2,271 women with breast cancer were initially identified as potentially eligible, 2,030 of these were identified by the physician as likely to be eligible and consent was obtained in 1,837 (90.5%). The main questionnaire was completed by 1,508 eligible cases (82%). ▪ Response rate to the telephone screener (controls) was 78%. Known response rate among controls under 65 years was 58% (unknown for the 65+ group). The main questionnaire was completed by 1,556 eligible cases (63%). ▪ >97% of residents in the study region are English speaking. ▪ Cases included both invasive and *in situ* disease. ▪ Recall bias needs to be considered. ▪ Observational study susceptible to residual confounding. Comments ▪ Aim was to determine whether breast cancer risk among women in the counties of Nassau and Suffolk, New York is associated with selected environmental exposures. ▪ Study conducted in the region due to high incidence of breast cancer and concern about effects of environmental contaminants such as DDT. ▪ Lab personnel blinded to case/control status. Reported conclusions (by authors). Established risk factors for breast cancer that were found to increase risk among Long Island women include lower parity, late age at first birth, little or no breast feeding and family history of breast cancer. Other conclusions of less relevance to this review topic were also presented.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Heinemann et al. 2002) Germany	Retrospective cohort study Level III-2.	Study setting. German Cohort Study on Women's Health is analysing the lifetime risk of tumours going back in time in a cohort of volunteers. Sample Mean age 39.1 years Mean number of children 1.3 Mean BMI 24.3 kg/m^2 University educated: 2.6% Employed: 62.6%	Study population (610,328 women-years of observation on 15,374 participants). Accrual of participants began in 1998. Participants were volunteers up to the age or 65 years at the time of inclusion. Data collection Self reported data were collected using a postal questionnaire. Outcome measures Benign and malignant breast tumours Analysis Initial cohort data collected until 2000 were analysed using logistic regression. Excluded women with previous malignant tumours from the analysis of benign tumours.	<u>Relative risk of breast cancer by use of oral contraceptives (Reference: never use): adjusted RR (95% CI)</u> Ever use: RR 0.6 (0.5-0.8) <u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: never use): adjusted RR (95% CI)</u> < 5 years: RR 0.7 (0.5-0.9) 5-10 years: RR 0.7 (0.5-1.0) 10+ years: RR 0.6 (0.4-0.8) <u>Relative risk of breast cancer by time since last use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> Current use: RR 0.5 (0.3-0.7) <5 years: RR 0.7 (0.5-0.9) 5-10 years: RR 0.6 (0.4-0.9) 10+ years: RR 0.6 (0.5-0.8) <u>Relative risk of breast cancer by use of only low estrogen oral contraceptives (Reference: never use): adjusted RR (95% CI)</u> Ever use: RR 0.8 (0.5-1.2) All estimates adjusted by age, use of other sex steroids, parity, gynaecological conditions.	Limitations ▪ Study population consisted of volunteers. May result in lack of representativeness and selection bias. However, characteristics of the sample were similar to German women as a whole (data not presented). ▪ Self –reported data may be susceptible to misclassification but such misclassification is likely to be non-differential, therefore diluting the association between exposure and risk of breast cancer. ▪ Utilised self-reported outcome data, which has not been validated. However, registry based estimates suggest a similar rate of breast cancer as that estimated in the study cohort. ▪ Exposed subjects may be more likely to participate in screening resulting in increased likelihood of tumour detection. ▪ Recall bias needs to be considered. ▪ Observational study susceptible to residual confounding. ▪ Participation rate and follow-up rate unclear. Comments ▪ Primarily aimed to investigate the role of lower estrogen dose OC on breast cancer risk. Reported conclusions (by authors). Ever-use of OCs is associated with a markedly decreased risk of developing malignant or benign breast tumours particularly in women under 50. In these younger women, the reduced risk associated with lifelong exclusive use of low estrogen OCs may be more pronounced.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Hemminki et al. 2002) Finland	Matched, case control study Level III-2.	Study setting. Study population had attended the Helsinki Student Health Service (HSHS) at least three times. Sample Current smoker (%): cases 23, controls 29 No alcohol use (%): cases 9, controls 15 Active sports (%): cases 21, controls 35 Mean weight (kg): cases 57.0, controls 56.2 Mean height (cm): cases 166, controls 165 Mean age at menarche (years): cases 12.8, controls 12.7 Any births (%): cases 73, controls 67 Mean age at first delivery: cases 28.1, controls 27.7	Cases (n=150) Identified by linking the Finnish Cancer Registry (1967-1997) to the HSHS databases. Visited HSHS at least three times. Exclusions: First HSHS visit after breast cancer diagnosis. Controls (n=316) Five random controls, matched for year of birth were selected for each case. Visited HSHS at least three times (except when unable to match controls to the case, when one control was selected from group who had not attended at least 3 times). Exclusions: died before or whose first visit was after the time of diagnosis of the case Data collection Collected from HSHS patient records. Analysis Conditional logistic regression used.	<u>Relative risk of breast cancer by ever use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> Ever use: OR 2.1 (1.1-4.2) Not recorded: OR 1.6 (0.6-4.0) Adjusted for parity and age at delivery, sports and smoking. <u>Relative risk of breast cancer related to age at start of OC use (Reference: 25+ years): adjusted OR (95% CI)</u> 16-19 years: OR 0.5 (0.2-1.6) 20-24 years: OR 0.9 (0.5-1.9) Adjusted for parity and age at delivery, sports and smoking. <u>Relative risk of breast cancer related to age at start of OC use in relation to first birth (Reference: user, no births): adjusted OR (95% CI)</u> User after first birth: OR 0.8 (0.2-2.5) User before first birth: OR 1.0 (0.5-1.7) Adjusted for parity and age at delivery, sports and smoking.	Limitations ▪ Breast cancer diagnosed in 396. 153 of these attended HSHS at least 3 times but three were excluded due to diagnosis of breast carcinoma before first visit to HSHS. ▪ Controls: 1,980 randomly selected, with 314 having visited HSHS at least 3 times. No control remained for 14 cases and one new control was selected from the 388 leftover controls. 12 were excluded as per the *a priori* exclusion criteria. ▪ Missing data of relevance from patient charts. ▪ Limited range of potential confounders included in the multivariate models – residual confounding likely. ▪ Broad confidence intervals reflecting low study power. ▪ Requirement for 3 visits probably excluded more non-users than OC users. This was likely to be greater amongst the controls than the cases, resulting in underestimation of the relationship between OC use and breast cancer. Comments ▪ Study aims were to investigate whether women starting OCs at a young age and before first birth have an increased risk for breast cancer and second, to report difficulties encountered in studying long-term health impacts of medical technologies. ▪ Finnish Cancer Registry relies on mandatory reporting and the notification rate and accuracy is thought to be high. ▪ Data extracted by trained nurse blind to case/control status. Reported conclusions (by authors). Because adoption of the modern pattern of OC use was not common among students, it is unlikely that the impact of early and extended OC use can be studied before 2010, when women born in the 1960s are 40-50 years old.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Kumle et al. 2002) Norway Sweden	Prospective cohort study Level III-2.	Study setting. Women's lifestyle and Health study conducted in Norway and Sweden. Sample (n=106,844) Country of residence (%): Norway: 54.1 Sweden: 45.9 Mean age at enrolment (years): 40.7 Mean BMI (kg/m^2): 23.2 Mean age at menarche (years): 13.1 Postmenopausal at entry (%): 4.0 Ever used HRT (%): 3.9 History of breast cancer in mother/sister (%): 4.9 Nulliparous (%): 11.8 Mean number of children: 2.0 Mean age at first birth (years): 24.0	Eligibility criteria Cohort enrolled during 1991-2 from 1. Women born between 1943 and 1957 in Norway (population randomly selected from the Central Population Register) and 2. women born between 1943-1962 in Sweden (population randomly selected from the Swedish Central Population Registry). Data collection Survey questionnaire sent to participants at the time of invitation to take part. Follow-up interval. Follow-up performed by linkage between the cohort data set and various population based registries (including death registers, migration registers, cancer registries) Analysis Start of follow-up defined by return of questionnaire. Follow-up ended on December 21, 1999, or at emigration, death or primary breast cancer diagnosis, whichever occurred first.	<u>Relative risk of breast cancer by ever use of oral contraceptives (Reference: never use): adjusted RR (95% CI)</u> RR 1.3 (1.1-1.5) <u>Relative risk of breast cancer by recency of use of OC (Reference: never used): RR (95% CI)</u> <2 years: OR 1.6 (1.2-2.3) 2-4 years: OR 1.2 (0.8-1.8) 5-9 years: OR 1.4 (1.0-1.8) 10-14 years: OR 1.2 (1.0-.6) 15+ years: OR 1.3 (1.0-1.5) <u>Relative risk of breast cancer by current/recent use of oral contraceptives at start of follow up (Reference: never use): adjusted RR (95% CI)</u> RR 1.6 (1.2-2.1) <u>Relative risk of breast cancer by former use of oral contraceptives at start of follow up (Reference: never use): adjusted RR (95% CI)</u> RR 1.2 (1.1-1.4) <u>Relative risk of breast cancer by duration use of oral contraceptives (Reference: never use): adjusted RR (95% CI)</u> < 5 years: RR 1.2 (1.0-1.5) 5-9 years: RR 1.2 (1.0-1.5) 10-14 years: RR 1.4 (1.1-1.8) 15+ years: RR 1.3 (1.0-1.8) *P*trend 0.005	Limitations ▪ Overall crude participation rate 54.5%. Analysis included 103,027 (with further exclusions due to lack of information on hormonal use, having an invasive breast cancer at enrolment or had died or emigrated at that time). ▪ Of the 106,844, 789 emigrated and 1,360 died during follow-up. ▪ Observational study susceptible to residual confounding. ▪ Self reported data susceptible to misclassification. However, this is most likely to be non-differential in this prospective study, which would dilute the estimated association. ▪ Good level of follow-up. Comments ▪ Study aimed to examine the role of hormonal contraception in breast cancer Reported conclusions (by authors). Current/recent use of OCs is associated with an increased breast cancer risk. Use of combined OCs and progestin only pills seem to increase the risk at the same level.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Kumle et al. 2002) *continued*			Relative hazards estimated using Cox proportional hazard models. Co-variates were determined for inclusion in the model *a priori*.	<u>Relative risk of breast cancer by duration use of oral contraceptives before first pregnancy (Reference: never use): adjusted RR (95% CI)</u> ≤12 months: RR 1.4 (1.0-1.8) 13-60 months: RR 1.2 (0.9-1.5) 61+ months: RR 1.0 (0.6-1.7) <u>Relative risk of breast cancer by type of oral contraceptives (Reference: never use): adjusted RR (95% CI)</u> Progestin only: RR 1.1 (0.8-1.7) Combined OC: RR 1.3 (1.1-1.6) All analyses adjusted for age, parity, age at first birth, age at menarche, use of HRT, menopausal status, history of breast cancer in first degree relatives, duration of breastfeeding, BMI, region and interaction between BMI and menopausal status.	

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Kuru et al. 2002) Turkey	Case control study Level III-2.	Study setting. Hospital based case control study Sample Mean age (years): cases 49.4, controls 46.4, *P*<0.001 Age <15 yrs at menarche (%): cases 76, controls 65, *P*<0.01 Nulliparous (%): cases 12, controls 5, *P*=0.75 Positive family history (%): cases 6, controls 2, *P*=0.005	Cases (n=504) All women admitted to surgical clinics of Ankara Oncology Education and Research Hospital with histologically proven breast cancer and resident in Ankara or five other regions of Turkey. Controls (n=610) Women residing in the same geographical areas as the cases and admitted to the wards or outpatient clinics of the same hospital during the same interval. Exclusions: women with malignant, endocrine or gynaecological disease. Data collection Collected through questionnaires and interview. Analysis Unconditional logistic regression used.	<u>Relative risk of breast cancer by ever use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> OR 1.51 (1.10-2.08) Adjusted for age, residence, age at menarche, menstrual irregularity, parity, nulliparity, age at first pregnancy, breast feeding, family history, BMI, education, previous benign breast biopsy, menopausal status and age at menopause.	Limitations ▪ Twelve potential cases and 26 potential controls were excluded due to inability to recall age at menarche/menopause (2% of potential cases, 4% of potential controls). ▪ Recall bias needs to be considered. However, unlikely to be an issue with use versus non-use of OCs. ▪ Observational study susceptible to residual confounding. ▪ Controls may not be representative of the population from which the cases were selected. Hospital based population used. Comments ▪ Study aim was to identify risk factors for breast cancer in Turkey ▪ None of the participants refused interview Reported conclusions (by authors). The results of the present study will lead to a better understanding of the risk factors for breast cancer in a developing country.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Marchbanks et al. 2002) USA	Matched, case control study Level III-2.	Study setting. Population based case control study in five US centres. Sample Age (years): cases 49.7, controls 49.5 Age at menarche (years): cases 12.4, controls 12.4 Age at menopause among postmenopausal women (years): cases 47.0, controls 45.2, *P*<0.01 Age at first term pregnancy among parous women (years): cases 23.1, controls 22.9, *P*=0.01 Number of term pregnancies: cases 2.1, controls 2.3, *P*<0.01 BMI 5 years before reference date (kg/m^2): cases 25.5, controls 25.8, *P*=0.01 Postmenopausal (%): cases 33.7, controls 34.1, *P*=0.04 Family history of breast cancer (%): cases 17.0, controls 9.7, *P*<0.01	Cases (n=4,576) Aged 35-64 years Resided in study locations Invasive breast cancer initially diagnosed between 1994 and 1998. Selection probabilities were specific for each study site with over sampling of younger women and black women. Controls (n=4,682) No diagnosis of invasive or *in situ* breast cancer. Identified from the same locations as the cases using random digit dialling. Controls were randomly selected from the group identified as eligible during telephone screening at rates designed to match the frequency of interviews with controls to the frequency of interviews with cases within strata of study site, race and age. Data collection Face to face interview using a standardised instrument.	<u>Risk of breast cancer according to the use of combination oral contraceptives, adjusted OR (95% CI)</u> 1. Use versus no use Any use: OR 0.9 (0.8-1.0) Current use: OR 1.0 (0.8-1.3) Former use: OR 0.9 (0.8-1.0) 2. Duration of use (no use as reference) <1yr: OR 0.9 (0.8-1.1) 1-4 yrs: OR 0.9 (0.8-1.0) 5-9 yrs: OR 0.9 (0.8-1.0) 10-14 yrs: OR 0.8 (0.7-1.0) 15+ yrs: OR 1.0 (0.8-1.3) 3. Age at first use (no use as reference) <15 yrs: OR 0.9 (0.6-1.2) 15-19 yrs: OR 1.0 (0.8-1.1) 20-24 yrs: OR 0.9 (0.8-1.0) 25-29 yrs: OR 0.9 (0.8-1.1) 30-34 yrs: OR 0.8 (0.6-1.) 35-39 yrs: OR 1.2 (0.8-1.6) 40+ yrs: OR 1.0 (0.6-1.6) 4. Recency of use (no use as reference) Current use: OR 1.0 (0.8-1.3) 7mo-4yrs: OR 0.7 (0.5-0.9) 5-9 yrs: OR 0.9 (0.8-1.2) 10-14 yrs: OR 0.9 (0.8-1.1) 15-19 yrs: OR 0.9 (0.7-1.0) 20+ yrs: OR 0.9 (0.8-1.0) 5. High oestrogen dose (no use as reference) Any use: OR 0.8 (0.7-0.9) Current use: OR 0.7 (0.2-1.8) Former use: OR 0.8 (0.7-0.9)	Limitations ▪ Of 5,982 eligible cases, 4,576 were interviewed (76%) ▪ Approximately 82% of "control households" were screened successfully. Of 5,956 eligible controls, 4,682 (79%) were interviewed. Actual response rate 65%. ▪ 0.5% of women did not know what type of OC they used – these were imputed as combined OC rather than progestin only OC (the combination OC accounted for 99.5% of all use). ▪ Recall bias needs to be considered. ▪ Observational study susceptible to residual confounding. ▪ Differences in study results across the different sites – authors unable to explain why this would be the case. Comments ▪ Aimed to determine the risk of breast cancer among former and current users of OCs. Reported conclusions (by authors). Among women from 35 to 64 years of age, current or former OC use was not associated with a significantly increased risk of breast cancer.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Marchbanks et al. 2002) *continued*			Analysis Conditional logistic regression used. Eight *a priori* factors were included in all models as potential confounders. Additional factors were assessed in selected models (however, these were not included in final models as their inclusion did not alter point estimates substantially).	6. Low oestrogen dose (no use as reference) Any use: OR 0.9 (0.8-1.0) Current use: OR 1.0 (0.8-1.3) Former use: OR 0.9 (0.8-1.0) All analyses adjusted for menopausal status, age at menarche, age at menopause, number of term pregnancies, age at first term pregnancy, BMI, family history of breast cancer, use of HRT.	

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Petro-Nustas et al. 2002) Jordan	Case control study Level III-2.	Study setting. Cases selected from Jordan Cancer Registry Sample Median age (years): cases 46-53, controls 46-53 Average age at menarche (years): cases 13.4, controls 13.8, *P*<0.05 Median number of children born: cases 5, controls 5	Cases (n=100) All Jordanian women with breast cancer listed in the Jordan Cancer Registry for 1996. Controls (n=100) Convenience proportionate sample based on the percentage of cases from each area of the country Data collection Face to face interviews conducted in the participants homes. Analysis Logistic regression was used.	<u>Relative risk of breast cancer by ever use of oral contraceptives (Reference: never use): OR (95% CI)</u> OR 6.28 (3.14-12.55)	Limitations ▪ From 451 cases of breast cancer included on the registry for 1996, 100 were included in the analysis. Reasons for non-inclusion were dead (n=156), could not be located (n=170), diagnosed before 1996 (n=17), refused to participate (n=8) ▪ From the 104 controls selected, four refused (participation rate 96%). ▪ Controls may not be representative of the population from which the cases were selected. Note a convenience sample was used. ▪ Adjusted OR not presented for oral contraceptive data. Result presented opposite does not control for potential confounders ▪ Recall bias needs to be considered. ▪ Difficult to interpret study results in relation to risk associated with OC use. Comments ▪ Aim was to investigate risk factors for breast cancer in Jordanian women Reported conclusions (by authors). Significant differences in correlates of breast cancer were found between the cases and the controls.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Tryggvadottir et al. 2002) Iceland	Nested, matched case control study Level III-2.	Study setting. Sample selected from a population based cancer registry (80,219 women attending breast and cervical screening during 1979-1995). Women were aged 20-81 years at the time of attending. Termed the CDC cohort. Sample <40years Age at menarche <13 (%): cases 45, controls 32 Nulliparous (%): cases 13, controls 12 Height (%): ≤160cm: cases 13, controls 15 161-169cm: cases 58, controls 56 170+cm: cases 29, controls 29 Weight (%): ≤60kg: cases 42, controls 43 61-79kg: cases 46, controls 48 80+kg: cases 11, controls 8 40-55 years Age at menarche <13 (%): cases 32, controls 28 Nulliparous (%): cases 8, controls 5 Height (%): ≤160cm: cases 17, controls 20 161-169cm: cases 59, controls 58 170+cm: cases 24, controls 22 Weight (%): ≤60kg: cases 29, controls 28 61-79kg: cases 55, controls 57 80+kg: cases 16, controls 15 >55 years Age at menarche <13 (%): cases 20, controls 19 Nulliparous (%): cases 13, controls 9 Height (%): ≤160cm: cases 33, controls 40 161-169cm: cases 56, controls 50 170+cm: cases 11, controls 10 Weight (%): ≤60kg: cases 21, controls 24 61-79kg: cases 58, controls 58 80+kg: cases 21, controls 18	Cases (n=1,120) First invasive breast cancer diagnosed between 1979-1995 identified in the Cancer Registry of Iceland. Controls (n=10,537) Sought 10 controls per case matched on birth year and age when giving information. Alive at least until the diagnosis year of the matched case. Data collection Only answers used before the diagnosis of a first breast cancer were used. Self reported data examining reproductive and menstrual risk factors were included. Analysis Study group stratified according to age of diagnosis of cases (<40, 40-55 and >55 years). Conditional multiple logistic regression was applied.	<u>Relative risk of breast cancer by increased duration of use of 12 weeks: adjusted OR (95% CI)</u> All ages OR 1.00 (0.99-1.01) Age <40 years OR 1.00 (0.97-1.03) Age 40-55 years OR 1.00 (0.98-1.02) Age >55 years OR 1.00 (0.98-1.03) Adjusted for age at menarche, parous, age at first birth, parity, lactation, height and weight.	Limitations ▪ Record linkage of the Cancer Registry of Iceland and CDC databank identified 85% of those in the CDC databank. ▪ 70% of the 1,601 cases were included in the analysis. ▪ Self reported data may be subject to misclassification. However, this is likely to be small and non-differential, resulting in dilution of relative risk estimates. ▪ Observational study susceptible to residual confounding. Comments ▪ Primary aim was to explore the relationship between breast cancer and established risk factors by specific age groups of diagnosis of breast cancer. ▪ Most of the data were collected from women attending cervical screening rather than mammography. ▪ Only answers used before the diagnosis of a first breast cancer were used. Reported conclusions (by authors). The results confirm that age at diagnosis should be taken into account when studying the effects of breast cancer risk factors.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Gomes et al. 2001) Brazil	Case control study Level III-2.	Study setting. Hospital based case control study in Brazil. Sample Median age group (years): 45-54 Education < 12 years (%): 89 Age < 13 years at menarche (%): 33 Age < 45 at menopause (%): 42 Nulliparous (%): 15 Family history of breast cancer (%): 7 Cigarette smoking (%): 23	Cases (n=300) Breast cancer cases aged 25-75 years admitted to Federal University Hospital between January 1978 and December 1987. Controls (n=600) Selected from the same hospital during the same period, free from any cancer, with normal breasts on examination and matched on age (± 2 years) and date of diagnosis (± 6 months) on a 2:1 ratio. Two series of controls used: 1. selected from general outpatient care unit, 2. admitted to gynaecological services. Data collection Medical records used. Analysis Conditional logistic regression used.	<u>Relative risk of breast cancer by ever use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> OR 1.93 (1.19-3.11) <u>Relative risk of breast cancer by ever use of oral contraceptives (Reference: never use): stratified by menopausal status, adjusted OR (95% CI)</u> 1. Premenopausal OR 1.46 (0.77-2.75) 2. Post-menopausal OR 2.92 (1.18-7.24)	Limitations ▪ 300 of 388 cases were included. Exclusions included presence of distant metastases (n=24), lost biopsy (n=1), nonepithelial tumours (n=9), lack of confirmed biopsy (n=41), male breast carcinoma (n=2), outside age range (n=11), lacking information on menopausal status (n=20). ▪ Data collected from medical records was incomplete leading to exclusion of some variables from the analysis. This may have lead to residual confounding. ▪ Loss of study power resulting from missing data. From the initial study population of 300 cases and 600 controls, complete information was available for 235 matched sets. ▪ The variables included in the final models were not documented. ▪ Controls may not be representative of the population from which the cases were selected ▪ Cases from this hospital based population may not be representative of all cases. ▪ Recall bias needs to be considered in this case control study – likely to overestimate level of risk associated with OC use. ▪ Observational study susceptible to residual confounding. Comments ▪ Diagnosis of breast cancer confirmed by second pathologist. Reported conclusions (by authors). The present study indicates that breast cancer diagnosed before and after menopause has a similar risk profile.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Parvez et al. 2001) Pakistan	Case control study Level III-2.	Study setting. Hospital based case control study – set in Oncology Department, Services Hospital Lahore from August 1999 to August 2000. Sample Median age group (years): cases 41-50, controls 21-30	Study population. Women aged over 15 years fulfilling the description provided under study setting. Cases (n=100) Breast cancer based on histopathological report of biopsy. Controls (n=100) "Attempt made to select those relatives or friends who attended the patient during her stay in hospital with more or less same age group etc." Control subjects had no history of malignancy. Data collection Proforma containing demographic factors and established risk factors for breast cancer were pre-developed and administered by briefed medical officers. Analysis Chi-square test used.	<u>Relative risk of breast cancer by use of IPC (Reference: never use): crude OR</u> OR 25, *P*<0.001 Note OR calculated by review authors based on data presented in the original study	Limitations ▪ Ill defined selection criteria for inclusion of controls ▪ Cases poorly defined – unclear if restricted to first incident cases and whether *in situ* cases were excluded ▪ Considerable susceptibility to selection bias ▪ No control for potential confounders ▪ Recall bias needs to be considered ▪ Small sample size Comments ▪ Objective was to evaluate established risk factors for breast cancer in the study population described under study setting. Reported conclusions (by authors). There is a family tendency for breast cancer and estrogenic hormones are playing some role. More possibility of breast cancer was found in infertile and those having early menarche.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Shapiro et al. 2000) South Africa	Case control study Level III-2.	Study setting. Hospital based case control study Sample Median age (years): cases 44, controls 41.	Population "Black" and "Coloured" women aged 20-54 years, hospitalised in Cape Town and resided in a defined area around Cape Town. Exclusions: Women with carcinoma *in situ*, previous history of cancer or had not resided in the study region for at least 6 of the last 12 months. Cases (n=419) First occurrence of invasive breast cancer treated between Jan 1994 and Oct 1997 at two tertiary care hospitals in Cape Town. Controls (n=1625) Women admitted for diagnoses judged to be independent of contraceptive use and breast cancer risk. Frequency matched to cases for decade of age, ethnic group and area of residence. Exclusions: admitted for conditions such as venous thromboembolism, ischaemic heart disease or benign breast disease. Data collection Questionnaire written in English, Afrikaans or Xhosa was administered in the subjects' preferred language by qualified nurses. Analysis Unconditional logistic regression used.	<u>Injectable Progestogen (IPC) results:</u> <u>Relative risk of breast cancer by use of IPC (Reference: never use): adjusted OR (95% CI)</u> Ever use: OR 0.9 (0.7-1.2) <u>Relative risk of breast cancer by duration of IPC use (Reference: 0 years use): adjusted OR (95% CI)</u> < 1 year: OR 0.8 (0.6-1.1) 1-4 years: OR 1.0 (0.7-1.3) 5-9 years: OR 0.8 (0.6-1.2) 10+ years: OR 1.0 (0.7-1.5) <u>Relative risk of breast cancer by time since first use of IPC (Reference: never use): adjusted OR (95% CI)</u> < 5 years: OR 1.2 (0.7-2.2) 5-9 years: OR 1.1 (0.7-1.8) 10-14 years: OR 1.2 (0.8-1.7) 15+ years: OR 0.8 (0.7-1.1) <u>Relative risk of breast cancer by time since last use of IPC (Reference: never use): adjusted OR (95% CI)</u> Current: OR 1.6 (1.1-2.3) 1-4 years: OR 1.0 (0.7-1.5) 5-9 years: OR 0.8 (0.5-1.2) 10-14 years: OR 1.0 (0.7-1.4) 15+ years: OR 0.8 (0.6-1.1) All estimates adjusted for age, ethnic group, socio-economic status, and any combined COC use.	Limitations ▪ Conditions considered as ineligible for inclusion as a control appear to be vague ▪ Limited baseline data provided ▪ Discrepancy between number of cases reported in the abstract and in the text ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered ▪ Hospital based controls may not be representative of the population from which the cases were drawn Comments ▪ Aim was to evaluate the risk of breast cancer among women exposed to injectable progestogen contraceptives (IPC) and Combined Estrogen/Progestogen Contraceptives (COC) ▪ High participation rate amongst cases (98.8%) and controls (99.9%) Reported conclusions (by authors). Findings suggest that IPCs do not increase the risk of breast cancer, and that COCs may increase the risk among women below age 35 years, although bias cannot be excluded.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Shapiro et al. 2000) *continued*				Combined oral contraceptive (COC) results: Relative risk of breast cancer by use of COC (Reference: never use): adjusted OR (95% CI) Ever use: OR 1.2 (1.0-1.5) Relative risk of breast cancer by duration of COC use (Reference: 0 years use): adjusted OR (95% CI) < 1 year: OR 1.1 (0.8-1.4) 1-4 years: OR 1.3 (1.0-1.8) 5-9 years: OR 1.4 (0.9-2.1) 10+ years: OR 1.2 (0.7-2.3) Relative risk of breast cancer by time since first use of COC (Reference: never use): adjusted OR (95% CI) < 5 years: OR 1.2 (0.7-2.0) 5-9 years: OR 1.7 (1.0-2.7) 10-14 years: OR 1.2 (0.8-1.9) 15+ years: OR 1.1 (0.8-1.4) Relative risk of breast cancer by time since last use of COC (Reference: never use): adjusted OR (95% CI) Current: OR 1.1 (0.6-2.1) 1-4 years: OR 1.6 (1.1-2.3) 5-9 years: OR 1.3 (0.9-2.1) 10-14 years: OR 1.4 (1.0-2.1) 15+ years: OR 0.9 (0.7-1.2) All estimates adjusted for age, ethnic group, socio-economic status, and any IPC use.	

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Van Hoften et al. 2000) The Netherlands	Nested case control study Level III-2.	Study setting. Nested case control study utilising the population based DOM3 cohort, Utrecht, The Netherlands. Sample Mean age (years): cases 45.4, controls 45.5 Ever married (%): cases 90.3, controls 95.1 Education (%): Elementary School: cases 26.9, controls 27.0 Lower vocational/general secondary: cases 44.7, controls 43.6 Intermediate vocational: cases 13.6, controls 9,7 Higher general secondary: cases 5.8, controls 8.5 Higher vocational/University: cases 9.1, controls 11.1 Mean BMI (kg/m^2): cases 24.7, controls 24.6 Nulliparity (%): cases 14.9, controls 12.6 Mean age at first delivery (years): cases 22.1, controls 22.6 Mean age at menarche (months): cases 161.1, controls 163.0 Premenopausal (%): cases 92.9, controls 85.9 Maternal history of breast cancer (%): cases 10.7, controls 3.8	Study population exclusions: History of breast cancer Used drugs for the treatment of menopausal symptoms Undergone oophorectomy, hysterectomy, medical or x-ray treatment of ovaries. Missing data. Cases (n=309) Breast cancer cases aged 42-63 years, diagnosed between Nov 1982 and May 1996. Cases were identified through linkage to the regional cancer registry. Controls (n=610) Random selection of non-cases from the DOM cohort. Data collection Mailed, self-administered questionnaire. Questionnaire was checked for completeness by clinical assistants. Analysis Logistic regression used. Variables were not considered as confounders when they did not change the magnitude of the association between OC use and breast cancer.	<u>Relative risk of breast cancer by use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> Ever use: OR 1.31 (0.96-1.79) <u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: 0 years use): adjusted OR (95% CI)</u> 1-10 years: OR 1.27 (0.92-1.77) > 10 years: OR 1.43 (0.92-2.22) Note only significant results for age group > 55 years (duration of OC use, reference of 0 years use): 1-10 years: OR 1.26 (0.74-2.14) > 10 years: OR 2.05 (1,07-3.95) All estimates adjusted for age, menopausal status, marital status, education, cigarette smoking, number of children at the time of the questionnaire, age at first delivery, age at menarche, and maternal history of breast cancer.	Limitations ▪ Missing data resulted in exclusion of 10 cases and 11 controls. Overall exclusions (which fulfilled the exclusion criteria): cases 90 (23%), controls 188 (24%). ▪ Observational study susceptible to residual confounding. ▪ Potential misclassification of exposure status. However, this is likely to be non-differential, resulting in underestimation of any association between OC use and breast cancer risk. ▪ Unable to consider risk for different OC preparations. Comments ▪ Examined the relationship between OC use and breast cancer in 42-63 year old women. Women aged over 55 years studied separately but it was unclear if this was an *a priori* study decision. ▪ Selection bias minimised through use of nested design. Reported conclusions (by authors). Long duration of OC use increases the risk of breast cancer in women over 55 years of age but not in younger women.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Magnusson et al. 1999) Sweden	Case control study Level III-2.	Study setting. Population based case-control study Sample Mean age (years): cases 62.6, controls 63.7 Mean age at menarche (years): cases 13.5, controls 13.6 Mean age at menopause (years): cases 50.5, controls 50.0 Mean parity: cases 1.8, controls 2.1 Mean age at first birth (years): cases 25.3, controls 24.6 Mean recent BMI (kg/m^2): cases 25.7, controls 25.5 Mean BMI at age 18 (kg/m^2): cases 20.6, controls 20.8 Family history of breast cancer (%): cases 16.0, controls 9.2 Benign breast disease (%): cases 13.8, controls 9.6	Cases (n= 3,016) Women aged 50-74 years with invasive breast cancer, without previously diagnosed breast cancer, born in Sweden and resident there between October 1993 and March 1995. Incident cases identified through six regional cancer registries. Women of unknown menopausal status or previous diagnosis of invasive cancer (other than non-melanoma skin cancer) were excluded. Controls (n=3,263) Women frequency matched to the expected age distribution of the cases randomly selected from a continuously updated register of all people residing in Sweden. Women of unknown menopausal status or previous diagnosis of invasive cancer (other than non-melanoma skin cancer) were excluded. Data collection Mailed questionnaires and telephone interviews used. Telephone interviews were restricted to 11% of controls who failed to return the mailed questionnaire. Analysis Unconditional logistic regression used.	<u>Relative risk of breast cancer by use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> Ever use: OR 0.98 (0.86-1.12) <u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: < 5 years use): adjusted OR (95% CI)</u> 5+ years: OR 0.98 (0.82-1.18) <u>Relative risk of breast cancer by recency of use of OC (Reference: never used): adjusted OR (95% CI)</u> < 10 years: OR 1.00 (0.69-1.44) 10-19 years: OR 0.95 (0.78-1.16) 20+ years: OR 1.02 (0.87-1.18) Estimates adjusted for age, age at menarche, parity, age at first birth, menopausal status, age at menopause, height, BMI one year prior to data collection and use of HRT for at least one year.	Limitations ▪ 16% of eligible cases and 18% of eligible controls did not participate in the study ▪ Mixed methods of data collection, including the use of telephone interviews in a proportion of controls, may have resulted in bias ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered ▪ Note reference for duration of OC use was < 5 years rather than never use Comments ▪ Aimed to examine whether age at menarche is causally involved in breast cancer aetiology or serves as a correlate of other early life exposures. Other aspects of reproductive life, including cycle length and regularity, climacteric symptoms, reproductive history and oral contraceptive use were also examined. ▪ Study restricted to women aged 50 to 74 years. Reported conclusions (by authors). Findings provide some evidence of a role of environmental correlates of early menarche in breast cancer aetiology, and underline the importance of childbirth, especially early in life, in the prevention of breast cancer. Our data are not readily compatible with an important influence of former oral contraceptive use on post-menopausal breast cancer risk.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Price et al. 1999) Australia	Case control study Level III-2.	Study setting. Women recalled for assessment after routine mammography. Sample Mean age (years): cases 61.2, controls 55.3 Married/defacto (%): cases 68.9, controls 74.5 Level of education: Primary: cases 3.4, controls 3.7 3-4 yrs secondary: cases 38.1, controls 37.6 5-6 yrs secondary: cases 17.3, controls 15.4 Diploma/certificate: cases 24.5, controls 24.1 University/college: cases 16.7, controls 19.3 Australian born (%): cases 74.7, controls 71.3 Family history of breast cancer (%): cases 17.5, controls 13.9 History of benign breast disease (%): cases 18.9, controls 16.2 Nulliparous (%): cases 12.9, controls 14.0	Study population Women aged 40-87 recalled following routine mammography during April 1994 to April 1997. Exclusions: prior personal history of breast cancer, non-English speaking, physical or psychiatric impairment preventing completion of the questionnaire. Cases (n=298) "Breast cancer cases" Controls (n=1,926) "No abnormality detected and those diagnosed with cysts or benign breast disease" Data collection Self-administered questionnaire completed on arrival (and before assessment) at the clinic. Analysis Logistic regression used.	<u>Relative risk of breast cancer by ever use of oral contraceptives (Reference: never used): adjusted OR (95% CI)</u> OR 1.44 (1.04-2.00) <u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: never used): adjusted OR (95% CI)</u> < 1 year: OR 1.11 (0.63-1.96) 1-3 yrs: OR 1.32 (0.83-2.09) 4-6 yrs: OR 1.53 (0.97-2.42) 7-10 yrs: OR 1.36 (0.83-2.22) 10+ yrs: OR 1.73 (1.13-2.65) Estimates adjusted for age, age first child, parity, family history and education.	Limitations ▪ 13% declined participation and 8% had incomplete questionnaires. ▪ controls may not be representative of the population from which the cases were drawn. The group selected may share risk factors of the cases, resulting in underestimation of true associations. ▪ Observational study susceptible to residual confounding. ▪ Non-differential misclassification of exposure data may have occurred – diluting the presence of any association. Comments ▪ Study investigates established risk factors for breast cancer in a cohort of older Australians. ▪ Collection of data before assessment should minimise risk of recall bias. Reported conclusions (by authors). Results suggest that the effects of weight reduction in reducing postmenopausal breast cancer risk should be assessed.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Tavani et al. 1999) Italy	Case control study Level III-2.	Study setting. Data derived from two case-control studies of breast cancer: 1. greater Milan area between 1983 and 1991 2. six areas of Italy between 1991 and 1994. Hospital based controls used. Less that 4% of cases and controls refused interview, on average. Overall dataset (including women 40+ years) included 5,984 cases and 5,504 controls. Sample Age: < 25 years: cases 2%, controls 7% 25-29 years: cases 10%, controls 15% 30-34 years: cases 27%, controls 28% 35-39 years: cases 61%, controls 49% Education < 9 years: cases 43%, controls 52% 9-13 years: cases 37%, controls 35% 13 years: cases 21%, controls 13% Family history of breast cancer (%): Cases 8, controls 4 History of benign breast disease (%): Cases 15, controls 8	Cases (n=579) Histologically confirmed incident breast cancer admitted to the major teaching and general hospitals in the areas under surveillance. Controls (n=668) Acute hospital admissions (to the same network of hospitals as the cases) for non-neoplastic, non-hormone-related diseases. Data collection Questionnaire administered by centrally trained interviewers. Included information on demographic and lifestyle characteristics. Analysis Unconditional multiple logistic regression used.	<u>Relative risk of breast cancer by use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> Ever use: OR 1.05 (0.81-1.36) <u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: never use): adjusted OR (95% CI)</u> ≤ 2 years: OR 1.19 (0.87-1.36) > 2-5 years: OR 0.96 (0.63-1.48) > 5 years: OR 0.86 (0.53-1.40) <u>Relative risk of breast cancer by time since first use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> < 10 years: OR 1.19 (0.86-1.64) 10+ years: OR 0.92 (0.66-1.28) <u>Relative risk of breast cancer by recency of use of OC (Reference: never used): adjusted OR (95% CI)</u> < 5 years: OR 1.17 (0.84-1.63) 5-9 years: OR 1.11 (0.75-1.65) 10+ years: OR 0.85 (0.54-1.36) <u>Relative risk of breast cancer by age of first use (Reference: never use): adjusted OR (95% CI)</u> < 20 years: OR 1.09 (0.61-1.96) 20-22 years: OR 0.60 (0.38-0.95) 23-25 years: OR 1.26 (0.89-1.78) 26 + years: OR 1.26 (0.89-1.78)	Limitations ▪ Hospital based controls may not be representative of the population from which the cases were drawn ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered. Comments ▪ Aimed to investigate the relationship between hormonal and lifestyle risk factors and breast cancer risk in women younger than 40 years ▪ Good participation rate in the two case-control studies from which the current dataset were derived. Reported conclusions (by authors). Most risk factors in this large dataset of women aged less than 40 years were similar to those described in breast cancer epidemiology at any age.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Tavani et al. 1999) *continued*				Relative risk of breast cancer in association with the first use of OCs in relation to first birth (Reference: never use): adjusted OR (95% CI) Before: OR 0.90 (0.57-1.44) Same year: OR 1.19 (0.60-2.37) After: OR 0.95 (0.67 – 1.33) All estimates adjusted for study, centre, year of recruitment, age, education, BMI, family history of breast cancer, parity and age at first birth.	

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Ursin et al. 1999) USA	Frequency matched case control study Level III-2.	Study setting. Population based case control study of Chinese, Filipino and Japanese-American women. Sample Age at diagnosis (years): < 30: cases 2%, controls 3% 30-39: cases 22%, controls 25% 40-49: cases 44%, controls 40% 50+: cases 33%, controls 32% Ethnicity: Chinese: cases 28%, controls 30% Japanese: cases 40%, controls 41% Filipino: cases 32%, controls 29% Years since migration: US born: cases 43%, controls 38% ≤ 1 year: cases 3%, controls 4% 2-7 years: cases 9%, controls 15% 8+ years: cases 37%, controls 35%	Cases (n=597) All women of Chinese, Japanese or Filipino ethnicity diagnosed with histologically confirmed, first primary breast cancer at ages 20-55 years in the San Francisco, Los Angeles and Oahu areas during April 1983-June 1987. Controls (n=966) Frequency matched to the expected case distribution on study area, ethnicity and year of birth (5 year groups) using a 2:1 ratio where possible. Potential subjects were selected with random digit dialling. Exclusions: previous breast cancer or double mastectomy. Data collection In home interviews by trained interviewers with standardised questionnaires. Analysis Unconditional logistic regression used.	<u>Relative risk of breast cancer by ever use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> OR 0.91 (0.72-1.15) <u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: never use): adjusted OR (95% CI)</u> 1-12 mths: OR 1.20 (0.86-1.69) 13-60 mths: OR 0.81 (0.58-1.12) 60+ mths: OR 0.71 (0.47-1.07) *P*trend 0.03 <u>Relative risk of breast cancer by first use of oral contraceptives before FFTP (Reference: no use before FFTP): adjusted OR (95% CI)</u> OR 0.80 (0.54-1.19) <u>Relative risk of breast cancer by age at first use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> > 35 yrs: OR 1.23 (0.62-2.44) 30-35 yrs: OR 0.87 (0.59-1.28) 25-29 yrs: OR 1.10 (0.77-1.58) 22-24 yrs: OR 0.86 (0.56-1.32) ≤ 21 yrs: OR 0.46 (0.24-0.87) <u>Relative risk of breast cancer by time since last use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> < 5 years: OR 0.68 (0.41-1.14) 6-10 years: OR 0.85 (0.57-1.27) 11-15 years: OR 0.92 (0.64-1.33) 16+ years: OR 1.09 (0.75-1.59)	Limitations ▪ Response rate for the screening interview amongst controls (random digit dialling) was 92% in Los Angeles and 91% in San Francisco. 966 of the 1287 eligible controls participated (75%) producing an overall response rate of 71% when taking into account the response to screening interview. ▪ 597 of 852 eligible cases participated (70%). ▪ 23 further cases were excluded due to missing information and 5 controls were excluded as their reference date was determined to be prior to migration. ▪ Observational study susceptible to residual confounding. ▪ Recall bias needs to be considered. Comments ▪ Primarily investigating whether increased use of OCs amongst women who have migrated from Asia explains the rapid rise if risk of breast cancer in this population. Reported conclusions (by authors). This study suggests that OC use cannot explain the elevated risk observed in Asian women who migrated to the United States 7+ years ago.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Brinton et al. 1998) USA	Case control study Level III-2.	Study setting. Case control study among women aged under 55 years in Atlanta, Georgia. Sample	Cases (n=1,031) All women in the Atlanta metropolitan area under the age of 55 years, newly diagnosed with *in situ* or invasive breast cancer during the period May 1990 through December 1992. Controls (n=919) Frequency matched by geographic area and age to the expected distribution of cases and were identified through random digit dialling. Data collection Hospital records abstracted to document details on the clinical and pathologic characteristics of the breast tumours. Personal interviews used to collect data. Analysis Logistic regression used.	<u>Relative risk of breast cancer by use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> Ever use: OR 1.14 (0.9-1.4) <u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: never use): adjusted OR (95% CI)</u> 6 mths-<5yrs: OR 1.11 (0.9-1.4) 5-9 yrs: OR 1.09 (0.8-1.4) 10+ yrs: OR 1.27 (0.9-1.7) <u>Relative risk of breast cancer by time since first use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> <15 yrs: OR 1.26 (0.9-1.8) 15-19 yrs: OR 1.32 (0.9-1.8) 20+ yrs: 1.09 (0.9-1.4) <u>Relative risk of breast cancer by time since last use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> < 5 years: OR 1.26 (0.9-1.8) 5-9 years: OR 1.22 (0.8-1.8) 10+ years: OR 1.11 (0.9-1.4) Adjusted for age, race, number of births and age at first childbirth and history of mammogram.	Limitations ▪ Included *in situ* cases ▪ Response rate of 91% to telephone screening of controls ▪ Proportion of residential numbers that were available for random selection from the population from which cases were selected was unclear ▪ Completed interviews obtained in 90% of eligible cases and 79% of eligible controls ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered ▪ Poor documentation of sample characteristics Comments ▪ Objective was to assess effects on breast cancer risk of exposure to both oral contraceptives and HRT. Reported conclusions (by authors). Although our results must be cautiously interpreted given small numbers within subgroups, they raise concern and emphasise the need for further evaluation on breast cancer risk of the increasingly common exposure to both oral contraceptives and HRT.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Chie et al. 1998) Taiwan	Matched case control study Level III-2.	Study setting. Case control study utilising hospital based controls. Sample Mean age (years): cases 47.7, controls 47.5 Education level: Illiterate: cases 11%, controls 16% Elementary school: cases 30%, controls 34% High school: cases 33%, controls 29% College: cases 26%, controls 21% Age at menarche: ≤ 12 years: cases 13%, controls 8% 13-14 years: cases 39%, controls 39% 15-16 years: cases 33%, controls 39% 17+ years: cases 14%, controls 14% Nulliparous (%): cases 10, controls 8 Age at FFTP < 20 years: cases 5%, controls 11% 20-24 years: cases 37%, controls 41% 25-29 years: cases 35%, controls 33% 30-34 years: cases 9%, controls 6% 35+ years: cases 4%, controls 1%	Cases (n=174) Pathologically confirmed, new incident cases of female breast cancer during February 1993 to June 1994. Controls (n=453) Inpatient controls without a history of obstetric-gynaecological, breast or malignant diseases individually matched for each case by age (± 3 years) and date of admission (± 1 week). Data collection Information obtained through direct interview (using pre-designed questionnaire administered by trained interviewers) and review of medical records. Analysis Conditional logistic regression used.	<u>Relative risk of breast cancer by use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> Ever use: OR 1.7 (0.9-3.2) <u>Relative risk of breast cancer by age of first use (Reference: never use): adjusted OR (95% CI)</u> < 25 years: OR 3.5 (1.2-9.7) 25-29 years: OR 1.7 (0.7-4.1) 30 + years: OR 0.7 (0.2-2.4) *P*trend 0.019 <u>Relative risk of breast cancer in association with the first use of OCs in relation to first birth (Reference: never use): adjusted OR (95% CI)</u> Before: OR 1.3 (0.3-6.0) After: OR 1.8 (0.9 – 3.5) <u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: never use): adjusted OR (95% CI)</u> < 1 year: OR 2.0 (0.8-4.7) 1-4 years: OR 0.9 (0.3-3.0) 5+ years: OR 2.1 (0.8-5.6) Estimates adjusted for education level, BMI, age at menarche and FFTP, parity, menopausal status and age at menopause, lifetime lactation, family history of breast cancer, hormone use other than OC and lactation suppression hormones.	Limitations ▪ Hospital based controls may not be representative of the population from which the cases were drawn ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered ▪ Cases were non-consecutive (included 81% of all cases according to cancer registry data) ▪ Small sample size reflected in broad confidence intervals Comments ▪ Aim was to assess the effects of OC use on the risk of breast cancer in a country of both low incidence of breast cancer and low use of OC. ▪ Pathological reports and medical records of cases were reviewed to rule out misclassification. Reported conclusions (by authors). Results support the notion that OC use in early life for younger women and in early calendar years increase breast cancer risk.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(McCredie et al. 1998b) Australia	Case control study Level III-2.	Study setting. Population based case control study among women aged under 40 years in Melbourne and Sydney, Australia. Sample Age at diagnosis or recruitment: 20-29 years: cases 11%, controls 11% 30-34 years: cases 27%, controls 29% 35-39 years: cases 62%, controls 60% Highest education level achieved: Year 10: cases 18%, controls 11% Year 11/12/vocational training: cases 59%, controls 58% University graduate: cases 23%, controls 31% Marital status: Ever married: cases 90%, controls 81% Never married: cases 10%, controls 19%	Population. Women who spoke English and lived in Sydney or Melbourne metropolitan areas during 1993-5. Cases (n=467). Histologically confirmed, invasive first primary breast cancer identified through population based registries among women aged under 40 years during January 1992 to July 1995 in Melbourne and January 1993 to July 1995 in Sydney. Controls (n=408) Selected from current electoral rolls using proportional random sampling on the expected age distribution of cases. Data collection Structured risk factor questionnaire and family pedigree completed during face to face interviews. Analysis Multiple logistic regression used.	<u>Relative risk of breast cancer by use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> Past use: OR 0.8 (0.5-1.3) Current use: OR 1.2 (0.7-2.0) <u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: never use): adjusted OR (95% CI)</u> < 12 months: OR 0.8 (0.4-1.6) 12-59 months: OR 0.7 (0.4-1.2) 60-119 months: OR 1.0 (0.6-1.7) 120+ months: OR 1.1 (0.6-1.9) <u>Relative risk of breast cancer by time since first use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> Current: OR 1.2 (0.7-2.0) < 12 months: 0R 0.5 (0.2-1.0) 12-59 months: OR 0.8 (0.5-1.5) 60-119 months: OR 1.1 (0.6-2.0) 120+ months: OR 0.7 (0.4-1.2) <u>Relative risk of breast cancer by recency of use of OC (Reference: never used): adjusted OR (95% CI)</u> Current: OR 1.2 (0.7-2.0) < 12 mths: OR 0.5 (0.2-1.0) 12-59 mths: OR 0.8 (0.5-1.5) 60-119 mths: OR 0.8 (0.5-1.5) 120+ mths: OR 0.7 (0.4-1.2) <u>Relative risk of breast cancer by first use of oral contraceptives before FFTP (Reference: no use before FFTP): adjusted RR (95% CI)</u> OR 0.8 (0.6-1.0)	Limitations ▪ 467 of 644 (73%) of eligible cases were interviewed ▪ 408 of 632 (64%) of eligible controls were interviewed ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered. Comments ▪ Aimed to determine lifestyle risk factors and genetic risk factors for breast cancer. ▪ Median time between diagnosis of case and interview was 8 months, and between selection of controls and interview was 2 months. Reported conclusions (by authors). The effects of other reproductive risk factors and oral contraceptive use, although not nominally significant, were in accord with published findings from similar studies in young women. This study of Australian women has indicated that some risk factors for breast cancer in women under age 40 differ from those reported for older women either in direction (e.g. weight) or relative importance (e.g. family history).

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(McCredie et al. 1998b) *continued*				All analyses adjusted for age at menarche, parity, age at first livebirth, reported first degree family history, benign breast disease and height. Other results presented in original paper.	

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Ursin et al. 1998) USA	Matched case control study Level III-2.	Study setting. Study set in LA County, using controls matched to cases by neighbourhood. Sample Characteristics not presented.	Cases (n=744) White female residents of Los Angeles County, aged 40 years or younger, diagnosed with *in situ* or invasive breast cancer between July 1, 1983 and January 1, 1989. Eligibility restricted to women born in the USA, Canada or Europe. Controls (n=744) One neighbourhood control, individually matched to each interviewed case on birth date (within 36 months), race (white), parity (nulliparity versus parous) and neighbourhood of residence. Eligibility restricted to women born in the USA, Canada or Europe. Data collection In person interviews conducted using the same female nurse interviewer. Reference date assigned to each case-control pair was 12 months prior to the date of diagnosis of the case. Analysis Conditional logistic regression used. Models included *a priori* risk factors	<u>Relative risk of breast cancer by ever use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> OR 0.83 (0.62-1.12) <u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: never use): adjusted OR (95% CI)</u> 1-48 mths: OR 0.85 (0.62-1.16) 49-96 mths: OR 0.71 (0.49-1.02) 97-144 mths: OR 0.79 (0.52-1.18) 145+ mths: OR 1.40 (0.81-2.40) <u>Relative risk of breast cancer by recency of use of OC (Reference: never used): OR (95% CI)</u> 0-12 mths: OR 1.14 (0.75-1.72) 13-36 mths: OR 0.76 (0.46-1.59) 37-59 mths: OR 0.78 (0.46-1.31) 60+ mths: OR 0.77 (0.57-1.06) <u>Relative risk of breast cancer by age of first use (Reference: never use): adjusted OR (95% CI)</u> 25+ yrs: OR 0.86 (0.51-1.44) 20-24 yrs: OR 0.78 (0.56-1.09) 17-19 yrs: OR 0.84 (0.60-1.17) < 17 yrs: OR 0.96 (0.60-1.55)	Limitations ▪ Cases included *in situ* and invasive breast cancer ▪ Interviews completed for 744 of the 969 eligible breast cancer patients (77%). Reasons for non-participation were physician refusal (61), patient refusal (111), deceased (20), moved out of LA County (12), could not be found (21). ▪ For 592 cases, the first eligible control participated (80%), for 124 cases, one eligible control refused (17%), and for the remaining 28 cases, 2-6 eligible persons refused prior to recruitment of the matched case (4%). ▪ OC use was defined as the use of combination type OCs and sequential pills but did not include progestin only pills or DepoProvera/Progestasert. ▪ Information about exercise patterns was only obtained for 545 case-control pairs, the remainder were coded the same. ▪ Observational study susceptible to residual confounding. ▪ Recall bias needs to be considered. Comments ▪ Study aim was to determine what particular aspects of OC use could be important for breast cancer development at an early age in the cohort of women who had the opportunity to use OCs all of their reproductive life Reported conclusions (by authors). This study is consistent with a modest effect of early OC use on breast cancer risk in young women.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Ursin et al. 1998) *continued*				Relative risk of breast cancer by duration use of oral contraceptives before first pregnancy (Reference: never use): adjusted OR (95% CI) 1-48 mths: OR 0.85 (0.62-1.18) 49-96 mths: OR 0.71 (0.47-1.06) 97+ mths: OR 0.78 (0.51-1.21) All results adjusted for family history, age at menarche, age at first term pregnancy, total term pregnancies, total months breast feeding, average hours/wk of exercise and use of HCG among low and high Quetelet's index women. Wide range of other results presented in original paper including: Age first used OC Total months OC use before age 20 Total months OC use before age 18 Total months OC use before age 18 and occurred before first pregnancy Time between menarche and first OC use Total months use after first pregnancy Total months ≥ 50μg estrogen OC. All results for these factors were not statistically significant.	

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Hankinson et al. 1997) USA	Prospective cohort Level III-2.	Study setting. Part of the Nurses Health Study (NHS). Began in 1976 among 121,700 female registered nurses. Sample Age at menarche: < 12 years: 22% 12-13 years: 56% 14+ years: 20% Parity: 0: 7% 1-2: 34% 3+: 57% Age at first birth: < 24 years: 50% 25-29 years: 32% 30+ years: 9% Family history of breast cancer: 6% BMI: <21 kg/m^2: 26% 21-<23 kg/m^2: 26% 23-<25 kg/m^2: 20% 25-<29 kg/m^2: 17% 29+ kg/m^2: 11%	Study population Participated in NHS (age 30-55 years at entry). Exclusions. Participants with a diagnosis of cancer (except non-melanoma skin cancer) at baseline. Missing data on OC use. Data collection Biennial mailed questionnaire to ascertain change in exposure status and newly diagnosed illnesses. OC use was investigated in 1976 and the biennial questionnaires during 1978-1982. Outcome measures Women contributing person-time data until the report of a cancer, death or 1 June 1992 – whichever came first. Cancer diagnosis enquired about on each questionnaire. Permission was sought to check medical records for each reported breast cancer. Mortality from breast cancer investigated through the National Death Index (NDI). Analysis Proportional hazard models used.	<u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: never use): adjusted RR (95% CI)</u> < 1 year: RR 1.01 (0.89-1.14) 1-2 years: RR 1.01 (0.89-1.14) 3-4 years: RR 1.08 (0.93-1.26) 5-9 years: RR 1.12 (0.99-1.27) 10+ years: RR 1.11 (0.94-1.32) <u>Relative risk of breast cancer by duration use of oral contraceptives before first pregnancy (Reference: never use): adjusted RR (95% CI)</u> < 1 year: RR 1.00 (0.80-1.24) 1-2 years: RR 0.95 (0.77-1.17) 3-4 years: RR 0.86 (0.59-1.26) 5+ years: RR 0.96 (0.65-1.43) <u>Relative risk of breast cancer by time since first use of oral contraceptives (Reference: never use): adjusted RR (95% CI)</u> < 10 years: RR 1.24 (0.99-1.56) 10-14 years: RR 1.02 (0.88-1.18) 15-19 years: RR 1.13 (1.01-1.27) 20-24 years: RR 1.02 (0.91-1.14) 25+ years: RR 0.97 (0.82-1.16) <u>Relative risk of breast cancer by recency of use of OC (Reference: never used): adjusted RR (95% CI)</u> < 5 years: RR 1.20 (1.00-1.44) 5-9 years: RR 1.02 (0.89-1.16) 10-14 years: RR 1.07 (0.96-1.20) 15-19 years: RR 1.07 (0.95-1.22) 20+ years: RR 0.91 (0.77-1.09) All analyses controlled for age, BMI, age at menarche, history of benign breast disease, family history of breast cancer in mother or sister, age at first birth, age at menopause, and postmenopausal hormone use.	Limitations ▪ Follow up rate of 90% among living participants through 1 June 1992 ▪ Potential misclassification of OC exposure data which is most likely to be non-differential resulting in dilution of any association between OC data and risk of breast cancer ▪ Parity status last assessed in 1984 and OC use in 1982 leading to potential misclassification of these two variables ▪ Observational study susceptible to residual confounding Comments ▪ Investigated whether young women who used OCs for extended periods or women who used OCs before their FFTP were at increased risk of breast cancer ▪ Mortality follow-up approximately 98% complete in the NDI. ▪ Medical diagnosis of breast cancer reviewed by medical personnel blind to exposure status when permission was granted (95% of cases). ▪ Full enrolment in study Reported conclusions (by authors). Study provides considerable evidence that long-term past OC use, either overall or prior to a FFTP, does not result in any appreciable increase in breast cancer risk in women over 40 years of age.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Tryggvadottir et al. 1997) Iceland	Matched, nested case control study Level III-2.	Study setting. Nested case control study set within a population based cohort study. Sample Age at menarche <13 years: cases 38%, controls 31% 13 years: cases 34%, controls 36% 14+ years: cases 28%, controls 33% Nulliparous (%): cases 14, controls 14 Age at first childbirth: < 20 years: cases 27, controls 28 20-29 years: cases 55, controls 58 30+ years: cases 3, controls 1	Cases (n=204) Born after 1944. All Icelandic women diagnosed with invasive breast cancer before July 1995. Information provided before the diagnosis of breast cancer. Controls (n=1,183) Randomly selected from the Cancer Detection Clinic databank, matched on birth year and year of first attendance to the Clinic. Data collection Interviewer administered questionnaires. A question on use of oral contraceptives was added in 1975 and a special survey conducted in 1991-2 determined changes in age at first use of OC with descending birth years. Outcome measures The Icelandic Cancer Registry and the databank of the Cancer Detection Clinic of the Icelandic Cancer Society were used as information sources. Analysis Conditional logistic regression used.	<u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: ≤ 4 years use): adjusted RR (95% CI)</u> > 4 years use: RR 1.1 (0.8-1.6) Adjusted for age at menarche, parity, number of children and age at first birth. Note when the association between OC use and breast cancer was restricted to women born after 1950, a statistically significant association was detected.	Limitations ▪ Note reference category for duration of use was ≤ 4 years – potentially underestimating the relative risk. ▪ OC data susceptible to misclassification given time between potential use and time of data collection. However, this bias is likely to be small and non-differential – leading to dilution of the RR estimate. ▪ 204 of 236 eligible cases participated (86%). ▪ Observational study susceptible to residual confounding. Comments ▪ Investigated the possible association between oral contraceptive use before age 20 and breast cancer risk. ▪ Nested design reduces risk of selection bias and recall bias is controlled given collection of exposure data before development of the outcome. Reported conclusions (by authors). The results of this study indicate an association between breast cancer and OC use at a young age. They also stress the importance of distinguishing between groups with different opportunities for exposure at young age.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Levi et al. 1996) Switzerland	Case-control study Level III-2.	Study setting. Case control study, using hospital based controls, set in Vaud canton, Switzerland. Sample Median age (years): cases 55, controls 57 Education < 13 years (%): cases 76, controls 77 Ever married (%): cases 11, controls 11 Age < 13 years at menarche (%): cases 37, controls 32 Nulliparous (%): cases 22, controls 22 Postmenopausal (%): cases 66, controls 66 Family history of breast cancer (%): cases 10, controls 3 History of benign breast disease (%): cases 17, controls 8 BMI < 25 kg/m^2 (%): cases 61, controls 59	Cases (n=230) Cases of incident, histologically confirmed, breast cancer aged 27-75 years who had been admitted to the University Hospital of Lausanne, Switzerland. Cases were linked with the Vaud cancer registry. Controls (n=507) Women ≤ 75 years residing in the same geographical area as the cases and were not admitted for breast, gynaecological, hormonal, metabolic or neoplastic diseases. Data collection In hospital interviews conducted using a structured questionnaire. Analysis Multiple logistic regression used.	<u>Relative risk of breast cancer by use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> Ever use: OR 1.5 (1.0-2.3) <u>Relative risk of breast cancer by first use of oral contraceptives in relation to FFTP (Reference: no use before FFTP): adjusted RR (95% CI)</u> Before: OR 1.3 (0.7-2.5) After: OR 1.6 (1.0-2.6) <u>Relative risk of breast cancer by time since last use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> < 5 years: OR 1.9 (0.9-3.6) 5-14 years: OR 2.4 (1.4-4.4) 15+ years: OR 1.0 (0.6-1.8) All estimates adjusted for age, marital status, education, BMI, age at menarche, age at first birth, age at menopause and family history of breast cancer.	Limitations ▪ Approximately 15% of women approached for an interview refused participation ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered ▪ Hospital based controls may not be representative of the population from which the cases were drawn Comments ▪ Explored the relationship between OC and HRT use and breast cancer risk. Reported conclusions (by authors). The present study confirms that breast cancer risk is moderately related to OC and HRT. The association, however, is essentially restricted to the 10-15 years after stopping use. This pattern of risk is consistent with a late stage effect of steroid hormone preparations in the process of breast carcinogenesis, and has relevant implications for any risk/benefit assessment and public health evaluation.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Newcomb et al. 1996) USA	Case control study Level III-2.	Study setting. Population based case control study Sample Age: < 50 years: cases 25%, controls 31% 50-59 years: cases 21%, controls 22% 60-69 years: cases 36%, controls 34% 70-74 years: cases 18%, controls 13% median age at menarche (years): cases 12, controls 13 Nulliparous (%): cases 14, controls 12 Family history of breast cancer (%): cases 18, controls 12. Median BMI group (kg/m^2): cases 23.51-26.56, controls 23.51-26.56 History of benign breast disease (%): cases 15, controls 12 Premenopausal (%): cases 24, controls 24	Cases (n=6,751) Women under 75 years who had a new diagnosis of breast cancer during April 1988 through December 1991. Breast cancer identified from state-wide registries in Wisconsin, Massachusetts, Maine and New Hampshire (January 1990 through December 1991 only). Eligibility restricted to people with a listed telephone number. Controls (n=9,311) Randomly selected from lists of licensed drivers (if aged under 65 years) and from lists of Medicare beneficiaries (65-74 years). Eligibility restricted to people with a listed telephone number. Data collection Telephone interview Analysis Only exposure status prior to an assigned reference date was used in this analysis (date of diagnosis for cases and, for controls, the average time between diagnosis and interview of cases in each state was applied). Logistic regression used.	<u>Relative risk of breast cancer by ever use of oral contraceptives (Reference: never use): adjusted RR (95% CI)</u> RR 1.1 (1.0-1.2) <u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: never use): adjusted RR (95% CI)</u> < 1 year: RR 1.1 (1.0-1.3) 1-4 years: RR 1.0 (0.9-1.1) 5-9 years: RR 1.1 (0.9-1.2) 10-14 years: RR 1.1 (0.9-1.3) 15+ years RR 1.0 (0.8-1.4) <u>Relative risk of breast cancer by time since last use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> < 2 years: RR 1.3 (0.9-2.0) 2-4 years: RR 1.2 (0.8-1.7) 5-9 years: RR 1.1 (0.9-1.3) 10-14 years: RR 1.1 (0.9-1.2) 15-19 years: RR 1.0 (0.9-1.2) 20+ years: RR 1.0 (0.9-1.2) <u>Relative risk of breast cancer by first use of oral contraceptives before FFTP (Reference: no use before FFTP): adjusted RR (95% CI)</u> RR 1.1 (0.9-1.3) All estimates adjusted for age, state, age at menarche, parity, age at menopause, age at first delivery and family history of breast cancer.	Limitations ▪ controls may not be representative of the population from which the cases were drawn. ▪ Response rate amongst eligible cases: 81%. Response rate amongst eligible controls: 84%. Suggests selection bias from non-participation is likely to be small in magnitude. ▪ Interviewers were unaware of the case/control status of the participant until the end of the interview in 78% of cases and 90% of controls. ▪ Current OC use defined as use within 2 years of the reference date. ▪ Observational study susceptible to residual confounding. ▪ Recall bias needs to be considered. Comments ▪ Examined the association between recent oral contraceptive use and the risk of breast cancer ▪ Reliability study conducted in 211 participants 6-12 months after initial data collection. Spearman correlation coefficient 0.98 indicating a high degree of correlation. ▪ Examination of Wisconsin data demonstrated that surveillance bias was unlikely to result in increased identification of cases amongst OC users. Reported conclusions (by authors). While these results suggest that, in general, breast cancer risk is not increased substantially among women who have used OCs, they are also consistent with a slight increased risk among subgroups of recent users.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Rosenberg et al. 1996) USA	Case control study Level III-2.	Study setting. Part of the case control surveillance study which has been in progress since 1976. Nurse interviewers stationed in hospitals in several cities administered standard questionnaires to patients under 70 years of age. Sample Age (years): 25-24: cases 9%, controls 20% 35-44: cases 31%, controls 35% 45-59: cases 60%, controls 45% Education (years): < 13: cases 40%, controls 52% 13-15: cases 23%, controls 22% 16: cases 16, controls 12 17+: cases 21, controls 31 History of benign breast disease (%): cases 28, controls 12 Family history of breast cancer (%): cases 15, controls 12 BMI (kg/m^2): ≤ 21: cases 25, controls 27 22-24: cases 42, controls 35 25+: cases 33, controls 36 Age at menarche (years) < 13: cases 50%, controls 47% 13-14: cases 41%, controls 40% 15+: cases 8%, controls 12% Nulliparous (%): cases 23, controls 23	Study population Based on data collected during 1977-1992 from white women aged 25-59 years. Cases (n=3,540) First occurrence of primary breast cancer (diagnosed within the previous year) and no concurrent cancer or history of cancer. Controls (n=4,488) No history of cancer. Admitted for non-gynaecologic, non-malignant conditions judged to be unrelated to OC use or reproductive factors. Frequency matched to cases on half decade of age and, if possible, geographic area, up to a ratio of 4:1. Data collection Nurse interviewers stationed in hospitals in several cities administered standard questionnaires. Analysis Unconditional logistic regression used.	<u>Relative risk of breast cancer by ever use (defined as 1+ years use) of oral contraceptives (Reference: use < 1 year): adjusted OR (95% CI)</u> RR 1.1 (1.0-1.3) <u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: use < 1 year): adjusted RR (95% CI)</u> 1-4 years: RR 1.1 (1.0-1.3) 5-9 years: RR 1.2 (1.0-1.5) 10+ years: RR 0.9 (0.7-1.1) Estimates adjusted for age, geographic area of hospital, interview year, age at first full term birth, nulliparity and years of education. Other results presented for dose of estrogen, duration of OC use before age 25 years, age and interval since last use but all were stratified by age groups with no overall estimates presented. The reader is referred to the original study for these results.	Limitations ▪ Hospital based controls may not be representative of the population from which the cases were drawn. ▪ Reference category for ever use and duration of use was less than one year of use, rather than no use – may have underestimated the association. This reference category was used in an attempt to reduce bias arising from cases who remembered short term use better than controls. Estimates derived with no use as the reference category produced similar results. ▪ Participation rate amongst cases and controls was unclear. ▪ Observational study susceptible to residual confounding. ▪ Recall bias needs to be considered. Comments ▪ Assessed the relation between OC use and the risk of breast cancer in white women aged 25-59 years. Reported conclusions (by authors). The results add to the evidence of an association between OC use and an increased risk of breast cancer at young ages.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Rossing et al. 1996) USA	Case control study Level III-2.	Study setting. Population based case control study among women aged 50-64 years during 1988-1990. Sample Age (years): 50-54: cases 28%, controls 31% 55-59: cases 36%, controls 35% 60-64: cases 36%, controls 34% Education (years) < 12: cases 8%, controls 8% 12: cases 31%, controls 36% 13+: cases 23%, controls 24% Nulliparous (%): cases 12, controls 9 Age at FFTP (years) 15-19: cases 17%, controls 23% 20-24: cases 51%, controls 48% 25-29: cases 24%, controls 23% 30+: cases 8%, controls 6% Premenopausal (%): cases 12, controls 14 BMI (kg/m^2): < 21.2: cases 21%, controls 25% 21.2-23.6: cases 25%, controls 25% 23.7-27.1: cases 26%, controls 27% 27.2+: cases 28%, controls 25% Family history of breast cancer (%): cases 34, controls 24	Cases (n=537) Identified through the Cancer Surveillance System. White women residing in King County, Washington State, aged 50-64 years and diagnosed with histologically confirmed first primary invasive or *in situ* carcinoma of the breast between Jan 1988 and June 1990. Controls (n=545) Identified through random digit dialling and selected to be similar in age to the cases. Exclusions previous diagnosis of breast cancer. Data collection In person interviews using a structured questionnaire. Analysis Logistic regression used.	<u>Relative risk of breast cancer by ever use (defined as 1+ years use) of oral contraceptives (Reference: never used): adjusted RR (95% CI)</u> RR 1.1 (0.8-1.4) <u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: never used): adjusted RR (95% CI)</u> ≤ 12 mths: RR 1.0 (0.7-1.4) 13-48 mths: RR 1.4 (0.9-2.2) 49-120 mths: RR1.3 (0.8-1.9) 120+ mths: RR 0.8 (0.5-1.3) <u>Relative risk of breast cancer by time since first use of oral contraceptives (Reference: never use): adjusted RR (95% CI)</u> ≤ 20 yrs: RR 1.9 (1.1-3.2) 21-25 yrs: RR 1.1 (0.7-1.6) 26-30 yrs: RR 0.9 (0.6-1.3) 30+ yrs: RR 1.0 (0.5-1.8) <u>Relative risk of breast cancer by time since last use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> ≤ 10 years: OR 1.1 (0.6-2.0) 11-15 years: OR 1.4 (0.9-2.1) 16-20 years: OR 1.1 (0.7-1.7) 21-25 years: OR 0.9 (0.6-1.4) 26+ years: OR 0.9 (0.6-1.5)	Limitations ▪ 537 of 660 eligible cases participated (81%) ▪ Cases included *in situ* disease ▪ Effective participation rate amongst controls approximated 70% (based on response to telephone screening and participation amongst screened eligible controls) ▪ Observational study susceptible to residual confounding ▪ Recall bias needs to be considered ▪ Large proportion of women were unable to recall brand and/or strength of OC preparations used Comments ▪ Examined the relationship between OC use and risk of breast cancer in women aged 50-64 years. Reported conclusions (by authors). Overall, this study supports the absence of any strong association between OC use and breast cancer risk during middle age in the cohort of women who first used these drugs.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Skegg et al. 1996) New Zealand	Case control study Level III-2.	Study setting. Population based case control study Sample Median age group: cases 45-49, controls 40-44. Maori ethnicity (%): cases 7, controls 5 Age at menarche (%) < 12 years: cases 17, controls 16 12-14 years: cases 66, controls 68 15+ years: cases 16, controls 16 Nulliparous (%): cases 11, controls 11 Premenopausal (%): cases 68, controls 77 History of surgery for benign breast disease (%): cases 13, controls 7 Family history of breast cancer in first degree relative (%): cases 11, controls 7.	Study population Selected from women whose names were in a current electoral roll and whose telephone number could be found. Cases (n=891) First diagnosis of breast cancer identified from the National Cancer Registry and the Auckland Breast Cancer Study Group. Women aged 25-54 years Histologically confirmed breast cancer diagnosed between July 1983 and June 1987. Exclusions: previous diagnosis of breast cancer Controls (n=1,864) Random selection from electoral roll. Age 25-54 years. Randomly excluded half the potential controls aged under 35 to approximate more closely the age distribution of the cases. Reference date calculated by subtracting six months from the date of interview. Data collection Telephone interview. Two nurse interviewers were used. Most began with the interviewer being blind to case status but case status was disclosed as the interview progressed. Analysis Logistic regression used.	<u>Relative risk of breast cancer by use of progestogen only contraceptives (Reference: never use): adjusted OR (95% CI)</u> Ever use: OR 1.1 (0.73-1.5) <u>Relative risk of breast cancer by duration of progestogen only use (Reference: never use): adjusted RR (95% CI)</u> < 2 years: RR 1.0 (0.65-1.5) 2-5 years: RR 1.2 (0.60-2.3) 6+ years: RR 1.2 (0.27-5.3) <u>Relative risk of breast cancer by time since first use of progestogen only contraceptives (Reference: never use): adjusted OR (95% CI)</u> < 10 years: RR 1.6 (1.0-2.4) 10+ years: RR 0.44 (0.22-0.90) <u>Relative risk of breast cancer by time since first use of progestogen only contraceptives (Reference: never use): adjusted OR (95% CI)</u> < 5 years: RR 1.4 (0.86-2.2) 5-9 years: RR 1.0 (0.56-1.9) 10+ years: RR 1.1 (0.73-1.5) <u>Relative risk of breast cancer by first use of oral contraceptives before FFTP (Reference: no use before FFTP): adjusted RR (95% CI)</u> RR 1.2 (0.46-2.9) All estimates adjusted for age, age at menarche, age at FFTP, parity, history of breast feeding, history of benign breast disease, family history of breast cancer, ethnic group and year of interview.	Limitations ▪ 891 of 1,126 (79%) eligible cases participated. ▪ Participation rate among controls cannot be estimated absolutely due to lack of age data in electoral rolls. However, 15.5% of the group selected from the electoral roll did not participate due to being untraceable, language difficulties, absence overseas, refused participation, illness or death. ▪ Inability to blind interviewers to case status but most interviewers were blind to case status when the contraceptive history was taken. ▪ Observational study susceptible to residual confounding. ▪ Recall bias needs to be considered although GP validation reduces the likelihood of this potential bias for OC use. Comments ▪ Examined the influence of progestogen-only OCs on a woman's risk of breast cancer. ▪ Validation of self reported OC use was obtained from the GPs of the participants. Like a nested study set within the total NZ population – which should reduce risk of selection bias. Reported conclusions (by authors). Further data are needed to confirm or refute the pattern of risk suggested by our findings. In the meantime, the lack of an overall association between progestogen-only OC and breast cancer is reassuring

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Tomasson and Tomasson 1996) Iceland	Matched, nested, case control study Level III-2.	Study setting. Utilised data collected over 25 years in a screening program cancer detection clinic for women aged 25 to 69 years. Sample Mean age at diagnosis 55.0 years Mean number of months of OC use: cases 15.6, controls 19.3.	Study population. Restricted to women who were healthy on entry to the screening program. Cases (n=1,062) Identified by linking the screening program records with the cancer registry. Cases restricted to those diagnosed between 1965-1989. Controls (n=5,662) Alive at the time of matching case was diagnosed. Matched on age (six closest controls to the case's birthday). Data collection Information on OC use, age at first delivery and number of children were recorded at time of first screening. Analysis Conditional logistic regression used.	<u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: never used): adjusted OR (95% CI)</u> 1-48 mths: OR 0.92 (0.73-1.16) 49-96 mths: OR 0.89 (0.64-1.24) 97+ mths: OR 0.96 (0.69-1.33) Adjusted for reproductive history and family history. Odds ratio for those ever taking OCs was presented as 0.92. No confidence interval was provided for this estimate and it was unclear if this was an adjusted OR.	Limitations ▪ Unclear if there was full participation in the study ▪ Observational study susceptible to residual confounding Comments ▪ Aim was to quantify the risk of breast cancer related to the use of OCs. ▪ Design should minimise selection bias ▪ Recall bias should not be an issue with the prospectively collected data Reported conclusions (by authors). Use of OCs does not seem to increase the risk of developing breast cancer among women in Iceland.

Table 11.2: Evidence tables for primary studies of hormonal contraceptives (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Traina et al. 1996) Italy	Case control study Level III-2.	Study setting. Case control study set in two areas of Italy with differing rates of breast cancer (Turin and Palermo). Sample Age: ≤ 30 years: cases 5%, controls 8% 31-35 years: cases 12%, controls 26% 36-40 years: cases 18%, controls 23% 40+ years: cases 65%, controls 44% Education: 0 years: cases 3%, controls 4% 1-8 years: cases 57%, controls 54% 9-14 years: cases 29%, controls 31% 15+ years: cases 11%, controls 11% Age at menarche: < 11 years: cases 9%, controls 10% 11-14 years: cases 71%, controls 70% 15+ years: cases 20%, controls 20% Nulliparous: cases 22%, controls 29% Family history of breast cancer: cases 14%, controls 6%.	Cases (n=300) Histologically proven breast cancer in women aged under 46 years. Registered in hospital between 1992 and 1994. Exclusions: metastatic disease at time of diagnosis, patients with epithelial tumours, contraindication to OC use. Controls (n=300) Selected from non-neoplastic women requiring hospitalisation for acute diseases in the same geographic area as the cases. Data collection Interviewers visited selected wards on selected days to identify eligible controls and interviewed all these controls. Cases were interviewed within one year of diagnosis. Analysis Logistic regression used.	<u>Relative risk of breast cancer by duration of oral contraceptive use (Reference: never use): age adjusted OR (95% CI)</u> < 12 mths: OR 0.84 (0.49-1.41) 12-35 mths: OR 0.71 (0.41-1.20) 36-59 mths: OR 0.88 (0.39-1.97) 60+ mths: OR 0.76 (0.35-1.64) <u>Relative risk of breast cancer by first use of oral contraceptives before FFTP (Reference: no use before FFTP): age adjusted OR (95% CI)</u> < 12 mths: OR 1.11 (0.57-2.20) 12-35 mths: OR 0.55 (0.26-1.11) 36-59 mths: OR 0.94 (0.28-3.12) 59+ mths: OR 0.60 (0.21-1.72) <u>Relative risk of breast cancer by age at first use of oral contraceptives (Reference: never use): age adjusted OR (95% CI)</u> < 25 years: OR 0.63 (0.38-1.01) 25+ years: OR 0.87 (0.56-1.36) <u>Relative risk of breast cancer by time since last use of oral contraceptives (Reference: never use): adjusted OR (95% CI)</u> < 35 mths: OR 0.65 (0.36-1.17) 35+ mths: OR 0.89 (0.89-1.33)	Limitations ▪ Hospital based controls may not be representative of the population from which the cases were drawn. ▪ Different timing of data collection interviews between cases and controls may have lead to bias. ▪ Observational study susceptible to residual confounding. Results presented were only adjusted for age. ▪ Recall bias needs to be considered. ▪ Appears to be a mistake in the estimate/confidence interval for time since last use 35+ months with the lower confidence interval bound being the same as the point estimate. Comments ▪ Primarily aimed to evaluate the relationship between OC use and breast cancer risk ▪ On average, fewer than 3% of cases and controls approached refused to participate in the study

Appendix 12: Other exogenous hormones

Table 12.1: Evidence tables for secondary studies of phyoestrogens

Authors	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Cassidy et al. 2006)	Level III-2.	Databases MEDLINE, EMBASE, Cochrane Library Search terms Phytoestrogens, isoflavones, genistein, diadzein, equol, soy – cross referenced with post-menopausal, hot flushes, osteoporosis, bone mineral density, bone metabolism, cardiovascular, endothelial function, vascular reactivity, blood pressure, lipid profile, breast, colon, cognition.	Inclusion criteria For areas with substantial research only well-conducted or high quality meta-analyses, systematic reviews of RCTs or RCTs were included. However, for breast disease (and other areas) well conducted case-control and cohort studies were included. Exclusion criteria Nil stated Data extraction Papers were reviewed by a panel. The panel weighted the evidence and formulated a statement for each health effect. Data analysis When a range of sources of isoflavones were used, the doses of isoflavones were calculated as aglycone equivalents. Evaluation of data quality was assessed using the method of Jadad et al 1996.	Eight case control studies identified that examined the relationship between soyabeans and breast cancer among Asian women. These studies showed an inverse relationship between intake and breast cancer in both premenopausal and post-menopausal women. A meta-analysis of these studies showed a 33% decreased risk of breast cancer for post-menopausal women when comparing highest consumption with lowest consumption (OR 0.67, 95% CI 0.48-0.93). Results were less clear cut in studies of "Caucasian" women. A meta-analysis of three studies found no significant effect (OR 0.96, 95% CI 0.71-1.2) and of three other primary research studies, two found no statistically significant association. Two studies of adolescent dietary exposure showed a strong inverse association with breast cancer risk (OR 0.49, 95% CI 0.33-0.74; and OR 0.41, *p* for trend 0.007). Two nested case control studies of pre-diagnostic urine in Caucasian women showed conflicting results although studies examining urine collected after diagnosis of breast cancer have shown significant inverse relationships.	Limitations • No detail on extraction methods – what was extracted, how many investigators extracted from each study, how were disagreements resolved • Lacking detail on specific selection processes- how many people were involved and how were disagreements resolved • Limited number of databases searched although the databases searched were likely to include at least most relevant studies Comments • Studied the health effects of soyabean phytoestrogens in post menopausal women. A wide range of outcomes were studied, including breast cancer. Reported conclusions (by authors). There are too few RCT studies to reach conclusions on the effects of isoflavones on breast cancer, colon cancer, diabetes or cognitive function.

Table 12.1: Evidence tables for secondary studies of phyoestrogens (continued)

Authors	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Qin et al. 2006)	Level III-2.	Databases MEDLINE (January 1966-April 2006) Japana Centra Revuo Medicina Chinese Journal Database Also reviewed references listed in the available publications. Search terms Soy (bean, soyabean, soy food, tofu, miso) and isoflavone (phytoestrogen, daidzein, genistein) combined with breast cancer.	Inclusion criteria Case control or cohort studies that evaluate exposure to soy food and breast cancer risk. When there were multiple publications that reported the same item, only the most recent data were included. Provided OR in case control studies and RR in cohort studies and the 95% CI or have sufficient data to calculate the same. Data extraction The OR/RR and 95% CI for the highest versus lowest (referent) category of consumption were extracted and the most adjusted estimate was used. Two researchers extracted the data independently. Data analysis When studies were stratified by menopausal status, the authors pooled the risk estimate for the two groups and weighted by the inverse of the variance. Pooled RR calculated by the DerSimonian-Laird method and homogeneity tested using the Q test. Random effects model used. Publication bias assessed by funnel plots and the Egger regression asymmetry test.	Pooled RR (95% CI) of breast cancer for soy food intake (highest category of intake versus lowest category): RR 0.75 (0.59-0.95) Pooled RR (95% CI) of breast cancer for isoflavone intake (highest category of intake versus lowest category): RR 0.81 (0.67-0.99)	Limitations • Limited databases searched for relevant articles so some articles may have been missed • Well defined research question • Focussed on the 27 studies published in English given the low quality of the remaining four studies that were published in Japanese and Chinese. • The included primary studies had limitations. For example, the common use of food frequency questionnaires may have been associated with misclassification of exposure. • Conflicting data regarding the number of studies published in Japanese and Chinese. • There is heterogeneity in the level of intake of soy food across different regions (higher consumption levels in Asia) thus comparison across studies conducted in different regions has limitations. Comments • Reviewed the results of observational studies to examine if the intake of soy products protects against breast cancer. • Double, independent extraction of data used • Appropriate methods used for the statistical components of the meta-analysis

Table 12.1: Evidence tables for secondary studies of phyoestrogens (continued)

Authors	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Qin et al. 2006) *continued*					Reported conclusions (by authors). This meta-analysis supported the hypothesis that soy food intake may be associated with a decreased risk of breast cancer due to the isoflavones. Further epidemiological studies need to be conducted with more comprehensive information about the soy food and more accurate assessment of the isoflavones.

Table 12.1: Evidence tables for secondary studies of phyoestrogens (continued)

Authors	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Trock et al. 2006)	Level III-2.	Databases MEDLINE EMBASE BIOSIS Search terms Genistein, daidzen, soy, tofu, miso, natto, soyabeans, diet, isoflavones, or phytoestrogens, and breast cancer. Search conducted through December 2004. Citation search conducted on each reference obtained. An Internet search was conducted to identify unpublished research.	Inclusion criteria Case control and cohort studies published between 1978 and 2004 inclusive Exclusion criteria Nil documented Data extraction No detail provided except noted that the OR and 95% CI was extracted for the comparison between highest and lowest exposure groups. Odds ratios adjusted for multiple confounding factors were used whenever these were available. Data analysis Two classifications of soy intake used: the original measure of soy intake from each study and an estimate of grams of soy protein consumed daily. The latter considered the soy protein composition of tofu, typical serving size of tofu and fraction of soy food in the diet contributed by tofu. Two studies examined risk associated with urinary isoflavone levels. Linear derived equations were used to convert these levels to soy food intake.	Pooled OR (95% CI) of breast cancer for soy food intake (highest category of intake versus lowest category): OR 0.86 (0.75-0.99) Pooled OR (95% CI) of breast cancer for soy food intake in premenopausal women (highest category of intake versus lowest category): OR 0.70 (0.58-0.85) Pooled OR (95% CI) of breast cancer for soy food intake in postmenopausal women (highest category of intake versus lowest category): OR 0.77 (0.60-0.98) Analysis based on daily soy intake: Only significant result was in the premenopausal group: OR 0.94 (0.92-0.97) There was no evidence of a dose response relationship based on a weighted linear regression of the log odds ratio versus the estimated soy protein exposure difference.	Limitations • Some assumptions required due to missing data in estimating grams of soy protein consumed daily • Fewer studies identified than by Qin et al above, suggesting possible missed studies (23 were identified for this review but one was excluded because it was based on husbands of breast cancer patients, one because of low numbers of participants and another because it didn't test for an association between soy consumption and breast cancer) • No details about specific selection and extraction processes • 12 case control studies, six cohort or nested case control studies. • Of the 18 studies selected, 8 studies did not provide sufficient information for pooled analyses by menopausal status Comments • Given the variability in epidemiologic study results, examined the association between high intake of soy foods and risk of breast cancer

Table 12.2: Evidence tables for primary studies of xenoestrogens

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Brody et al. 2006) USA	Frequency matched, case control study Level III-2	Study setting. Set in Cape Cod, an area which has a history of waste water contamination in many of its public water supplies. Wastewater contaminated water supplies are considered to be a potential source of endocrine disrupting compounds. Cape Cod also has unexplained elevated breast cancer incidence. Sample Family history of breast cancer: Cases 25% Controls 19% Age under 30 at first birth Cases 62% Controls 71% Prior breast cancer Cases 8% Controls 9%	Cases (n=824) Diagnosed with breast cancer during 1988-1995. Resident for at least six months in Cape Cod at the time of an invasive breast cancer diagnosis. Controls (n=745) Lived in homes served by a Cape Cod public water supply and never lived in a home served by a Cape Cod private well. Permanent residents in Cape Cod for at least six months. Frequency matched on date of birth (in decades) and vital status. Living controls under age 65 were selected using random digit dialling. Living controls aged 65+ selected from Medicare lists. Deceased controls were selected randomly from Massachusetts Department of Vital Statistics death certificates who died after January 1988 and were frequency matched to cases by age and year of death. Data collection Assessed each woman's yearly exposure to nitrate nitrogen levels since 1972. Missing values were interpolated. Also calculated the fraction of recharge zones in residential, commercial, and pesticide land use areas. Telephone interview of each participant, including collection of potential breast cancer risk factors and water use behaviours.	Average annual excess nitrate-N concentration (adjusted OR with 0 to <0.3 as the reference): 0.3-<0.6: OR 1.0 (0.7-1.3) 0.6-<0.9: OR 0.9 (0.6-1.2) 0.9-<1.2: OR 0.9 (0.6-1.2) 1.2+: OR 0.9 (0.5-1.7) Sum of annual excess niotrate-N concentrations (mg/L), (adjusted OR with 1-<10 as reference) 0-<0.01: OR 0.8 (0.4-1.6) 0.01-<0.1: OR 0.9 (0.6-1.5) 0.1-<1: OR 0.9 (0.7-1.2) 1-<10: reference 10+: OR 1.0 (0.8-1.3) Number of years exposed to excess nitrate-N concentration>1mg/L (adjusted OR with 0 as reference): <2: OR 1.0 (0.7-1.5) 2-<4: OR 1.0 (0.7-1.4) 4-<6: OR 0.8 (0.5-1.2) 6-<8: OR 1.0 (0.6-1.5) 8+: OR 0.9 (0.5-1.7)	Limitations • May not have been sufficient variation in exposure to detect a difference in outcome • Proxy measures used in the assessment of exposure to potentially harmful compounds • Observational study susceptible to residual confounding • Method of selection of controls may have minimised the difference in exposure levels between cases and controls • 1165 of 1578 (74%) eligible cases participated and 1016 of 1503 (68%) eligible controls participated. Further exclusions occurred subsequently who lived in residences that were not supplied by public water during part of the previous 16 years or if the assigned reference year of the control was earlier than the time of moving to Cape Cod. Comments • Investigated whether exposure to drinking water contaminated by wastewater increases the risk of breast cancer • Exposure assessments are unlikely to be subject to self report bias Reported conclusions (by authors). Results did not provide evidence of an association between breast cancer and drinking water contaminated by wastewater.

Table 12.2: Evidence tables for primary studies of xenoestrogens (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Brody et al. 2006) *continued*			Analysis Unconditional logistic regression used. In all adjusted analyses the following variables were controlled: age (continuous term), birth decade, PCE versus Cape Cod study, vital status, year of diagnosis/reference year, prior breast cancer, age at birth of first child, family history of breast cancer in first degree female relative, and education. Further potential confounders were considered but did not change estimated odds ratios by ≥10% so were not included.		

Table 12.2: Evidence tables for primary studies of xenoestrogens (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Thompson et al. 2005) USA	Nested, matched case control study Level III-2.	Study setting. Nested in a cohort study of 4,680 female automobile workers employed for at least 3 years between 1/1/41 and 1/1/85, with follow up through 1994. Sample Mean age started work (years) Cases 32 Controls 34 Mean age stopped work (years) Cases 49 Controls 50 Race: White: cases 51%, controls 51% Black: cases 21%, controls 20% Missing: cases 28%, controls 29% Deceased Cases 45%, controls 12%	Cases (n=99) Cases were identified using the National Death Index, Michigan Cancer Registries and company records. Incident cases were supplemented with deceased cases identified during two cohort follow-up periods. Controls (n=626) Selected 6:1 from the cohort using incidence density sampling. Matching was performed on date of birth (+/-1 5 years), race and being alive at the date of diagnosis of the case. Data collection Exposure assessment was performed by experienced industrial hygienists based on company records. Scale factors were developed to account for changes in production over time and a job-exposure matrix was formed. This matrix was used to estimate cumulative exposure (mg/m^3-years). Cumulative exposure was divided into three time windows: 1-10, 11-20 and 21 + years preceding diagnosis. Analysis Conditional logistic regression used. Exposure-response associations were estimated in separate models for the three separate time windows preceding diagnosis. To adjust for potential confounding of exposure in one time-period by subsequent exposure in other time periods, all three exposure-windows were included in a single model.	<u>Time: 1-10 years before diagnosis</u> Straight metalworking fluid OR 1.05 (95% CI 0.97-1.14) Soluble metal working fluid OR 1.18 (95% CI 2.02-1.35) Synthetic metal working fluid OR 0.90 (95% CI 0.62-1.30) <u>Time 11-20 years before diagnosis</u> Straight metalworking fluid OR 1.01 (95% CI 0.93-1.11) Soluble metal working fluid OR 0.93 (95% CI 0.84-1.04) Synthetic metal working fluid OR 1.01 (95% CI 0.84-1.21) <u>Time: 20+ years before diagnosis</u> Straight metalworking fluid OR 1.04 (95% CI 0.98-1.11) Soluble metal working fluid OR 1.03 (95% CI 0.99-1.06) Synthetic metal working fluid OR 1.00 (95% CI 0.88-1.14)	Limitations • Observational study susceptible to residual confounding and lack of data on important risk factors significantly increases the risk of confounding • Susceptible to misclassification of exposure due to the method of assignment of exposure. However, this misclassification is likely to be non-differential and is therefore likely to dilute the association Comments • Authors hypothesised that metalworking fluids may be associated with risk of breast cancer because they can contain carcinogenic or endocrine-disrupting chemicals. • Nested design minimises the risk of selection bias Reported conclusions (by authors). Study provides some preliminary evidence for an association between exposure to metalworking fluids and increased risk of breast cancer. Additional studies with data on known breast cancer risk factors are warranted.

Table 12.2: Evidence tables for primary studies of xenoestrogens (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Charlier et al. 2004b) Belgium	Frequency matched case control study Level III-2	Study setting. Selected from patients who were to undergo surgery for breast cancer and controls attending for cervical screening. Sample Mean age (years) Cases 54.8 Controls 54.8 Mean age of menarche (years) Cases 11.4 Controls 11.5 Menopause (%) Cases 82 Controls 65 HRT use among menopausal women (%) Cases 61 Controls 67 Parity (%) Cases 57 Controls 55 Breast feeding among parous women (%) Cases 71 Controls 76 Family history of breast cancer (%) Cases 15 Controls 8	Cases (n=60) Diagnosed with breast cancer and undergoing a surgical intervention. Controls (n=60) Randomly selected from women consulting for routine cervico-vaginal cytological screening. Data collection Gas chromatography/mass spectrometry used to quantify seven polychlorinated biphenyl congeners. Collected information on age at menarche, pregnancy, breast feeding, menopausal status and family history of breast cancer. Analysis PCB measurements were log transformed to normalise their distribution. Risk factors and PCB levels in cases and controls were compared using logistic regression.	Adjusted OR (95% CI) for PCB concentration in cases compared to controls PCB52: OR 0.95 (0.74-1.2) PCB101: OR 1.0 (0.77-1.3) PCB138: OR 1.2 (0.88-1.5) PCB153: OR 1.8 (1.4-2.5) PCB180: OR 1.1 (0.76-1.5) Adjusted for age, age at menache, menopausal status, HRT use, parity, breast feeding and family history of breast cancer.	Limitations • Measurement of PCBs made at time of diagnosis of breast cancer. Levels at that time may not reflect levels preceding the diagnosis. • Controls may not be representative of the population from which the cases were drawn. The method of selection of controls is likely to have selected a health conscious population (attending for screening) • No information provided on participation rates • Observational study susceptible to residual confounding Comments • Aimed to compare PCB contamination in women suffering from breast cancer with presumably healthy women Reported conclusions (by authors). Results suggest that environmental exposure to PCBs may contribute to multi-factorial pathogenesis of breast cancer.

Table 12.2: Evidence tables for primary studies of xenoestrogens (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Charlier et al. 2004a) Belgium	Matched case control study Level III-2	Study setting. Women attending the University Hospitla in Liege during June 2001 to January 2002. Sample Mean age (years) Cases 53.6 Controls 51.7 BMI (kg/m^2) Cases 23.3 Controls 22.8 Smoking (%) Cases 43.3 Controls 44.9 Age at menarche (years) Cases 13.2 Controls 12.8 Nuliparous (%) Cases 18.6 Controls 23.4 Breast feeding among parous (%) Cases 57.8 Controls 60.4 Menopausal (%) Cases 69.3 Controls 52.8 HRT use in post-menopausal women (%) Cases 43.8 Controls 66.6 Family history of breast cancer (%) Cases 30.4 Controls 24.0	Cases (n=231) Evaluated at time of surgery Controls (n=290) Age-matched (±2 years) randomly selected from women consulting for routine cervico-vaginal cytological screening. Data collection Measured p,p'-1,1-dichloro-2,2-bis (4-chlorophenyl) ethylene (DDE) and hexachlorobenzene (HCB) using gas chromatography. Details of the process are supplied in the paper. Collected information on age at menarche, pregnancy, breast feeding, menopausal status and family history of breast cancer. Analysis Serum levels of organochlorines were corrected for lipid content. Chi-squared test was used to compare the proportion of smokers and non-smokers and distribution between rural and urban living in the cases and controls. BMI, DDE and HCB were compared using the Mann-Whitney U-test. Multiple logistic regression was used to measure the association between DDE and HCB and breast cancer.	Adjusted OR (95% CI) for DDE concentration in cases compared to controls OR 1.53 (0.89-2.60) Adjusted OR (95% CI) for HCB concentration in cases compared to controls OR 1.65 (0.95-2.85) Both analyses adjusted for parity, parity x breast feeding, menopause, menopause x HRT, and family history of breast cancer.	Limitations • Measurement of PCBs made at time of preparation for surgery. Levels at that time may not reflect levels preceding the diagnosis. • Controls may not be representative of the population from which the cases were drawn. The method of selection of controls is likely to have selected a health conscious population (attending for screening) • No information provided on participation rates • Observational study susceptible to residual confounding Comments • Compared the serum levels of DDE and HCB in women with and without breast cancer Reported conclusions (by authors). Despite the inclusion of established breast cancer risk factors in our data, whether or not environmental hormonally active agents have a causal role in initiation or promotion of breast cancer is difficult to definitively conclude.

Table 12.2: Evidence tables for primary studies of xenoestrogens (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Ibarluzea et al. 2004) Spain	Matched case control study Level III-2	Study setting. Hospital based case control study conducted from April 1996 through June 1998 in the three largest public hospitals in Granada and Almeria provinces of Spain. Sample Mean age (years) Cases 54.8 Controls 56.8 BMI (kg/m^2) Cases 27.3 Controls 29.6 Details provided of significant differences or significant trends between cases and controls for marital status, education level, occupation, number of full term pregnancies, age at first full term pregnancy, months of lactation, family history of breast cancer, menopausal status, tobacco use and alcohol use.	Cases (n=198) Aged 35-70 years Undergoing surgery for newly diagnosed malignant breast carcinoma (invasive or *in situ)* No past history of breast cancer Controls (n=260) Matched for age (±3 years) and hospital Undergoing non-cancer-related surgery. Excluded women with gynaecological/endocrine disease and history of cancer. Data collection Breast or abdominal adipose tissue were obtained from cases and controls respectively during surgery and before initiation of chemotherapy or radiotherapy. Identity of relevant chemicals identified by gas chromatography and mass spectrometry. Measurements included various pesticides and total effective xenoestrogen burden (TEXB). Face to face interviews used to collect interview data. .	Adjusted OR (95% CI): DDE (ng/g of lipid) ≤201.72: reference 201.73-397.67: 1.04 (0.59-1.84) 397.68-675.97: 1.23 (0.69-2.17) 675.98+: 1.22 (0.68-2.21) *P* for trend = 0.40 Aldrin (ng/g of lipid) < LD reference >LD: 1.55 ((1.00-2.40) Endosulfanether (ng/g of lipid) < LD reference >LD 1.35 (0.90-2.02) Lindane (ng/g of lipid) <LD reference >LD 1.40 (0.92-2.13) TEXB-alpha (picomolar of estradiol equivalent/g of lipid) ≤0.25 reference 0.26-41.00 1.15 (0.64-2.05) 41.01-197.50 1.33 (0.76-2.33) 197.51+ 1.31 (0.74-2.31) *P* for trend = 0.30 TEXB-beta (picomolar of estradiol equivalent/g of lipid) ≤9.95 reference 9.96-100.00 1.08 (0.61-1.90) 100.01-550.00 1.05 (0.59-1.86) 550.01+ 0.99 (0.55-1.79) *P* for trend 0.99	Limitations • Controls may not be representative of the population from which the cases were drawn given the use of hospital controls. • 10 eligible cases (4%) and 12 eligible controls (3%) declined to participate. Further exclusions due to inadequate adipose tissue samples and interview reports • Measurements made at time of preparation for surgery. Levels at that time may not reflect levels preceding the diagnosis. • Observational study susceptible to residual confounding • Adipose tissue sampling site differed between cases and controls although it is noted other studies have shown good correlations between these sites. Comments • Aimed to determine whether total effective xenoestrogen burden is a risk factor for breast cancer over and above the risk potentially linked to specific pesticides Reported conclusions (by authors). Found an increased risk for breast cancer in leaner women, especially in the leaner postmenopausal subgroup, related to the TEXB-alpha. The pesticides aldrin and lindane are also individually associated with risk.

Table 12.2: Evidence tables for primary studies of xenoestrogens (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Ibarluzea et al. 2004) *continued*			Analysis Student's t test used to compare log transformed adipose concentrations between cases and controls. Unconditional logistic regression was used. Adjustment was made for potential confounders and matching variables. Potential confounders included marital status, education level, social class, occupation, number of full term pregnancies, age at first full term pregnancy, months of lactation, natural logarithm of BMI, family history of breast cancer, use of OCs/HRT, menopausal status, age at menarche, age at menopause and tobacco and alcohol consumption. The modifying effect of these variables and the association with organochlorine levels and TEXB values was examined.	Above analyses adjusted for age, reference hospital, ln BMI, number of children, age at first full term pregnancy, family history of breast cancer, and alcohol and tobacco consumption. Note there was a significant trend of increasing risk associated with increasing levels of TEXB-alpha in participants with a BMI<median.	

Table 12.2: Evidence tables for primary studies of xenoestrogens (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Reynolds et al. 2004) USA	Prospective cohort study Level III-2	Study setting. Part of the California Teachers study (CTS) cohort, followed for cancer incidence since 1995. Cohort established from respondents to a 1995 mailing of all 329,000 active and retired female enrolees in the State Teachers Retirement System. All California public school employees must pay into this retirement system. Sample (n=114,835) Median age group 50-59 years Non-Hispanic White race/ethnicity 86.2% Socioeconomic status 1st quartile (low) 1.8% 2nd quartile 20.3% 3rd quartile 45.7% 4th quartile (high) 32.2% Menopausal status Premenopausal 38.3% Post menopausal 50.7% Unable to determine 11.0% Family history of breast cancer 11.8% (note unknown in 1.6%)	Study population Cohort established from respondents to a 1995 mailing of all 329,000 active and retired female enrolees in the State Teachers Retirement System. Follow-up and cancer incidence data CTS follows its cohort members annually for deaths, change of address and cancer diagnoses. Mortality files and confirmed reports from relatives are used to ascertain date and cause of death. Change of address was identified by searching motor vehicles and postal services databases. Cancer outcomes were identified by linkage with the California Cancer Registry. Data collection The CTS baseline questionnaire collected residential address information at baseline. The addresses were geocoded. The PUR database of the California Department of Pesticide Regulation was examined for agricultural pesticide applications in the state during the period 1993-1995. Pesticides were divided into six groups (though there was some overlap between groups). Five specific pesticides were also selected for individual analysis. 1990 census data was used to characterise SES and degree of urbanisation of cohort members neighbourhoods.	Hazard ratio (95% CI) is association between selected groups of pesticides and breast cancer Probable or likely human carcinogens <1 lb/mi² Reference 1st-49th 0.95 (0.81-1.10) 50th-74th 0.93 (0.75-1.15) ≥75th 1.07 (0.86-1.32) Possible or suggestive human carcinogens <1 lb/mi² Reference 1st-49th 0.96 (0.84-1.11) 50th-74th 0.82 (0.67-1.01) ≥75th 1.06 (0.87-1.29) Mammary carcinogens <1 lb/mi² Reference 1st-49th 0.82 (0.67-1.00) 50th-74th 0.86 (0.65-1.13) ≥75th 1.15 (0.90-1.48) Endocrine disruptors <1 lb/mi² Reference 1st-49th 0.97 (0.84-1.11) 50th-74th 0.87 (0.71-1.05) ≥75th 1.03 (0.86-1.25) Anticholinesterases <1 lb/mi² Reference 1st-49th 1.04 (0.90-1.19) 50th-74th 0.83 (0.68-1.03) ≥75th 1.09 (0.89-1.33) Organochlorines <1 lb/mi² Reference 1st-49th 1.06 (0.79-1.43) 50th-74th 0.82 (0.52-1.32) ≥75th 0.99 (0.63-1.55)	Limitations • Approximately 40% of the eligible population joined the CTS cohort. • Potential misclassification of exposure but such misclassification is likely to be non-differential, thus resulting in dilution of the association with breast cancer • Observational study susceptible to residual confounding • No consideration of exposure to pesticides from other sources such as own home or work environment was made. Comments • Examined the association between residential proximity to agricultural pesticide use and breast cancer incidence. Reported conclusions (by authors). Analyses suggest that breast cancer incidence is not elevated in areas of recent, high agricultural pesticide use in California.

Table 12.2: Evidence tables for primary studies of xenoestrogens (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Reynolds et al. 2004) *continued*			Analysis Follow-up period was based on either the date of breast cancer diagnosis, date of death or December 31 1999, whichever came first. Cox proportional hazard rate ratios were calculated for breast cancer associated with pesticide use density, adjusting for age, race, SES and urbanisation.	The association between individual pesticides and breast cancer was also investigated. No statistically significant results were identified. Pesticides assessed included simazine, diuron, oryzalin, propargite and methyl bromide. All analyses were adjusted for age, race/ethnicity, SES and urbanisation.	

Table 12.2: Evidence tables for primary studies of xenoestrogens (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Charlier et al. 2003) Belgium	Case control study Level III-2	Study setting. Cases were selected from 600 women who underwent a medical examination between September 1999 and February 2000 following referral after a doubtful mammographic screening. Patients who were scheduled for mastectomy or tumourectomy were considered as cases. Sample Mean age (years) Cases 54.2 Controls 53.3	Cases (n=159) Diagnosed with breast cancer and undergoing a surgical intervention. Controls (n=250) Randomly selected from women consulting for routine cervico-vaginal cytological screening. Controls matched to cases on year of birth, menopausal status, reproductive history and date of blood sampling. Data collection Blood samples were collected and then frozen at -18^{0}C and assayed within one week. DDT and HCB were quantified using gas chromatography and mass spectrometry. Samples were analysed in duplicate. Analytical personnel were blind to the nature of the samples. Questionnaire data on breast cancer risk factors was also collected. Analysis Concentrations of DDT and HCB were compared between cases and controls using the Mann-Whitney U test. Chi squared test was used in the comparison of proportions (e.g. smoking status, breast feeding history, rural/urban status). Adjusted ORs were calculated using conditional logistic regression.	Adjusted OR (95% CI) and risk of breast cancer: Total DDT: 5.64 (1.81-17.65) HCB: 9.14 (2.84-29.41) Both analyses adjusted for breast feeding history	Limitations • Measurement of DDT and HCBs made at time of preparation for surgery. Levels at that time may not reflect levels preceding the diagnosis. • Controls may not be representative of the population from which the cases were drawn. The method of selection of controls is likely to have selected a health conscious population (attending for screening) • No information provided on participation rates • Observational study susceptible to residual confounding and limited control of potential confounders in the analysis. • Groups compared by smoking, living environment and breast feeding history but it was unclear how the documented results related to case/control status. Most notably, though, there was no significant difference in proportions between the cases and controls across these attributes. Comments • Aimed to investigate the breast carcinogenic properties of environmental xenoestrogens Reported conclusions (by authors). These results add to the growing evidence that certain persistent pollutants may occur in higher concentrations in blood samples from breast cancer patients than controls.

Table 12.2: Evidence tables for primary studies of xenoestrogens (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Warner et al. 2002) USA	Cohort study Level III-2	Study setting. Set in Seveso, Italy amongst women exposed to a large industrial explosion (1976). Sample (n=981) Characteristics at time of baseline interview Mean age 40.8 years Nulliparous 27% Mean age at first pregnancy among the parous women 24.2 years Lactation among parous 87% Family history of breast cancer 8%.	Study population Seveso Women's Health Study (SWHS) cohort eligibility: Infants to 40 years old in 1976 Resided in one of the most highly contaminated zones Had adequate stored sera collected soon after the explosion. Enrolment took place from March 1996 to July 1998. Data collection Sources of information: Serum – measured 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD). Used the first serum sample of adequate volume that was collected between 1976 and 1981. Samples had been stored at -20^{0}C. Measurement by mass spectrometry. Levels were back extrapolated to estimate 1976 levels. Interview – by trained nurse-interviewer blind to TCDD levels and zone of residence. Gynaecologic examination and transvaginal ultrasound (in a subset of women). Analysis Analysed serum TCDD as a continuous and categorical variable. Cox proportional hazards modelling used for the main analysis. Confounders considered included gravidity, parity, age at first pregnancy, age at last pregnancy, lactation, family history of breast cancer, age at menarche, current BMI, OC use, menarcheal status at explosion, menopause status at diagnosis, weight, height, smoking and alcohol consumption.	Hazard ratio (95% CI) is association between TCDD (as a continuous variable) and breast cancer Log_{10}TCDD: HR 2.1 (1.0-4.6) Meaning for a 10 fold increase in TCDD, a doubling of the hazard ratio is predicted.	Limitations • 80% of the eligible women who could be contracted agreed to take part. • Back extrapolation of TCDD level may have resulted in inaccurate estimation of the TCDD levels in 1976 – resulting in misclassification of exposure • Observational study susceptible to residual confounding • Small number of cases (n=15) Comments • Examined the association between individual serum TCDD levels and breast cancer risk in women residing in Seveso, Italy at the time of an industrial explosion Reported conclusions (by authors). Individual serum TCDD is significantly associated with breast cancer incidence among women in the SWHS cohort. Continued follow up of the cohort will help shed light on the possible role of TCDD in the pathogenesis of breast cancer.

Table 12.2: Evidence tables for primary studies of xenoestrogens (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Demers et al. 2000) Canada	Case control study Level III-2	Study setting. Study set in Quebec, Canada. Used both hospital and population controls. Sample Age (years) Cases 53 Hospital controls 51 Population controls 53 Age at menarche Cases 13 Hospital controls 13 Population controls 13 Age at first birth Cases 25 Hospital controls 24 Population controls 25 Number of deliveries Cases 2.2 Hospital controls 2.4 Population controls 2.2 BMI (kg/m^2) Cases 25 Hospital controls 26 Population controls 24 Breast fed > 6 months (%) Cases 11 Hospital controls 8 Population controls 11 OC use (%) Cases 68 Hospital controls 65 Population controls 62	Cases (n=315) Histologically confirmed infiltrating primary breast cancer Aged 30-70 Excluded if they had a past history of breast cancer or any other cancer (except CIN/BCC) or if they showed distant metastases at diagnosis. Controls (n=219 hospital based controls, n=307 population controls) Hospital based controls recruited from the same four hospitals as the cases. Free of gynaecological disease. Population based controls randomly selected from the general population files of the Regie de l'Assurance maladie du Quebec. Aged 30-70 Cases and controls matched for age (five year age groups) and region of residence (rural/urban). Data collection Blood samples obtained after surgery and before chemotherapy and radiotherapy. Plasma samples were frozen at -20^{0}C until time of analysis. Fourteen PCB congeners and 11 chlorinated pesticides were measured using gas chromatography. Telephone interview used to collect demographic and risk factor data.	Adjusted OR (95% CI) comparing cases with population based controls for specified organochlorines ((quintile 1 – lowest level- as reference) β-HCH: Quintile 2 0.60 (0.35-1.01) Quintile 3 0.62 (0.37-1.04) Quintile 4 0.86 (0.50-1.49) Quintile 5 0.80 (0.47-1.35) *p, p'-DDE:* Quintile 2 0.75 (0.45-1.25) Quintile 3 1.06 (0.62-1.79) Quintile 4 0.86 (0.52-1.42) Quintile 5 1.00 (0.60-1.67) *p,p'*-DDT: Quintile 2 0.57 (0.34-0.95) Quintile 3 0.50 (0.30-0.84) Quintile 4 0.71 (0.43-1.19) Quintile 5 0.81 (0.48-1.37) Oxychlordane: Quintile 2 1.09 (0.65-1.82) Quintile 3 1.00 (0.59-1.69) Quintile 4 1.26 (0.74-2.16) Quintile 5 1.47 (0.83-2.62) *trans*-Nonachlor Quintile 2 0.82 (0.49-1.40) Quintile 3 1.53 (0.91-2.59) Quintile 4 0.63 (0.39-1.23) Quintile 5 1.20 (0.68-2.13) PCB-153: Quintile 2 1.12 (0.66-1.88) Quintile 3 0.94 (0.55-1.62) Quintile 4 1.18 (0.68-2.05) Quintile 5 1.28 (0.74-2.19)	Limitations • Participation rates: cases 91%, hospital controls 89%, population controls 47% • Blood samples for cases and hospital controls obtained after surgery - levels at that time may not reflect levels preceding the diagnosis. • Observational study susceptible to residual confounding Comments • Assessed breast cancer risk and disease aggressiveness in relation to plasma concentrations of several organochlorine compounds • Population controls may be more representative of the population from which the cases came than the hospital based controls Reported conclusions (by authors). Exposure to persistent, hormonally active organochlorines during adulthood is not associated with breast cancer risk.

Table 12.2: Evidence tables for primary studies of xenoestrogens (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Demers et al. 2000) *Continued*		HRT use (%) Cases 42 Hospital controls 35 Population controls 36 Family history of breast cancer (%) Cases 22 Hospital controls 16 Population controls 12 History of benign breast disease (%) Cases 35 Hospital controls 20 Population controls 17	Analysis Characteristics of cases and controls were compared using the t test for continuous variables and chi squared test for categorical variables. Variance analysis was used to compare mean concentrations of organochlorines between cases and controls. Unconditional logistic regression used. Age and region of residence were included in all models. Other variables tested for confounding were BMI, total energy consumed, alcohol consumption, age at first cigarette, number of fertile years, age at first child, total breast feeding duration, OC use, HRT use, family history of breast cancer, history of benign breast disease, and time separating blood sampling from surgery. A variable was considered as a confounder when its inclusion modified OR by >10%.	All analyses adjusted for age and region of residence. Note: no statistically significant results were found when comparing cases with the hospital controls.	

Table 12.2: Evidence tables for primary studies of xenoestrogens (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Hoyer et al. 1998) Denmark	Nested, matched case control study Level III-2	Study setting. Case control study set within the Copenhagen City Heart Study (CCHS). This cohort was selected randomly through the Civil Registration System in defined areas of Copenhagen. Sample Nulliparous (%) Cases 27 Controls 23 Postmenopausal (%) Cases 70 Controls 69 HRT (%) Cases 26 Controls 22 Smoker (%) Cases 53 Controls 54	Cases (n=240) Selected cases from the group of women who developed invasive breast cancer over 17 years of follow up in the CCHS. Identified cases by linkage to the Danish Cancer Registry. Excluded women who had breast cancer before the start of the study. Controls (n=477) Matched with two breast cancer free women from the CCHS. Matched on age, date of examination and vital status at time of diagnosis. Data collection Each participant in the CCHS completed a questionnaire and had blood taken. The serum was stored in a freezer. The samples were analysed for 18 organochlorine pesticides/metabolites and 28 PCB congeners. Gas chromatography was used in the analysis. Analysis Conditional multiple logistic regression used to estimate ORs associated with quartiles of pesticides and PCB exposure. Adjustment was made for potential confounders including weight, height, number of full term pregnancies, alcohol consumption, smoking, physical activity, menopausal status, household income, marital status, and education. A backwards stepwise procedure was used and only variables that reached significance ($p<0.05$) remained in the model.	Adjusted OR (95% CI) comparing cases with controls for specified organochlorines ((quartile 1 – lowest level- as reference) Total PCB Quartile 2 0.92 (0.58-1.45) Quartile 3 0.78 (0.48-1.26) Quartile 4 1.11 (0.70-1.77) Total DDT Quartile 2 0.79 (0.45-1.39) Quartile 3 0.92 (0.54-1.58) Quartile 4 0.84 (0.49-1.45) *p,p'*-DDT Quartile 2 1.07 (0.68-1.68) Quartile 3 0.91 (0.56-1.47) Quartile 4 1.19 (0.76-1.87) *p,p'*-DDE Quartile 2 0.83 (0.53-1.31) Quartile 3 0.77 (0.49-1.22) Quartile 4 0.88 (0.56-1.37) β-HCH Quartile 2 1.13 (0.69-1.86) Quartile 3 1.35 (0.79-2.30) Quartile 4 1.36 (0.79-2.33) Dieldrin Quartile 2 1.58 (0.93-2.67) Quartile 3 1.96 (1.14-3.39) Quartile 4 2.05 (1.17-3.57) *P* for trend 0.01 Results adjusted for number of full term pregnancies and weight.	Limitations • Proportion who agreed to participate in the original cohort study was unclear • Observational study susceptible to residual confounding • Unclear if personnel conducting the analyses were blind to case/control status • Minor potential for misclassification of exposure levels due to sample deterioration Comments • Prospectively assessed the risk of breast cancer in relation to serum concentrations of several organochlorine compounds • Nested case control design reduces risk of selection bias Reported conclusions (by authors). Findings support the hypothesis that exposure to xeno-oestrogens may increase the risk of breast cancer.

Table 12.2: Evidence tables for primary studies of xenoestrogens (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Aschengrau et al. 1998) USA	Case control study Level III-2	Study setting. Population based case control study in Cape Cod, Massachusetts Sample Median age group (years) Cases 60-69 Controls 60-69 More than high school education (%) Cases 48.1 Controls 42.3 Alive at interview (%) Cases 67.4 Controls 55.0 Family history of breast cancer (%) Cases 19.3 Controls 8.9 History of benign breast disease (%) Cases 11.1 Controls 15.4 Nulliparous (%) Cases 30.6 Controls 24.1 OC use (%) Cases 17.6 Controls 11.6 Postmenopausal (%) Cases 88.1 Controls 91.6	Cases (n=261) Incident cases of breast cancer diagnosed from 1983 through 1986 Permanent resident of one of five Cape Cod towns. Controls (n=753) Controls selected by random digit dialling (RDD), lists of Medicare beneficiaries provided by the Health Care Financing Administration (HCFA) and death certificates. Controls were chosen based on similar age and race characterisation from the same five Cape Cod towns as the cases. Data collection Blinded exposure assessments were employed using the data from the NIOSH National Occupational Exposure Survey, chemical production and usage information, and the expert judgement of a certified industrial hygienist. Permission to interview the living cases was obtained from physicians. Occupational information was collected on all full time jobs held for at least one year from age 18. Trained personnel were used to obtain information on demographic characteristics and breast cancer risk factors. Index years were randomly assigned to the controls to match the frequency distribution of the cases' diagnosis years.	Adjusted OR (95% CI) comparing cases and controls across specified exposures 1 xenoestrogen: 1.1 (0.8-1.7) 2 xenoestrogens: 0.6 (0.3-1.2) 3 xenoestrogens: 0.9 (0.5-1.9) 4+ xenoestrogens: 0.9 (0.5-1.9) Any methoxychlor: 0.8 (0.2-3.0) Any endosulfan: 0.8 (0.2-3.2) Any PCB: 3.2 (0.8-12.2) Any 4-sec-butylphenol: 3.2 (0.8-12.2) Any 4-tert-butylphenol: 0.5 (0.2-1.2) Any 4-hydroxybiphenyl: 0.4 (0.1-1.0) Any nonlyphenol: 1.0 (0.7-1.5) Any 4-octylphenol: 2.9 (0.8-10.8) Any butyl benzyl phthalate: 0.7 (0.4-1.2) Any BHA: 0.8 (0.5-1.5) Any bisphenol A: 0.8 (0.5-1.4)	Limitations • 79% of reported cases were interviewed. • RDD used to select residents under 65 years. 95% of housing units in Massachusetts had a telephone service in 1980. • From 2,236 residences identified, 63% had no respondents who met the eligibility criteria, 20% did not answer the phone, 6% refused the screening questionnaire resulting in 254 eligible households being identified and 189 residents being interviewed. • HCFA is estimated to have enumerated 95% of subjects 65 years and over. 3% of the randomly selected controls were never found/contacted and 12% refused or were too unwell to take part. • Exposure information susceptible to misclassification. The exposure assessment was blind to case/control status so any misclassification is most likely to dilute the associations. • Next of kin used to collect some data. May have been differentially used between cases and controls since there were more deaths amongst the controls. • No information on intensity of exposure • Small numbers of cases exposed to xenoestrogens of interest.

Table 12.2: Evidence tables for primary studies of xenoestrogens (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Aschengrau et al. 1998) *continued*		HRT use (%) Cases 26.2 Controls 25.0 Ever regular cigarette smoker (%) Cases 58.7 Controls 53.3 Ever regular alcohol drinker (%) Cases 81.2 Controls 77.4	Analysis Women were classified as having probable or possible exposure to xenoestrogens. Odds ratios (ORs) were calculated for specific groups, number of xenoestrogens exposed to, duration of exposure and menopausal status. Logistic regression was used for adjusted analyses. A group of core confounders were included in all models: age at diagnosis/index year, vital status at interview, family history of breast cancer, age at first birth, prior breast cancer and benign breast disease. Other potential confounders that changed the crude estimate by more than 10% were also included.		Comments • Aimed to describe the relationship between occupational exposure to oestrogenic chemicals and the occurrence of breast cancer in Cape Cod Reported conclusions (by authors). Additional research is required to corroborate findings

Table 12.2: Evidence tables for primary studies of stilbestrol

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Palmer et al. 2002) USA	Prospective, cohort study Level III-2 19y follow-up	Study setting. A collaborative prospective follow-up study of DES-exposed daughters & un-exposed women of same age in progress since 1992 (3 existing cohorts since 1978 and 4th cohort added in 1994) Sample (n= 6916) women (4821 exposed, 2095 not exposed) Characteristics: Mean age at start (1978): E (24y), NE (26y) Median number of years followed (E= 19Y, NE=18Y) Lost to follow-up E (18%), NE (16%) Deceased E (1%), NE (1%) Responded to 1997 questionnaire E (81%), NE (83%)	Cohort come from combining 3 existing cohorts of: - women previously followed in National Cooperative Diethylstilbestrol Adenosis Project (DESAD), - daughters of women participated in RCT of DES in 1951-1952 (Dieckmann) & - daughters of women treated with DES by infertility specialist in the Boston, MA area - In 1994, several hundred women were added to the cohort (not studied before, but were offspring of women who participated in Women's Health Study-WHS) Data collection Follow-up started on 1January 1978 (1995 for WHS) Data collection by mailing 2 questionnaires - in 1994 (detailed questionnaire about reproductive, behavioural factors, and adverse health outcomes) & - 1997 (shorter questionnaire about new occurrences of disease). Also used the National Death Index to ascertain breast cancers in dead participants and lost to follow-up. Analysis Person-years at risk computed from start until date of first breast cancer diagnosis, date of last known follow-up, date of death, or date of response to 1997 questionnaire. Poisson regression analysis (adjusted for year of birth, age at menarche, age at first birth, number of births) Nelson-Aalen cumulative incidence curves created for exposed & not exposed	Exposed women: 83,370 person-years of follow-up, 34 cases of breast cancer, Not exposed women 29,224 person-years of follow-up, 15 cases of breast cancer, Rate ratio (RR) for incidence of invasive breast cancer in exposed versus not exposed women 1.4 (95% CI 0.7-2.6) Similar results when including 19 additional *in situ* breast tumours (RR 1.3, 95%CI 0.7-2.1). DES exposure & incidence of breast cancer: - women <40y not associated with increased incidence (RR 0.7, 95%CI 0.3-1.7) - women ≥40y twofold increase (RR 2.5, 95% CI 1.0-6.3). - Stronger relationship for estrogen receptor-positive cancers (RR 1.9, 95%CI 0.8-4.5) DES exposure and tumour size: - Size <2cm RR 1.1 - Size ≥2cm RR 1.5 DES exposure and nodal involvement: - breast cancer with no nodal involvement RR 3.6 (95%CI 0.9-17) - metastatic disease RR 0.8 (95% CI 0.3-2.1) Timing of first DES exposure and risk of breast cancer - at ≥ 13 weeks of gestation RR 1.7 (95% CI 0.7-3.8), person-year follow-up 20,814.	Limitations • Observational • Not randomised, not blinded • Potential for selection bias • Very small number of cases • Disparity between exposed women and not exposed women in parity, age at first birth and education • Used mailed questionnaires • Prone to recall bias • breast cancer incidence may be underestimated as the mean age of the cohort was 43y • Study power to detect lower RR may be inadequate • Follow-up was incomplete for nearly 25% of the cohort more than 10 years ago • Cohort from WHS daughters were older when invited to participate in 1994 (median age 42y), contributed to follow-up from 1995 only (shorter follow-up period) Reported conclusions (by authors). While not statistically significant, the overall 40% excess risk, arising exclusively from the subset of estrogen receptor-positive cases, raises a concern calling for continued investigation.

E= Exposed, NE= not exposed, RR= Rate ratio

Table 12.2: Evidence tables for primary studies of stilbestrol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Titus-Ernstoff et al. 2001) USA	Cohort study (combined analysis from two cohort studies) Level III-2.	Study setting. Mothers Study: Mayo Clinic (Rochester), Mary Hitchcock Memorial Hospital (MHMH) in Hanover, high-risk pregnancy clinic at Boston Lying-In Hospital (BLI) in Boston, and private obstetrics practice in Portland. Dieckmann Study: University of Chicago Sample (initial from two cohorts N= 7758) Exposed = 3879, Not exposed =3879 From each individual study: Mothers Study cohort [E=3053, NE= 3075]. Age at study entry for exposed women 29% aged <25y, 35% aged 25-29y, 21% aged 30-34, and 15% aged ≥35y For not exposed women 29% aged <25y, 35% aged 25-29y, 22% aged 30-34, and 14% aged ≥35y Main differences in percent of women (2% or more) in baseline characters between exposed and not exposed Body mass index, Family history of breast cancer, age at menarche, pregnancy losses (0, 1 loss, or ≥2 losses), Age at first full-term birth, parity (≥ 5 children), age at menopause, HRT, and hysterectomy	Cohort comes from combining the cohort from the two studies (Mothers Study cohort + Dieckmann Study cohort) In 1992 tracing efforts to locate women who had been previously followed from both cohorts. Original studies: <u>Mothers Study</u> Women identified through retrospective review of obstetrics records for period 1940-1960. Eligibility- DES-exposed women (whose records indicated DES or another non-steroidal oestrogen prescribed during at least one pregnancy resulting in a live birth). Study entry date = Date of 1st DES-exposed live birth Unexposed women (matched±2y) selected from same settings who had delivered at least one live birth during the same time period and whose charts did not indicate exogenous oestrogen use during any of their pregnancies Study entry date = same date as matched exposed women. Follow-ups in 1981, 1986 &1989 <u>Dieckmann Study</u> Conducted in early 1950: Women participating in a clinical trial examined effects of DES on pregnancy outcomes. Eligibility- Enrolled women who were 6-20 wk pregnant. Alternately assigned to receive DES or placebo; date of pregnancy outcome was the study entry date. Evaluations performed in 1976 for cancer outcomes.	Mothers Study participants had higher parity, younger age at first full-term birth, younger age at menarche, and higher frequency of smoking than women participating in Dieckmann Study. They also reported more pregnancy losses (primary indicator for DES use). DES Exposed vs. not exposed results- Both had slightly increased cancer risk (combined RR 1.10 (95%CI 0.99-1.23) Risk of breast cancer was the only cancer significantly increased and accounted for most of the excess observed in all cancer. Association between DES exposure and breast cancer risk- Combined from both cohorts RR=1.27 (95%CI 1.07-1.52), adjusted for potential confounders RR 1.25 (95% CI 1.05-1.52) Individual studies- Mothers Study RR 1.29 (95% CI 1.06-1.57), Dieckmann study RR 1.26 (95% CI 0.88-1.82)	Limitations • Observational • Not randomised, not blinded • Selection bias • One setting was a high-risk pregnancy clinic (BLI) • Used self-reported breast cancer • 8% of initial cohorts could not be located (7% of exposed, 9% of not exposed) • Combined cohort results were similar when study exit dates for non-respondents and women lost to follow-up were extended to end of follow-up period • Dose of DES were missing from records therefore, dose-response relationship could not be evaluated Reported conclusions (by authors). Women who took DES while they were pregnant experience a 20-30% increased rate of breast cancer for many years after. This modest increase in risk does not appear to be greater or lesser depending upon family history of breast cancer. It also appears not to be exacerbated by use of oral contraceptives or HRT. DES appeared not to increase the risk of other cancers, including endometrial or ovarian cancer.

Table 12.2: Evidence tables for primary studies of stilbestrol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Titus-Ernstoff et al. 2001) *Continued*		Dieckmann study cohort E=826, NE=804] Age at study entry for exposed women 26.4% aged <25y, 36.6% aged 25-29y, 22.9% aged 30-34, and 14.2% aged ≥35y For not exposed women 27.2% aged <25y, 36.4% aged 25-29y, 24.4% aged 30-34, and 11.9% aged ≥35y Main differences in percent of women (2% or more) in baseline characters between exposed and not exposed Body mass index, age at menarche, oral contraceptive use, Age at first full-term birth, age at menopause (≥55), HRT, and hysterectomy In 1994 sample from both cohorts- (N=5474) E = 2761 NE = 2713	Data collection DES exposure status assessed by review of medical records (Mothers Study cohort), and clinical trial records (Dieckmann Study) Sample in 1992 (start of this follow-up study)- (262 exposed and 363 not exposed were not located) In 1994 follow-up questionnaires to women presumed alive were completed by 88% of the cohort [4836 women (E= 2434, NE= 2402)] Others refused to participate or did not respond to contact (327 exposed, 311 not exposed) Analysis Poisson regression analyses in terms of relative risk (RR) and 95% CI for the association between DES exposure and breast cancer occurrence	Age-standardized breast cancer rates per 100 000 were 106.9 for exposed women versus 83.9 for non-exposed women in the combined cohort. Incidence rate (relative to general US population) was slightly increased among DES-exposed women (SIR= 1.10, 95% CI= 0.98-1.23), and slightly but significantly reduced among unexposed women (SIR =0.86, 95% CI= 0.75-0.98). Association between DES exposure & breast cancer risk not significantly modified by family history of breast cancer, oral contraceptive or HRT use. RR for breast cancer associated with DES exposure during a first pregnancy compared to a subsequent pregnancy 1.15 (95%CI 0.9-1.47)	

Table 12.2: Evidence tables for primary studies of stilbestrol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Hatch et al. 1998) USA	Prospective, cohort (combined) Level III-2. 16-y follow-up	Study setting. National Cooperative Diethylstilbestrol Adenosis (DESAD) study (mid 1970s)-- Five centres (3 stated= Baylor College of Medicine/Houston-Texas, the Mayo Clinic (Rochester), and Massachusetts General Hospital (Boston) + physician referral + self referral Dieckmann Study (1950s) The Horne cohort (infertility specialist) Boston (mid 1970s). Sample (Total N= 6080) of which 4536 Exposed and 1544 not exposed. Median age at start of follow-up for Exposed is 24.3y (25th percentile 20.1y and 75th percentile 26.6y) and for unexposed is 25.3y (25th percentile 21.1y and 75th percentile 26.6y). Median No. of years followed (25th percentile, 75th percentile) for exposed women 16.4y (14.6, 16.9) and not exposed women 16.3 (14.2, 16.7) Exclusions • Lost to follow-up before 1978 (3% of exposed, 5% of not exposed) • Cancer or death before 1978 (0.7% of exposed, 1.1% of not exposed) Missing information on year of birth (0.4% of exposed, 0.9% of not exposed)	Cohort comes from combining 3 cohorts: National Cooperative Diethylstilbestrol Adenosis (DESAD), Diechmann Study and Horne Study All exposed women had documented exposure to DES during pregnancy. Not exposed women had their non-exposure status documented by either review of prenatal records (DESAD & Dickmann) or by report of the mother (Horne cohort). In 1994 subjects sent detailed questionnaire on cancer risk factors & health history – including occurrence of cancer (not only breast cancer) Median DES dose from Dieckmann & Horne cohorts = 12g, dose from DESAD cohort ranged 1.5-4.5g (incomplete data) Data collection from individual studies <u>DESAD cohort-</u> (Exposed women) identified by prenatal record review at 5 centres + physicians referrals + self-referrals (required to document exposure to DES) Not-exposed women *in utero* selected from same record sources or sisters of exposed women. Follow-up yearly: Clinical examinations through 1980 or Mailed questionnaires (1984 -1989)	• Response rate (88%) for both exposed and not exposed women who were mailed the 1994 questionnaire from all cohorts. • Response in 3650 exposed women (81%), 1202 not exposed women (79%) • Lost to follow-up (850 exposed women, 331 not exposed women) • Died (36 exposed women, 11 not exposed women) *In-utero* DES exposure and risk of breast cancer • RR 1.18 (95%CI 0.56-2.49) • SIR of breast cancer in exposed women is 1.19 (95% CI 0.83-1.72) compared to 0.98 (95% CI 0.51-1.88) in women not exposed to DES • Results similar when including 9 additional breast tumours (*in situ)* SIR 1.22 (95% CI 0.87-1.71), RR 0.99 (95%CI 0.52-1.88) • SIR of breast cancer in women aged ≥40y was 0.83; 95%CI 0.51-1.35 compared to general population • Among entire cohort, no evidence of an increased risk of breast cancer • Among women aged ≥40y a higher risk of breast cancer suggested in the DES exposed daughters compared to unexposed daughters (not significant)	Limitations • Observational • Not randomised, not blinded • Some demographic differences between the two groups • Relatively young age of cohort (limiting study power for breast cancer risk) • 2 cohorts exposed to high doses of DES • Doses given to DESAD cohort difficult to estimate (incomplete data in medical charts) • Some subjects not approached during 1994 follow-up • Observations (and rate ratios) for breast cancer may be compromised by the young age of studied women at the time of study (<50y) which is not the usual age range of the disease • Response rate good, similar losses to follow-up for both groups, and when adjust for the loss to follow up group similar results were obtained Reported conclusions (by authors). Thus far, DES-exposed daughters show no increased cancer risk, except for clear cell adenocarcinoma (CCA). Nevertheless, because exposed daughters included in our study were, on average, only 38 years old at last follow-up, continued surveillance is warranted to determine whether any increases in cancer risk occur during the menopausal years.

Table 12.2: Evidence tables for primary studies of stilbestrol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Hatch et al. 1998) *continued*		Baseline characteristics Baseline characteristics differed between the two groups in age at menarche (earlier in DES exposed), DES exposed more likely nulliparous, and have fewer live births Sample from individual cohorts- DEASD cohort: n=4936 women (3919 exposed, 1017 not exposed) Dieckmann cohort n= 644 female offspring whose mothers participated in RCT of DES (336 exposed, 308 not exposed) Horne cohort n= 500 (281 exposed daughters, 219 not exposed sisters whose pregnant mothers were treated with DES)	<u>Dieckmann cohort-</u> (Exposed women) female offspring whose mothers participated in RCT of efficacy of DES during pregnancy in early 1950s. In 1974 attempts made to trace all subjects in this cohort (83% exposed & 77% not exposed women) responded to questionnaire. Follow-up episodic during 1980s (last contacted in 1990). <u>Horne cohort-</u> assembled in the mid-1970s, exposed daughters were mailed yearly questionnaires through the 1980s, data not been previously analysed Outcome measures Cancer incidence in DES-exposed daughters compared with population-based rates and compared with cancer incidence in unexposed daughters Analysis Person-years at risk calculated for each individual from January 1, 1978 (or date of first enrolment) to date of first cancer diagnosis, date of last known follow-up, or date of questionnaire response. Poisson regression analysis (for internal and external comparisons) Potential confounders considered were: education, age at menarche, age at first live birth, and menopausal status Standardised incidence ratio (SIR) calculated & 95% CI	This did not differ by follow-up time. • Breast cancer risk in daughters exposed to DES attained age < 40 y rate ratio 0.66 (95% CI 0.26-1.68), number of cases 20 • Breast cancer risk in daughters exposed to DES attained age ≥ 40 y rate ratio 3.17 (95% CI 0.73-13.83), number of cases 18	

Table 12.2: Evidence tables for primary studies of stilbestrol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Sanderson et al. 1998) USA	Case-control Study Level III-2.	Study setting. 3 western Washington counties Sample (N= 946) Eligible From two population-based case-control studies (N= 2331), eligible cases = 1034 eligible proxies for deceased cases = 210, eligible controls = 1087	Data collected from mothers of women in two population-based case-control studies of breast cancer in women under the age of 45y who were diagnosed with breast cancer between 1983-1992 Cases (n= 510) Controls (n= 436) Eligibility- First study--Diagnosed with primary invasive breast cancer between January 1983 & April 1990, born after 1944, resided in King, Pierce or Snohomish counties at time of diagnosis Second study—Diagnosed with primary invasive breast cancer between May 1990 & December 1992, aged <45y & resided in the three-county area. Cases selected using population-based cancer registry, controls selected using random digit dialling (controls were age and county of residence matched with cases) Data collection From two studies subjects or proxies were re-contacted, asked to provide information pertaining to their birth (including subject's mother for information on pregnancy). Excluded mothers who were either deceased or unable to complete questionnaire, adopted subjects were also excluded. Subjects completed mailed questionnaires or telephone interviews between May 1994 & August 1996	83% eligible cases, 80% eligible controls completed standardised personal interview Use of DES and risk of breast cancer— • OR = 2.3, 95% CI 0.8-6.4 • OR= 2.0, 95% CI 0.7-5.9 when analysis restricted to women with no first-degree family history of breast cancer	Limitations • Observational • Random digit dialling selection for controls • Selection bias for cases • No information on blinding • Data from mothers reports so potential for recall bias • Proxy respondents for deceased women were excluded if maternal DES exposure of mothers who did not participate differed from those who did the association • Number of mothers reporting DES exposure low (13 mothers/cases, 5 mothers/controls) and wide 95% CI • No information on DES dosage so no actual measurement of the extent of DES exposure • Measurement error • Misclassification bias • Lack of statistical power as the study is severely limited by the small number of women exposed to DES in both cases and controls Reported conclusions (by authors). The results from this study provide limited support for the hypothesis that *in utero* oestrogen exposure may be related to subsequent breast cancer risk among young women.

Table 12.2: Evidence tables for primary studies of stilbestrol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Sanderson et al. 1998) *continued*			Analysis Unconditional logistic regression to compare risk of breast cancer in association with maternal factors for both cases and controls Potential cofounders— Age, birth year, reference year, first-degree family history of breast cancer, age at menarche, menopausal status, occurrence of full-term pregnancy, age at first full-term pregnancy, BMI, infertility, use of oral contraceptive, birth weight, maternal age, birth order, and maternal smoking.		

Table 12.2: Evidence tables for primary studies of stilbestrol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Weiss et al. 1997) USA	Case-control study (population-based) Level III-2.	Study setting. 3 areas of US covered by cancer registries= Atlanta, Seattle/Puget Sound & 5 counties in central New Jersey Sample (N=4211, cases = 2002, controls = 2009) women under the age of 55y, of those 1031 aged <45 (534 cases and 497 controls)	Cases (n= 534), Controls (n= 497) Selection of cases – Women aged 20-44y in Seattle &New Jersey & women aged 20-54y in Atlanta (newly diagnosed with breast cancer between May 1, 1990 & through December 31, 1992) Selection of controls – Random-digit-dialling, matched by geographical area & age to the expected distribution of cases. Exclusions— No residential telephones (29 cases), previous diagnosis with breast cancer (19 controls) Data collection First telephone screener (reference date) Then interviews included demographic factors, reproductive, menstrual & screening history, use of exogenous hormones & smoking & alcohol consumption Mother and daughter questionnaires Administered questionnaire to daughters which included a question regarding mother's date of birth, used this information to calculate maternal age at birth. Analysis Multiple logistic regression to calculate relative risks (RR) & 95% CIs adjusting for potential risk factors for breast cancer	Analyses of breast cancer risk by maternal age and twin status. Subset of white women under the age of 45 years with a completed mothers' questionnaire. Response rate for completed questionnaires from the Mothers of White Women under Age 45y 70% cases, 69% controls Number of women reported an exposure to DES (14 cases and 17 controls) Results • Exposure to DES *in utero* showed little evidence of altered breast cancer risk (RR 0.75; 95%CI 0.4-1.6).	Limitations • Observational • Random selection for controls, not blinded • Potential for selection bias • Potential for recall bias from mothers' questionnaires due to time from pregnancy to interview • Response rate low and varied by site • Potential for response bias • Analysis included only white women as response rate among African women was very low (generalisability questioned) • Variation in characters between respondents and non-respondents • Number of women who reported an exposure to DES small compared to women who did not know their exposure status Reported conclusions (by authors). Findings indicate some effect of early life exposure on breast cancer risk, although the role of estrogen exposure may be less central than previously suggested.

Appendix 13: Evidence tables for dietary factors

Table 13.1: Evidence tables for secondary studies of dietary factors

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Saadatian-Elahi et al. 2004)	Level III-2.	MEDLINE (1966-2002) MeSH terms: biomarkers, dietary fat, breast cancer.	Inclusion criteria Published studies providing relative risk and 95% confidence intervals Exclusion criteria Nil stated Data extraction Not documented. Data analysis Random effects meta-analysis. Pooled estimates presented separately for case-control and cohort studies. Pooled relative risk estimate for the highest category of fatty acid. For intermediate categories, averaged the RR of second categories and penultimate category.	<u>Saturated fatty acids and risk of breast cancer</u> Cohort studies: RR 1.74 (95% CI 1.15-2.63) Case-control studies: RR 0.91 (95% CI 0.66-1.28) <u>Monounsaturated fatty acids and risk of breast cancer</u> Cohort studies: Oleic acid RR 2.15 (95% CI 1.68-2.74) Case-control studies: No significant association <u>n-6 polyunsaturated fatty acids and risk of breast cancer</u> Cohort studies: RR 0.67 (95% CI 0.44-1.02) Case-control studies: No significant association <u>n-3 polyunsaturated fatty acids and risk of breast cancer</u> Cohort studies: RR 0.61 (95% CI 0.40-0.93) Case-control studies: RR 0.90 (95% CI 0.59-1.36)	Limitations ▪ Only searched MEDLINE. ▪ Limited MeSH terms used. ▪ Methods of data extraction not described. ▪ No information on the accuracy of the biomarker assays used. ▪ Controls were hospital based in seven of the nine case control studies selected. Two of these case-control studies were excluded (both used hospital based controls). ▪ Total 10 studies included in the meta-analyses (three cohort, seven case-control). Included 2,031 cases and 2,334 controls. ▪ Different results between cohort and case-control studies may be due to different biomarkers used, later timing of samples in case-control studies (once breast cancer diagnosis has been made), and different population groups. ▪ Lack of adjustment for some confounding factors in these observational designs. Few studies conducted using biomarkers and multiple comparisons made (with multiple sub-analyses of specific fatty acids). Reported conclusions (by authors). More epidemiological cohort studies that integrate biological markers of dietary fatty acid intake are needed in order to determine the contribution of different types of fatty acids in the aetiology of breast cancer.

Table 13.1: Evidence tables for secondary studies of dietary factors (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Boyd et al. 2003)	Level III-2.	MEDLINE and PUBMED from 1966 to July 2003. Reference lists of review articles and primary studies were also searched.	Inclusion criteria Case control and cohort studies that provided estimate of breast cancer risk related to dietary intake of fat and certain food groups (meat, milk and cheese). If study results were presented in more than one article, the most recent analysis was used. Exclusion criteria Nil stated. Data extraction Descriptive data, relative risk estimates and confidence intervals by level of fat/food group were extracted. Estimates that reflected the highest degree of control for confounders were extracted. Population controls were used in preference to hospital controls. Four investigators independently assessed methodological quality using preset criteria. Data analysis Nested case control studies were treated as cohort studies. Case control studies and cohort studies were analysed separately as well as combined. Subgroup analyses were also performed based on quality score, geographical area and type of control population. A random effects model was used for meta-analysis.	<u>Total fat intake and risk of breast cancer</u> Highest versus lowest levels of dietary fat: RR 1.13 (95% CI 1.03-1.25) Cohort studies: RR 1.11 (95% CI 0.99-1.25) Case control studies: RR 1.14 (95% CI 0.99-1.32) <u>Saturated fat intake and risk of breast cancer</u> RR 1.19 (95% CI 1.06-1.35) <u>Monounsaturated fat intake and risk of breast cancer</u> RR 1.11 (95% CI 0.96-1.28) <u>Polyunsaturated fat intake and risk of breast cancer</u> RR 0.94 (95% CI 0.80-1.10) <u>Meat intake and risk of breast cancer</u> RR 1.17 (95% CI 1.06-1.29) <u>Milk intake and risk of breast cancer</u> RR 1.12 (95% CI 0.88-1.43) <u>Cheese intake and risk of breast cancer</u> RR 1.26 (95% CI 0.96-1.66)	Limitations and comments ▪ 45 studies, 25,015 cases and over 580,000 control/comparison subjects. (Food group data restricted to 37 studies). ▪ Susceptible to confounding given use of observational studies. ▪ Details about study identification process unclear e.g. how many reviewers independently selected studies. ▪ Search strategy/terms not presented. ▪ Susceptibility to usual issues of misclassification of dietary intake using self report data. Such error is expected to attenuate the estimated RR. ▪ Studies of higher quality had higher overall relative risk estimates, suggesting the effect size may have been underestimated in the various pooled results. ▪ Substantial variation in estimate by geographical location was present. Reported conclusions (by authors). Experimental trials, in which the range of fat intake is increased beyond that seen in most Western populations, are a means of overcoming the limitations of observational epidemiology. Such trials are the only means available to determine whether breast cancer risk can be reduced by changing dietary fat intake.

Table 13.1: Evidence tables for secondary studies of dietary factors (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Missmer et al. 2002)	Level III-2.	Not stated	Inclusion criteria Prospective cohort study conducted in Western Europe and North America Study initially included ≥ 200 incident cases of breast cancer Diet assessment at baseline used a comprehensive food frequency questionnaire Availability of a validation study of the diet assessment instrument or closely related instrument. Exclusion criteria Women were excluded if they met study specific exclusion criteria, reported total energy intakes greater than or less than 3 SDs from the study specific log transformed mean energy intake or had been diagnosed before baseline with any cancer other than non-melanoma skin cancer. Data extraction Food intake measured at baseline by food frequency questionnaire. Food categorised according to stipulated criteria. In six cohort studies the results were analysed as a nested case control study with 10 controls per case. One study had already used a nested case control design with two controls per case and the final study used a case-cohort design. Data analysis For the nested case control studies, rate ratios were estimated using conditional logistic regression. All meat and dairy groups were analysed as continuous variables (and also as quartiles). Egg consumption was analysed as a categorical variable. Menopausal status was assigned using an algorithm based on the Nurses' Health Study. A random effects model was used to combine study specific estimates.	<u>Risk of breast cancer by red meat consumption</u> RR 0.98 (95% CI 0.93-1.04), per 100g per day increment <u>Risk of breast cancer by white meat consumption</u> RR 1.02 (95% CI 0.94-1.11) , per 100g per day increment <u>Risk of breast cancer by dairy fluid consumption</u> RR 0.99 (95% CI 0.97-1.00) , per 100g per day increment <u>Risk of breast cancer by dairy solid consumption</u> RR 1.03 (95% CI 0.95-1.11) , per 100g per day increment <u>Risk of breast cancer by egg consumption</u> 0-<14g/day: RR 0.93 (95% CI 0.82-1.05) 14-<25g/day: RR 0.94 (95% CI 0.82-1.09) 25-<50g/day: RR 0.98 (95% CI 0.80-1.21) ≥50g/day: RR 1.07 (95% CI 0.90-1.28)	Limitations and comments ▪ Source of data not stated – not possible to judge the completeness of the literature identification. Therefore, consider as prone to publication bias. ▪ Geographical restriction also limits the review. ▪ All missing dietary responses coded as zero intake. ▪ Menopausal status may have been misclassified based on the approach using extrapolation from the Nurses' Health Study. ▪ Susceptible to confounding given use of cohort study data. ▪ Unable to assess adequacy of selection processes. ▪ No evidence of heterogeneity across the group specific analyses. ▪ Similar effect levels when stratified by menopausal status. ▪ Unable to assess the influence of cooking. ▪ Unable to correct for measurement error due to lack of food group based analyses in the validation studies. Reported conclusions (by authors). No significant associations between intake of meat or dairy products and risk of breast cancer. An inconsistent relation between egg consumption and risk of breast cancer merits further investigation.

Table 13.1: Evidence tables for secondary studies of dietary factors (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Zock and Katan 1998)	Level III-2.	MEDLINE (1966-1996) Biological abstracts (1989-1996). Citations in retrieved articles.	Inclusion criteria Epidemiologic studies that provided quantitative estimates of cancer risk and its standard error with high compared with low intakes of linoleic acid or polyunsaturated fat. Exclusion criteria Nil stated Data extraction Extracted the risk estimate from individual studies that represented the largest difference in intake and reflected the greatest level of control over other environmental and dietary risk factors. Data analysis Random effects model was used to combine estimates	<u>Risk of breast cancer with high versus low levels of linoleic acid intake: case control studies</u> RR 0.84 (95% CI 0.71-1.00) Risk was not significantly increased in any of the 16 studies <u>Risk of breast cancer with high versus low levels of linoleic acid intake: cohort studies</u> RR 1.05 (95% CI 0.83-1.34)	Limitations and comments ▪ Original studies included in the review published up to 1996. ▪ Included observational studies that controlled for different variables – results therefore susceptible to confounding. ▪ Included analytic, ecological and animal studies examining breast, colon and prostate cancer. ▪ Use of self report data alone in most studies. ▪ Corrected for measurement error. ▪ Possible study limitations that could explain the lack of significant associations include recall bias, non-differential error in dietary intake measurement, narrow range of linoleic acid intake and confounding. However, case control studies using biomarkers also found reduced risks and pooled estimates that corrected for measurement error were consistent with studies that had no such correction Reported conclusions (by authors). Although current evidence cannot exclude a small increase in risk, it seems unlikely that a high intake of linoleic acid substantially raises the risk of breast, colorectal, or prostate cancer in humans.

Table 13.2: Evidence tables for primary studies of dietary factors

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Lee et al. 2005a) Taiwan	Case control study Level III-2.	Study setting. Case control study selecting cases from leading cancer hospital in Taiwan. Controls selected from a mammography screening clinic and a medical check up clinic at the same hospital as the cases. Sample Mean age (years): cases 47.2, controls 46.4 Mean weight (kg): cases 56.3, controls 55.6 Mean height (cm): cases 157.1, controls 157.5 Education (≤12 years): cases 62%, controls 52%) Education (13-16 years): cases 34%, controls 42% Education (>16 years): cases 4%, controls 6%. Single: cases 7%, controls 10% Urban residence: cases 64%, controls 67%. No statistically significant differences between cases and controls across the above variables.	Cases (n=250) Newly diagnosed, pathologically confirmed breast cancer between 1996 and 1999, treated either as an outpatient or an inpatient. Aged 25-79 and alive at time of contact. Controls (n=219) One healthy control matched to the case by five year age group. Aged 25-79 and alive at time of contact. Excluded if diagnosed with cancer, gastric problems or heart disease. Data collection Trained interviewers conducted face to face interviews at the hospital outpatient clinic. The same interviewer interviewed the case and matching control. Diet assessed for one year prior to diagnosis in cases and one year prior to interview in controls. Questions included the frequency and quantity of consumption of 100 food items. Analysis Nutrient intake estimated after excluding women whose total daily caloric intake was > 5000 kcal or < 500 Kcal. Odds ratios obtained by unconditional logistic regression. Covariates were included in the model (1) if they were determined to be independently associated with breast cancer on univariate analysis, (2) if their inclusion significantly altered the log-likelihood statistic of the nested model, and (3) if they affected the magnitude of the nutrient ORs by more than 10%. ORs were presented for each quartile.	<u>Association between total energy and breast cancer</u> (lowest quartile as the reference): Quartile 2: OR 1.0 (95% CI 0.6-1.7) Quartile 3: OR 1.4 (95% CI 0.8-2.4) Quartile 4: OR 2.1 (95% CI 1.2-3.6) <u>Association between total fat and breast cancer</u> (lowest quartile as the reference): Quartile 2: OR 0.9 (95% CI 0.5-1.6) Quartile 3: OR 1.5 (95% CI 0.9-2.6) Quartile 4: OR 1.9 (95% CI 1.1-3.2) All estimates adjusted for age and education.	Limitations ▪ Controls may not be representative of the population from which the cases were selected ▪ Response rate 89% among cases and 84% among controls ▪ Incomplete matching with fewer controls than cases ▪ Self reported diet data ▪ Observational study susceptible to residual confounding ▪ Risk of recall bias Reported conclusions (by authors). Results indicate a strong protective effect of dietary supplements and a harmful effect of dietary fats on the risk of breast cancer among women in Taiwan. These findings should be confirmed in future follow up studies. Specific amount of dietary supplements and dietary fats should be quantified for a more accurate evaluation on the risk for breast cancer in this population.

Table 13.2: Evidence tables for primary studies of dietary factors (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Mannisto et al. 2005) Netherlands, Sweden, Italy	Prospective cohort study Level III-2.	Study setting. Four European cohort studies included in the greater DIETSCAN project and three that had female participants were selected. Sample Follow up years: Netherlands: 7 Italy: 9 Sweden: 13 Age range (years) Netherlands:55-69 Italy: 35-69 Sweden: 40-74 BMI (kg/m^2) Netherlands: 25.1 Italy: 25.4 Sweden: 24.8 Age at menarche (years): Netherlands: 13.7 Italy: 12.9 Sweden: 13.4 Age at menopause (years): Netherlands: 49 Italy: 48 Sweden: 49 Parity (yes, %): Netherlands: 83 Italy: 89 Sweden: 85	Netherlands study: population based cohort study. Participants between 55 and 69 years at start of study (1986). Italian study: Cohort study on hormonal factors and diet in Italian women aged 34-70 Swedish study: Participants aged between 40 and 74 years when they were invited to participate in a population based mammography screening program between 1987 and 1990. Data collection Validated semi quantitative food frequency questionnaires. Outcome measures Histologically confirmed invasive breast cancer cases were identified through national or local registers. Follow-up interval 7-13 years. Analysis Common food groupings developed across the three settings. Exploratory factor analysis was used to develop the food patterns at each setting.	<u>Vegetable pattern and breast cancer</u> (linear model), adjusted RR (95% CI) Netherlands: 0.93 (0.84-1.04) Italy: 0.88 (0.72-1.07) Sweden: 0.97 (0.91-1.03) <u>Pork, processed meat and potatoes pattern and breast cancer</u> (linear model), adjusted RR (95% CI) Netherlands: 0.90 (0.81-0.99) Italy: 0.93 (0.70-1.22) Sweden: 1.02 (0.94-1.14)	Limitations ▪ Netherlands study included 62,753 women but a random cohort of 1,812 women were sampled after baseline measurement. Due to missing data, 1,598 were included in the present analysis. ▪ Different age groups studied in the three cohorts. ▪ Differences in the food frequency questionnaires (FFQ) between the three cohorts. ▪ Period covered by the FFQ was 12 months for the Netherlands and Italian sites and 6 months for the Swedish site. ▪ Potential for misclassification of food groupings. ▪ Differences in method of analysis between sites. ▪ Self reported diet data. ▪ Observational study susceptible to residual confounding. Comments ▪ Examined whether dietary patterns derived from a common approach and risk of breast cancer are consistent across different populations; and whether dietary patterns contribute additional information to the investigation of any relationship between diet and breast cancer on top of looking simply at specific nutrients. ▪ Performed a validation study of the dietary assessment method ▪ Included a complete dietary assessment

Table 13.2: Evidence tables for primary studies of dietary factors (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Mannisto et al. 2005) Netherlands, Sweden, Italy *(Continued)*		Age at first birth (years) Netherlands: 22 Italy: 26 Sweden: 24 Oral contraceptive use (yes, %) Netherlands: 25 Italy: 33 Sweden: 46 HRT use (yes, %) Netherlands: 15 Italy: 7 Sweden: 19 Family history of breast cancer (%) Netherlands: 8 Italy: 7 Sweden: 7	Italian and Swedish studies used Cox proportional hazard models while the Netherlands used survival analysis with exponential distribution to estimate the standard errors. Models adjusted for age, energy intake and other potential confounding variables.		Reported conclusions (by authors). In general, the dietary patterns showed consistent results across the three cohorts except for the possible protective effect of pork, processed meat and potatoes in the Netherlands cohort, which could be explained by a difference in that pattern for the Netherlands. The results supported the suggestion derived from traditional epidemiology that relatively recent diet may not have an important role in the aetiology of breast cancer.

Table 13.2: Evidence tables for primary studies of dietary factors (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Wakai et al. 2005) Japan	Prospective cohort study Level III-2.	Study setting. Participants enrolled from 45 study areas throughout Japan participated in the umbrella Japan Collaborative Cohort Study (JACC). The source population included general populations and participants in municipal health check ups. Participants in the present analysis were selected from 22 study areas. Sample (n=26,291) Mean age 56.6 years Mean age at menarche 14.8 years Mean age at menopause 48.7 years Mean age at first birth 25.1 years Mean height 151.5 cm Mean BMI 22.8 kg/m^2 Education beyond high school 11.4% Family history of breast cancer 1.6% Menopause 69.3% Ever used exogenous female hormones 5.2% Current drinker 24.2% Former drinker 1.7% Current smoker 5.0% Former smoker 1.5% Proportion of highly educated women increased with increasing total fat intake (P<0.001) Proportion of women who were menopausal at baseline declined with increasing total fat intake (P<0.001).	Inclusion criteria Lived in an area where information on cancer incidence available and for whom a food frequency questionnaire (FFQ) was included at baseline. Exclusion criteria History of breast cancer Insufficient responses on the FFQ to estimate nutrient intake Implausibly low or high calorie intake (<500 or >3,500 kcal/day) Data collection Dietary component included 40 food items. Energy adjusted intakes of nutrients were calculated by the residual method. Outcome measures Incidence of cancers ascertained by means of a linkage with records of population based cancer registries supplemented by review of death certificates. In three areas, population based cancer registries were not available – hospital based cancer registries or inpatient records were used to collect information in these areas. Follow-up interval. Mean 7.7 years	<u>Total fat and risk of breast cancer</u> (lowest quartile as reference): multivariate adjusted RR (95% CI) Quartile 2: 1.29 (0.80-2.08) Quartile 3: 0.95 (0.57-1.59) Quartile 4: 0.80 (0.46-1.38) *P*trend 0.32 <u>Animal fat and risk of breast cancer</u> (lowest quartile as reference): multivariate adjusted RR (95% CI) Quartile 2: 0.90 (0.56-1.46) Quartile 3: 0.96 (0.60-1.56) Quartile 4: 0.61 (0.36-1.06) *P*trend 0.13 <u>Vegetable fat and risk of breast cancer</u> (lowest quartile as reference): multivariate adjusted RR (95% CI) Quartile 2: 1.06 (0.64-1.76) Quartile 3: 1.08 (0.65-1.81) Quartile 4: 1.21 (0.72-2.02) *P*trend 0.49 <u>Fish fat and risk of breast cancer</u> (lowest quartile as reference): multivariate adjusted RR (95% CI) Quartile 2: 0.71 (0.44-1.14) Quartile 3: 0.80 (0.50-1.27) Quartile 4: 0.56 (0.33-0.94) *P*trend 0.04	Limitations ▪ Self reported dietary data ▪ Observational study susceptible to residual confounding ▪ Source population may not be representative of overall Japanese population ▪ Based on the validation study, the FFQ underestimated total energy intake by 33%, but it was able to appropriately rank respondents according to intakes of several nutrients. ▪ 73% of potential participants were included in the analysis ▪ Significant differences in response between women omitted with implausibly low/high calorie intake and insufficient responses on FFQ versus those included in the analysis ▪ Did not follow up on vital status of participants who moved out of their given study areas (2.7% of initial participants) ▪ Accuracy of cancer registry recording unclear Comments ▪ Aim was to examine the association between dietary fat and fatty acids with the risk of breast cancer in a population with a low total fat intake and high consumption of fish ▪ FFQ was validated by referring to four 3 day weighted dietary records over a 1 year period as a standard.

Table 13.2: Evidence tables for primary studies of dietary factors (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Wakai et al. 2005) Japan			Analysis Energy adjusted intakes of nutrients were calculated by the residual method. Difference between two proportions tested by chi squared. Person-time of follow up counted from the time of filling in the baseline questionnaire to the date of diagnosis of breast cancer, date of death from any cause, date of emigration outside study area, or the end of the follow up period, whichever came first. Rate ratios for breast cancer over quartiles of energy-adjusted intakes of fat or fatty acids were estimated using proportional hazards models adjusted for age and other potential confounders. For tests of trend, median values of each quartile of fat/fatty acid intake were included in the model.	<u>Long chain n-3 fatty acids and risk of breast cancer</u> (lowest quartile as reference): multivariate adjusted RR (95% CI) Quartile 2: 0.68 (0.42-1.10) Quartile 3: 0.83 (0.52-1.30) Quartile 4: 0.50 (0.30-0.85) *P*trend 0.02 No significant association with other variables and breast cancer including: Saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, n-3 fatty acids and n-6 fatty acids	Reported conclusions (by authors). This prospective study did not support any increase in the risk of breast cancer associated with total or saturated fat intake, but it suggested the protective effects of the long chain n-3 fatty acids that are abundant in fish.

Table 13.2: Evidence tables for primary studies of dietary factors (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Zaroukian et al. 2005) Canada	Case control Level III-2.	Study setting. Conducted through an established network of hospitals in Montreal in which diet and cancer risk had previously been investigated. Sample BMI (1 year before cancer diagnosis): >24.05: cases 44%, controls 44% Ever breast fed: Cases 21%, Controls 28% Age at FFTP (years): Nulliparous: cases 31%, Controls 25% ≤22: cases 18%, controls 22% 23-29: cases 37%, controls 42% ≥30: cases 13%, controls 11% Age ≥13 years at menarche Cases 51%, Controls 53% Age at menopause (years) <35: cases 7%, controls 11% 35-45: cases 21%, controls 29% >45: cases 41%, controls 34% Ever used oral contraceptives Cases 46%, controls 47% Ever used hormone therapy Cases 39%, controls 48% Ever cigarette smoker Cases 47%, controls 42% Personal income (CAN$) <19,999: Cases 52%, controls 66% 20,000-39,999: cases 31%, controls 26% >40,000: cases 13%, controls 7%	Cases (n=223): newly diagnosed, histologically confirmed breast cancer cases aged 35-79 years. Permission given by attending specialist to interview the patient. Controls (n= 85) population based controls matched for age (within 5 years) and place of residence selected by modified random digit dialling Data collection Face to face interviews conducted by trained interviewers using a structured questionnaire. Blood, adipose tissue and cheek cells collected for carotene, retinol and tocopherol measurement. Analysis Adjusted odds ratios calculated using unconditional logistic regression. For each biomarker the third tercile (highest concentration) and second tercile were compared with the first tercile. Students t test was used to compare mean concentration for each biomarker. Conducted a sensitivity analysis to consider the implications of low participation amongst the controls.	Adjusted odds ratio*, (95% CI)) <u>Retinoid</u> (reference lowest tercile concentration) Adipose tissue: Tercile 2: 1.01 (0.56-1.84) Tercile 3: 2.11 (1.09-4.08) Cheek Tercile 2: 0.92 (0.46-1.83) Tercile 3 0.34 (0.18-0.65) Plasma Tercile 2: 0.54 (0.29-1.20) Tercile 3: 0.67 (0.35-1.28) <u>Tocopherol</u> (reference lowest tercile concentration) Adipose tissue: Tercile 2: 1.52 (0.81-2.83) Tercile 3: 1.34 (0.73-2.47) Cheek Tercile 2: 1.19 (0.64-2.19) Tercile 3: 1.36 (0.73-2.55) Plasma Tercile 2: 0.87 (0.47-1.62) Tercile 3: 0.85 (0.45-1.59) <u>Beta carotene</u> (reference lowest tercile concentration) Adipose tissue: Tercile 2: 5.22 (2.63-10.36) Tercile 3: 3.18 (1.70-5.93) Cheek Tercile 2: 5.46 (2.69-11.10) Tercile 3: 2.22 (1.21-4.50)	Limitations ▪ Only 287/414 cases completed both the FFQ and CQ and provided at least one tissue sample. Of these, 223 were considered in the final analysis (further drop outs due to inadequate specimens or specimens not provided for analysis (54% participation)). ▪ Proportion of controls approached who were not willing to participate was unclear. ▪ 112/429 completed the FFQ, CQ and provided at least one tissue sample. Of these 85 were considered in the final analysis (further drop outs due to inadequate specimens or specimens not provided for analysis (20% participation)). ▪ Interviews of controls conducted up to 3 months after the matching case was interviewed. ▪ Diet and metabolism may have been altered due to breast cancer diagnosis, so exposure measurements may represent post diagnostic rather than pre diagnostic exposure levels. ▪ Observational study susceptible to residual confounding. For example, no adjustment for plasma lipids which was a potential confounder in this study. No control over unknown confounders. ▪ Low study power given the significant non participation in cases and, particularly, controls. ▪ Selection bias due to non-participation, particularly amongst controls

Table 13.2: Evidence tables for primary studies of dietary factors (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Zaroukian et al. 2005) *continued*		History of breast, ovarian or colon cancer in first degree relative Cases 19%, Controls 12% Ever married Cases 78%, controls 86%.		Plasma Tercile 2: 0.78 (0.42-1.42) Tercile 3: 1.53 (0.80-2.93) <u>Total carotene</u> (reference lowest tercile concentration) Adipose tissue: Tercile 2: 3.81 (1.90-7.64) Tercile 3: 1.27 (0.70-2.30) Cheek Tercile 2: 5.66 (2.83-11.32) Tercile 3: 2.94 (1.59-5.42) Plasma Tercile 2: 0.38 (0.20-0.71) Tercile 3: 1.04 (0.53-2.05) Adjusted for age, age at FFTP and history of cancer in first degree relatives.	Comments ▪ 1% of families in the Montreal region do not have a telephone – but unclear how many have an unlisted telephone number. ▪ Controls initially asked to consent to dietary interview and subsequently asked for biological specimens. ▪ Assay methodologies documented in sufficient detail to allow repeating by other laboratories. ▪ Estimated number of cases needed to detect an association between each biomarker at 5% significance level, 80% power and relative risk of 1.7 would be around 225 cases and the same number of controls. Reported conclusions (by authors). Suggest either that high levels of biomarkers may be due to the disease process that affects the pharmacokinetics of the biomarker or that the disease causes a change in dietary habits. In studies involving application of biomarkers to cancer epidemiology it is imperative that a typical biomarker concentration is not associated with breast cancer risk before further examination of the methodological limitations of epidemiological studies investigating this relationship. Therefore, sample size, selection bias, information bias and confounding should be considered in the design of studies investigating the aetiological relationship between biomarkers and breast cancer.

Table 13.2: Evidence tables for primary studies of dietary factors (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Alothaimeen et al. 2004) Saudi Arabia	Case control Level III-2.	Study setting. Cases selected from referrals to breast cancer clinic at King Faisal Specialist Hospital in Riyadh. Sample Age (mean in years): cases 44.8, controls 36.8, P=0.0001 Age at menarche (mean in years): Cases 13.2, controls 13.0, P=0.04 Age at menopause (mean in years): Cases 48.2, Controls 47.9, P=0.76 Age at first pregnancy (mean in years): Cases 20.6, Controls 20.7, P=0.76 Age at marriage (mean in years): Cases 20.6, Controls 20.7, P=0.17 Number of pregnancies (mean): Cases 6.6, Controls 5.3, P=0.001 BMI (mean): Cases 29.5, Controls 29.4, P=0.82 Ever used oral contraceptives (%): Cases 54.1, Controls 62.5, P=0.01 Family history of breast cancer (%): Cases 15.0, Controls 12.1, P=0.17	Cases (n=499): prospectively recruited. Newly diagnosed and prospectively confirmed breast cancer. Controls (n=498): selected from patients' attendants and relatives. Frequency matched for age, parity, breastfeeding practice and age at marriage. Data collection: Existing food frequency questionnaire (with 40 food items) administered at face to face interview by trained nutritionists. Cross checked with three day food record. Risk factor questionnaire also used. Serum levels of total cholesterol and triglycerides were obtained. Diet analysis software and food tables used to calculate nutrients from reported intake of individual foods. Analysis: Means and standard deviations were compared using students t test, Frequencies compared using chi squared test. Odds ratios estimated from logistic regression adjusting for age, nationality, province and menopausal status. Nutrients modelled by quartile.	Serum triglycerides level (<0.9 mM/L reference): Multivariate adjusted OR*: 0.9-1.3: 0.73 (95% CI 0.40-1.32) >1.3-2.0: 1.67 (95% CI 0.96-2.93) >2.0: 2.16 (95% CI 1.21-3.88) Serum cholesterol (<4.3 mM/L reference): Multivariate adjusted OR*: 4.3-5.0: 0.80 (95% CI 0.51-1.25) >5.0-5.7: 0.92 (95% CI 0.59-1.43) >5.7: 0.96 (95% CI 0.63-1.55) Total energy from fat (<1084.1 kcal reference) Multivariate adjusted OR*: 1084.1-1426.1: 2.65 (1.44-4.86) 1426.2-1872.8: 3.19 (1.74-5.83) >1872.9: 2.69 (1.51-4.81) Total protein (<52.2 g reference) Multivariate adjusted OR*: 52.2-68.8: 2.65 (1.41-4.98) 68.9-88.0: 3.12 (1.71-5.70) >88.1: 2.25 (1.27-3.99) Total fat (<35.4 g reference) Multivariate adjusted OR*: 35.4-51.0: 1.65 (0.90-3.02) 51.1-70.8: 2.67 (1.47-4.83) >70.9: 1.64 (0.92-2.95) Saturated fat (<19.9 g reference) Multivariate adjusted OR*: 19.9-30.3: 2.15 (1.17-3.92) 30.4-41.2: 2.43 (1.30-4.53) >41.3: 2.43 (1.36-4.34)	Limitations ▪ Controls selected from patients' attendants and relatives. ▪ Cases selected from specialist hospital in Riyadh (referred from all regions of Saudi Arabia). ▪ One case and two controls excluded due to unacceptably low or high nutrient values. ▪ Self reported dietary data. ▪ Possible recall bias. ▪ Diet and metabolism may have been altered due to breast cancer diagnosis, so exposure measurements may represent post diagnostic rather than pre diagnostic exposure levels. ▪ Number of eligible cases and controls who refused participation was not stated. ▪ Multivariate model did not adjust for all differences between case and control groups, including: age at menarche, number of pregnancies and ever used oral contraceptives. Therefore, residual confounding likely. ▪ Some discrepancies between text and key results tables. Comments ▪ Newly incident cases of breast cancer ▪ Power calculations suggested 500 cases and controls would be required to detect an odds ratio of 1.78 for high fat intake with 80% power at the 5% significance level ▪ No association between serum cholesterol and breast cancer but an association was present between self reported cholesterol intake and breast cancer

Table 13.2: Evidence tables for primary studies of dietary factors (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Alothaimeen et al. 2004) *continued*				Polyunsaturated fat (<15.6 g reference) Multivariate adjusted OR*: 15.6-21.2: 2.19 (1.18-4.07) 21.3-29.1: 2.73 (1.53-4.87) >29.2: 2.12 (1.17-3.83) Cholesterol (<169.6 mg reference) Multivariate adjusted OR*: 169.6-266.3: 1.64 (0.90-2.98) 266.4-400.6: 2.11 (1.16-3.84) >400.7: 1.88 (1.03-3.44) *Multivariate adjusted OR: adjusted for age, nationality, province and menopause	Reported conclusions (by authors). High consumption of sugar rich foods, meat and other animal products rich in saturated fats has been recorded in Saudi Arabia. Despite the inconclusive evidence about diet and disease, it is important to educate the population about the possibility of a link between dietary habits and cancer and to encourage them to adopt a diet that is low in calories, saturated fat and meat intake.

Table 13.2: Evidence tables for primary studies of dietary factors (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Frazier et al. 2004) USA	Retrospective cohort study Level III-2.	Study setting. Conducted as part of the Nurses Health Study II (NHS II) who answered a food frequency questionnaire (FFQ) about diet during high school. Sample (n=47,355) Mean age in 1989 (years) Cases 40.9, non-cases 38.3, P<0.0001 Mean age at first birth (years) Cases 26.5, non-cases 26.1, P=0.04 Mean BMI at 18 (kg/m^2) Cases 20.8, non-cases 21.2, p=0.17 Mean BMI in 1989 (kg/m^2) Cases 23.2, non-cases 23.8, P=0.34 Mean weight gain since 18 (kg) Cases 8.3, non-cases 9.2, P=0.10 Mean height (cm) Cases 65.3, non-cases 64.9, P=0.02 Postmenopausal (%) Cases 5.2, non-cases 5.8, P=0.52 Age at menarche < 12 (%) Cases 29, non-cases 25, P=0.002 Parity > 2 (%) Cases 19.5, non-cases 22.3, P=0.55	Inclusion criteria Participating in NHS II study Agreed to complete FFQ Exclusion criteria Total calories reported were implausible (<500 or >5000) Previously diagnosed with cancer other than breast cancer Diagnosed with breast cancer prior to initiation of the study Data collection 131 item FFQ about diet during high school. Outcome measures Incident case of invasive breast cancer, confirmed by medical record review, who were diagnosed after initiation of the study (1989) and before completion of the FFQ (June 1998).	<u>Total calories and risk of breast cancer</u> (lowest quintile as reference): multivariate adjusted RR (95% CI) Quintile 2: 0.99 (0.68-1.42) Quintile 3: 1.29 (0.91-1.81) Quintile 4: 1.48 (1.06-2.07) Quintile 5: 1.39 (0.99-1.96) *P*trend 0.01 <u>Total fat and risk of breast cancer</u> (lowest quintile as reference): multivariate adjusted RR (95% CI) Quintile 2: 0.72 (0.52-1.00) Quintile 3: 0.61 (0.43-0.85) Quintile 4: 0.74 (0.53-1.02) Quintile 5: 0.91 (0.67-1.24) *P*trend 0.68 <u>Animal fat and risk of breast cancer</u> (lowest quintile as reference): multivariate adjusted RR (95% CI) Quintile 2: 1.02 (0.70-1.48) Quintile 3: 0.99 (0.69-1.44) Quintile 4: 1.15 (0.81-1.66) Quintile 5: 1.12 (0.78-1.61) *P*trend 0.38	Limitations 49% of cohort in the NHS II study agreed to answer food frequency questionnaire and 83% of these actually took part (including 80% of the cases) Potential exposure misclassification due to long time period (15-35 years) between completion of FFQ and the time of being at high school. However, recall of adolescent diet has been shown to be reproducible and not highly correlated with adult diet Included cases had later age at menarche, more likely to be postmenopausal and were more likely to report a family history of breast cancer than cases not included in the analysis. Observational study susceptible to residual confounding Reported conclusions (by authors). The apparent protective effects of vegetable fat and vitamin E and adverse effect of high glycemic foods on risk of breast cancer need confirmation in prospective analyses.

Table 13.2: Evidence tables for primary studies of dietary factors (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Frazier et al. 2004) *continued*		Current oral contraceptive use (%) Cases 9.8, non-cases 9.9, P=0.51 Current smoker (%) Cases 13.7, non-cases 10.2, P=0.64 Family history of breast cancer (%) Cases 18.8, non-cases 9.5, P<0.0001 History of benign breast disease (%) Cases 51.2, non-cases 38.5, P<0.0001.	Analysis Nutrient intakes were computed for each subject. Risk factor status of cases and non-cases was updated from the questionnaire most recently completed before date of diagnosis. Person-months of follow-up were counted from the date of return of the 1989 questionnaire to the date of diagnosis, death or June 1988, whichever came first. Cox proportional hazards regression used to derive relative risks (and 95% confidence intervals). Monotonic trends across quintiles of nutrient intake were tested by modelling median intake per quintile as a continuous variable. Models included age, family history of breast cancer, benign breast disease, age at menarche, BMI at 18, weight gain since 18, adult height, adult alcohol consumption, total caloric intake at high school, menopausal status, current oral contraceptive use and reproductive history.	<u>Vegetable fat and risk of breast cancer</u> (lowest quintile as reference): multivariate adjusted RR (95% CI) Quintile 2: 1.15 (0.86-1.54) Quintile 3: 1.08 (0.80-1.46) Quintile 4: 0.86 (0.61-1.19) Quintile 5: 0.58 (0.38-0.86) *P*trend 0.005 <u>Adolescent glycemic load index and risk of breast cancer</u> (lowest quintile as reference): multivariate adjusted RR (95% CI) Quintile 2: 1.18 (0.84-1.66) Quintile 3: 1.26 (0.89-1.77) Quintile 4: 1.49 (1.06-2.08) Quintile 5: 1.47 (1.04-2.08) *P*trend 0.01	

Table 13.2: Evidence tables for primary studies of dietary factors (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Mattisson et al. 2004) Sweden	Prospective cohort study Level III-2.	Study setting. Source population was, in 1991, all persons living in Malmo, Sweden and born during 1926-1945. Extended in 1995, to include all women born during 1923-1950 and all men born during 1923-1945. Sample at baseline Age (years): noncases 60.4, cases 59.4, P<0.01 Age at menarche (years): noncases 13.7, cases 13.6, P=0.54 Current hormone therapy (%): noncases 20.1, cases 31.9, P<0.01 Age at first child (years): ≤24, noncases 44.3, Cases 42.1 24-30, noncases 32.4, cases 32.2 >30, noncases 9.0, cases 10.2 No children, noncases 14.2, cases 15.5 P=0.74 Smoking status (%) Smoker, Noncases 25.9, cases 26.6 Ex-smoker, noncases 26.5, cases 29.8 Never smoker, noncases 47.6, cases 43.6 P = 0.28	Study population Included women aged 50+ years. Excluded: People from the source population with inadequate Swedish language skills or mental incapacity. Prevalent cancer cases except cervical cancer *in situ* and non-malignant melanoma skin cancer Data collection Participants visited the screening centre twice. At first visit they were instructed about how to register meals and how to complete the diet questionnaire. Blood samples, blood pressure and anthropometric measurements were taken. At second visit, socioeconomic questionnaire was checked for completeness and dietary interview was conducted. National Swedish Cancer Registry provided data until December 1999. Cases were women with invasive breast cancer or breast cancer *in situ*. Food intake was converted to energy and nutrient intakes using a specifically designed nutrient database.	<u>Model comparing fat with total energy intake</u> (quintile 1 – lowest fat intake category – as reference) Rate ratio (95% CI): Quintile 2 0.81 (0.55-1.18) Quintile 3 1.36 (0.97-1.92) Quintile 4 1.26 (0.89-1.79) Quintile 5 1.36 (0.96-1.94) *P*trend = 0.02 <u>Model comparing fat with non-alcohol energy intake</u> (quintile 1 – lowest fat intake category – as reference) Rate ratio (95% CI): Quintile 2 1.05 (0.73-1.51) Quintile 3 1.23 (0.86-1.76) Quintile 4 1.38 (0.97-1.96) Quintile 5 1.35 (0.94-1.93) *P*trend = 0.05 Models adjusted for diet interviewer, method version, season of diet interview, age at baseline, change of dietary habits, height, waist, current hormone use, age at first child, age at menarche, leisure time physical activity, smoking habits and educational level. Exclusion of *in situ* cancer cases led to more significant p values for trend across fat quintiles in both energy adjustment models.	Limitations ▪ At baseline 28,098 of 74,138 had completed all parts ▪ Postmenopausal status subject to misclassification as it was based on the median natural menopause age in a subgroup of the source population ▪ Self reported dietary data ▪ Residual confounding likely in this observational study both with known confounders (due to categorisation of these confounders) and unknown confounders Comments ▪ Aims: 1. is breast cancer risk associated with intakes of total alcohol, specific alcoholic beverages or total fat in postmenopausal women, 2. effects of total alcohol and fat intakes when adjusted for each other, 3. determine if the specific energy adjustment approach influences these associations. ▪ Cases were women with invasive breast cancer or breast cancer *in situ*. ▪ Validity of the dietary data was assessed in a sample of Malmo residents using weighed food records. Correlation coefficients between the reference and the "MDC method" for energy adjusted fat intake was 0.69 and for energy adjusted total alcohol was 0.78. ▪ Low energy reporting was evaluated by comparing the total reported energy intake with the basal metabolic rate. ▪ Well conducted study.

Table 13.2: Evidence tables for primary studies of dietary factors (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Mattisson et al. 2004) *continued*			Analysis Fat intake converted into two relative fat intake variables and five exposure categories were created. Total alcohol intake was converted into a four category variable. Two models of energy adjustment were developed, adjusting for total energy intake and non-alcohol energy intake. Student's t test and chi squared tests were used as appropriate. Cox regression was used to examine the associations between alcohol, fat and breast cancer. The models included known non-dietary risk factors and potential confounders. Follow-up interval: average 7.6 years		Reported conclusions (by authors). There were significant trends of increased breast cancer risk across quintiles of relative fat intake. Mutual adjustment did not affect risk estimates for total alcohol or relative fat intakes. The specific energy-adjustment approach did not influence associations differentially.

Table 13.2: Evidence tables for primary studies of dietary factors (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Nkondjock and Ghadirian 2004) Canada	Case control study Level III-2.	Study setting. Population based case control study conducted in French Canadians in Montreal. Sample Mean age (years): cases: 55.03, controls 55.73. Family history of breast cancer: cases 16.2%, controls 8.2%, P ≤ 0.005. Nulliparity (%): cases 30, controls 25, P<0.05 Oral contraceptive use (%): cases 48, controls 48 HRT use (%): cases 35, controls 38 Ever married (%): cases 78.5, controls 84.8	Cases (n=414): newly diagnosed, histologically confirmed breast cancer cases aged 35-79 years. Permission given by attending specialist to interview the patient. Controls (n= 429) population based controls matched for age (within 5 years) and place of residence selected by modified random digit dialling. Data collection Face to face interviews conducted by trained interviewers using a structured questionnaire. Food consumption data collected using a valid and reproducible food frequency questionnaire covering a two year period. Analysis Food intake converted to specific carotenoids. Intakes divided into quartiles based on control population data. Adjusted odds ratios calculated using categories of residuals from the regression of carotenoids on total energy intake in unconditional logistic regression. All estimates were adjusted for age at FFTP and history of cancer (ovary, breast or colon) in first degree relatives, history of benign breast disease, marital status, parity and total energy intake. Subgroup analysis by menopausal status performed.	<u>Association between specific and total carotenoids and breast cancer</u> No significant association detected. <u>Premenopausal women</u> Amongst ever smokers, association between α-carotene intake and breast cancer: OR (upper versus lowest quartile): 2.40 (95% CI 0.90-6.41) <u>Postmenopausal women</u> Amongst people with high arachidonic acid intake association between total -carotene intake and breast cancer: OR (upper versus lowest quartile): 1.92 (95% CI 0.93-3.94) and inverse association with a high docosahexaenoic acid intake: OR 0.52 (95% CI 0.25-1.07)	Limitations ▪ 77% of eligible cases participated. Unclear what proportion of eligible female controls participated. Population based controls included males (who were excluded for this study) – participation amongst controls including males was 49% ▪ Self reported data ▪ Risk of recall bias: particularly with the long (two year) diet recall period ▪ Observational study susceptible to residual confounding Comments ▪ Carotenoid supplementation common in source population ▪ 1% of families in the Montreal region do not have a telephone – but unclear how many have an unlisted telephone number. Reported conclusions (by authors). Findings suggest that the combined high intake of total carotenoids and docosahexaenoic acid may reduce the risk of breast cancer.

Table 13.2: Evidence tables for primary studies of dietary factors (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Romieu et al. 2004) Mexico	Case control study Level III-2.	Study setting. Population based case control study among a Mexican population characterised by relatively low fat and high carbohydrate intakes. Sample SES: Low: cases 30%, controls 27% Middle: cases 50%, controls 42% High: cases 20%, controls 30% Familial breast cancer Cases 2%, controls 4% Premenopausal Cases 49%, controls 40% Nulliparous Cases 12%, controls 17%	Cases (n=475) Resident ≥ 1 year in Mexico city. Recruited from six hospitals in metropolitan Mexico City. Biopsy confirmed breast cancer in women aged 20-75. Controls (n=1,391) Age stratified random sample of metropolitan Mexico City residents. Controls were selected using a hierarchical approach with household being the primary unit. Only one eligible control was selected per household. Data collection Face to face interviews conducted with cases being interviewed at gynaecology clinics before breast cancer was confirmed and controls having the interview in their own home. A dietary questionnaire was adapted for the Mexican population, taking the form of a semi-quantitative food frequency questionnaire. Period covered was a year prior to interview. Analysis Main dietary variables categorised as quartiles based on distribution in the control group, and relative risks were estimated using the lowest quartile as the base group. Multivariate logistic regression model included age (5 year groups), SES, age at first birth, parity, and family history of breast cancer. All models were adjusted for total energy intake.	<u>Carbohydrates</u> Adjusted OR (highest quartile versus lowest quartile) OR 2.22 (95% CI 1.63-3.04) *P*trend < 0.001 <u>Sucrose</u> Adjusted OR (highest quartile versus lowest quartile) OR 2.00 (95% CI 1.47-2.71) Ptrend < 0.001 <u>Fructose</u> Adjusted OR (highest quartile versus lowest quartile) OR 1.36 (95% CI 1.00-1.86) *P*trend 0.06 <u>Lactose</u> Adjusted OR (highest quartile versus lowest quartile) OR 1.06 (95% CI 0.78-1.45) *P*trend 0.52 <u>Starch</u> Adjusted OR (highest quartile versus lowest quartile) OR 1.04 (95% CI 0.76-1.44) *P*trend 0.53 <u>Glucose</u> Adjusted OR (highest quartile versus lowest quartile) OR 1.28 (95% CI 0.94-1.75) *P*trend 0.14	Limitations ▪ 88% of eligible cases and 90% of eligible controls participated ▪ Participating hospitals provide medical care to 80% of breast cancer cases reported to the Mexico City Tumour Registry ▪ Controls may not be truly representative of the population from which the cases were selected, given lack of total Mexico city coverage from the source of cases ▪ Missing data for some variables. In particular an accurate height and weight was available for only 48% of all cases and 50% of all controls ▪ Self reported diet data. ▪ Observational study susceptible to residual confounding ▪ Correlations between food frequency questionnaire and dietary records for total energy, carbohydrate, protein and total fat intakes were 0.52, 0.57, 0.32 and 0.63 respectively Comments ▪ Questionnaire validated against 24 hour recall data. Reported conclusions (by authors). In this population a high percentage of calories from carbohydrate but not from fat was associated with increased breast cancer risk. This relation deserves to be investigated further, particularly in populations highly susceptible to insulin resistance.

Appendix 14: Evidence tables for alcohol

Table 14.1: Evidence tables for secondary studies of alcohol

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Corrao et al. 2004)	Level III-2.	Search: 1966-1998. Sources: MEDLINE, Current contents, EMBASE, Core Medical Collection. Reviewed references in all selected studies. Hand search of most relevant epidemiology and medical journals.	Inclusion criteria Case control or cohort study published as an original article Findings expressed as odds ratio or relative risk considering at least 3 levels of alcohol consumption Papers reporting the number of cases and non-cases and the estimates of the odds ratios or RR for each exposure level. When the results of a study were published more than once the most recent complete article was included. Data extraction Two readers blinded to authors' names and affiliations and to the results pertaining to alcohol consumption independently determined eligibility of each paper. Same two readers evaluated quality and derived a quality score for the study. Data analysis Pooled estimates based on: 1. several weighted least squares regression models were fitted by pre-pooling the results of all studies included, accounting for correlation between estimates within each study 2. Several meta-regression models were fitted 3. studies with higher quality scores, those conducted with a cohort design or those reporting estimates adjusted for covariates were selected only if at least one of these characteristics was a significant effect modifier Consistency of the model based RR was evaluated with reference studies reporting relative risks for light consumption	<u>RR of breast cancer at specified levels of alcohol intake</u> 25 g/day: RR 1.25 (95% CI 1.20-1.29) 50 g/day: RR 1.55 (95% CI 1.44-1.67) 100 g/day: RR 2.41 (95% CI 2.07-2.80)	Limitations and comments ▪ Meta-analysis of alcohol consumption and risk of 15 diseases, including breast cancer. ▪ Thorough and systematic literature search ▪ Well conducted extraction and analysis. ▪ 561 studies retrieved, 240 included in the analysis, 156 selected for final analysis because of their higher quality. Reported conclusions (by authors). No specific conclusions reported for breast cancer. The meta-analysis shows no evidence of a threshold effect for both neoplasms and several non-neoplastic diseases.

Table 14.1: Evidence tables for secondary studies of alcohol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
Collaborative Group on Hormonal Factors in Breast cancer, 2002	Level III-2.	Studies were identified from review articles, literature searches and discussions with colleagues. All collaborators (196 collaborators were listed on the original HRT publication in 1997) were sent a list of studies and key references and asked if they knew of additional studies (published or unpublished).	Inclusion criteria Case-control and cohort studies Included ≥100 women with incident, invasive breast cancer Recorded information on reproductive factors and use of hormonal therapies Exclusion criteria Not stated Data extraction Data for individual women were collated centrally Data analysis Data analysis was conducted centrally. Data from different studies combined using Mantel-Haenszel techniques, estimating odds ratios, confidence intervals and P values. Results were routinely stratified by study, centre within study, age group, parity. Where appropriate, results were also stratified by age at first birth and smoking history.	Included a total of 66,426 women with invasive breast cancer and 126,953 women without breast cancer. Odds ratio of breast cancer increased significantly with increasing intake of alcohol: 7.1% (95% CI 5.5-8.7%) increase for each additional 10g per day intake of alcohol (P<0.00001). Little change in OR and SE after stratification for variables listed under data analysis.	Limitations and comments ▪ estimated that the studies incorporated over 80% of the worldwide information on the topic (63 published and two unpublished studies) ▪ Made use of individual patient data ▪ Focus was on estimating the relative risk of both alcohol and tobacco on breast cancer while adequately controlling the confounding effect of one another ▪ Clear description of data collection and statistical analysis ▪ Information collected on both alcohol and tobacco in 53 studies (58,515 cases and 95,067 controls) ▪ No evidence of statistical heterogeneity between studies ▪ Most of the information on alcohol intake was self-reported (systematic under-reporting in cases and controls would overestimate the risk of breast cancer for a given level of alcohol consumption but random misclassification would have the opposite effect) ▪ The databases searched and search strategy was not described

Table 14.1: Evidence tables for secondary studies of alcohol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Ellison et al. 2001)	Level III-2.	MEDLINE (January 1966 to October 1999), references cited in previous meta-analyses, pooled analyses and reviews.	Inclusion criteria Original article or other report on a cohort or case-control study Report alcohol intake that could be quantified as grams of alcohol per day Incident rather than prevalent cases of breast cancer Report point estimates and an estimate of variability for the primary outcome Exclusion criteria Based on data from another publication that was included in the meta-analysis From reports published only as a letter or abstract Had implausible outcomes Data extraction Extracted exposure data that was presented in various formats in the original studies. Data analysis Estimated a median consumption of alcohol in each study. Examined the shape of the dose-response relation between alcohol consumption and risk of breast cancer. Dose-specific confounder-adjusted logarithms on the relative risks were pooled and a curve fitted using weighted quadratic spline regression. Weights were the inverse of the covariance-adjusted variance of the logarithms on the relative risks. Linear regression used to assess heterogeneity according to various characteristics of the studies. An interaction term as created to assess whether these characteristics modified the estimated alcohol effect.	<u>Risk ratio of breast cancer (non-drinkers as the reference group)</u> 6g of alcohol/day: 1.05 (95% CI 1.03-1.07) 12g of alcohol/day: 1.10 (95% CI 1.06-1.14) 24g of alcohol/day: 1.21 (95% CI 1.13-1.30). <u>Effect of study characteristics on the risk ratio</u> (all comparisons being between consumption of 12g alcohol/day versus no non-drinker) <u>Study design</u> Cohort study: RR 1.10 Hospital based case control: RR 1.17 Community based case control: RR 1.09 *Data adjusted for publication year and location of study <u>Publication year</u> ≥1990: RR 1.08 <1990: RR 1.12 * Data adjusted for study design and location of study <u>Length of follow up (cohort studies)</u> ≥ 10 years: RR 1.04 < 10 years: RR 1.15 * Data adjusted for publication year and location of study <u>Menopausal status of cases</u> Postmenopausal: RR 1.17 Premenopausal: RR 1.19 *Data adjusted for study design, publication year and location of study.	Limitations and comments ▪ Database search restricted to MEDLINE ▪ Search strategy not clear ▪ Few details about data extraction, including lack of detail about number of reviewers extracting the data ▪ No details about appraisal given and no discussion about the potential limitations of the original research included in the review ▪ Stratification of key characteristics (including study design) allowed greater understanding of the results ▪ Reviewer suggests greater reliance should be placed on the non hospital based estimates due to the potential selection bias associated with hospital based case control studies. Reported conclusions (by authors). Results showed a modest relation of alcohol consumption to risk of breast cancer, with a 10% higher risk being seen among women reporting approximately one alcoholic drink per day as compared with non drinkers. Study also suggests the magnitude of the association between alcohol consumption and breast cancer risk appears to be lower with longer term follow up. The question of causality remains unclear.

Table 14.2: Evidence tables for primary studies of alcohol

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Tjonneland et al. 2006) Denmark	Nested case control study Level III-2.	Study setting. Nested case control study set within a prospective study "Diet, cancer and Health". The prospective study was conducted in Copenhagen and Aarhus. Sample Up to 7 years of school. Cases 30%, controls 34% 8-10 years of school. Cases 47%, controls 49% 11+ years of school. Cases 23%, controls 18%. BMI<18.5. Cases 2%, controls 2% BMI 18.5-<25. cases 51%, controls 52% BMI 25-<30. Cases 33%, controls 34% BMI 30+. Cases 13%, controls 13%. Nulliparity. Cases 13%, controls 13% Previous benign breast surgery. Cases 20%, controls 14%. <1 year HRT. Cases 20%, controls 20% 1-4 years HRT. Cases 23%, controls 24% 5-9 years HRT. Cases 28%, controls 25% 10+ years HRT. Cases 29%, controls 30%.	Inclusion criteria for prospective study (participants in this nested case control study were selected from the prospective participants). Age between 50 and 64 at recruitment (December 1993-May 1997) Not registered with a previous cancer diagnosis in the Danish Cancer Registry. Cases (n=388) Incident cases of breast cancer identified during follow up of the prospective cohort. Controls (n=388) Control selected at random from the entire cohort who were cancer free at the exact age of diagnosis of the case, stratified on certainty of postmenopausal status, use of HRT at baseline and age at baseline. Data collection Participants in the prospective study completed a food frequency questionnaire and asked to report their average intake over the preceding year. Lifestyle questionnaire was completed at a clinic visit. Outcome measures Cancers were identified by linkage with the Danish Cancer Registry. Analysis Conditional logistic regression used to estimate breast cancer incidence rate ratios corresponding to proportional hazard ratio with age as the time axis. All quantitative variables were considered as continuous variables.	<u>All analyses presented adjusted incidence rate ratios (95% CI) for each additional 10g of alcohol per day.</u> Total folate intake ≤ 300µg/day RR 1.19 (0.99-1.42) Total folate intake 301-350µg/day RR 1.09 (0.82-1.46) Total folate intake 351-400µg/day RR 1.00 (0.81-1.23) Total folate intake >400µg/day RR 1.01 (0.85-1.20) All analyses adjusted for vitamin C intake, total energy intake, school education, BMI, parous/nulliparous, number of births, age at birth of first child, history of benign breast tumour surgery.	Limitations ▪ 29,875 women enrolled in the prospective study, 326 excluded due to preceding cancer, 8 excluded due to not completing lifestyle questionnaire, 37 due to missing information on use of HRT and 9 due to lifetime history of no menstruations. 54 women emigrated during the study period. ▪ 388 of 434 cases included due to the presence of missing data from the cases or matching control. ▪ Final analysis included 377 cases and 378 controls following removal of alcohol abstainers. ▪ Self administered questionnaire. ▪ Observational study susceptible to residual confounding. Comments ▪ Study primarily assessing the impact of folate on the association between alcohol intake and breast cancer ▪ Compared with case control studies, reduced risk of selection bias (due to sampling from the same source population) and of recall bias (due to prospective collection of exposure data) ▪ Appropriate statistical analytic methods Reported conclusions (by authors). Findings support the evidence that adequate folate intake may attenuate the risk of breast cancer associated with high alcohol intake. Additional observational studies are needed to explore this finding and the possible causal mechanisms.

Table 14.2: Evidence tables for primary studies of alcohol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Baglietto et al. 2005) Australia	Prospective cohort study Level III-2.	Study setting. Part of the Melbourne collaborative cohort study that recruited men and women aged between 27 and 75 years (n=41,528). This analysis was restricted to women aged 40-69. Sample (n=17,447; 537 incident cases) Mean age at baseline 54.7 years Alcohol consumption < 20g per day: 86%	Inclusion criteria Anglo-Australian women resident in Melbourne Aged 40-69 years at recruitment in 1990-4 Followed up until 31 December 2003 Exclusion criteria Confirmed diagnosis of invasive breast cancer at baseline Diagnosis of angina, heart attack, or diabetes at baseline Missing data on alcohol or food intake Extreme values for self reported total energy intake (<1st centile or >99th centile) Recruitment Electoral roll, advertisements and community announcements Data collection Structured interview schedule used at baseline. Non lifetime abstainers were asked about their current average quantity and frequency of intake of beer, wine and spirits. They were then asked about intake of alcoholic beverages on each day during the week before interview. Outcome measures Invasive breast cancers diagnosed during follow up and ascertained through the Victorian cancer registry. Follow-up interval. Follow up began at baseline and continued until diagnosis of breast cancer, death, date of leaving Victoria or 31 December 2003 – whichever came first. Average of 10.1 years follow up. Analysis Hazard ratios estimated using Cox regression with age as the time variable.	Adjusted hazard ratio (95% CI) for risk of breast cancer by levels of alcohol consumption (compared with alcohol abstainers). Ex drinkers: HR 1.03 (0.62-1.73) 1-19g/day: HR 1.12 (0.93-1.36) 20-39g/day: HR 0.87 (0.62-1.22) >40g/day: HR 1.41 (0.90-2.23). Adjusted for total energy and folate intake Adjusted hazard ratio (95% CI) for each additional 10g of alcohol per day HR 1.03 (0.95-1.09) Analyses stratified by folate intake Only significant result was in the group with the lowest level of folate intake. Alcohol intake 40+ g/day: HR 2.00 (1.14-3.49).	Limitations ▪ Recruitment strategy may not produce a representative sample given the use of advertising ▪ Self report data ▪ Observational study susceptible to residual confounding ▪ There were small numbers of women with high levels of alcohol and folate intake Comments ▪ Study primarily assessing the impact of folate on the association between alcohol intake and breast cancer ▪ People who had never consumed at least 12 alcoholic drinks in a year were considered lifetime abstainers Reported conclusions (by authors). Support the hypothesis that alcohol consumption may increase the risk of breast cancer through an interaction with folate and suggest that any adverse effect of alcohol consumption may be reduced by sufficient dietary intake of folate.

Table 14.2: Evidence tables for primary studies of alcohol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Lin et al. 2005) Japan	Prospective cohort study Level III-2.	Study setting. Study population selected from a prospective study initiated between 1988 and 1990 in Japan. The population included men and women aged 40-79 years. The present analysis was restricted to women whose incident data were available from 24 areas. Sample (n=35,844; 271,412 person-years; 151 cases) Mean age at enrolment 58.0 years Mean BMI 22.9 kg/m^2 Mean age at menarche 15.0 years Mean age at first birth 25.0 years Mean age at menopause 48.7 years More than high school education 9.3% Hormone use 4.3% Current smokers 4.7% Family history of breast cancer 1.4% Daily walking 30+ minutes 75.0%	Inclusion criteria Aged 40-79 at enrolment Followed up for cancer incidence in areas where a cancer registry system existed. Data collection Self administered questionnaire Outcome measures All cause mortality Breast cancer incidence (mainly obtained by record linkage – medical records were reviewed in some areas). Follow-up interval. Follow up was conducted from enrolment to December 31, 1997. Analysis Person-years were calculated from enrolment to diagnosis of breast cancer, death from any cause or December 31, 1997, whichever occurred first. Cox proportional hazards models were used to calculate RRs and 95% CIs. Non drinkers served as the reference group.	<u>Adjusted relative risk (95% CI) for breast cancer in relation to alcohol consumption</u> Ex drinkers: 0.82 (0.20-3.33) Current drinkers 1.27 (0.87-1.84) 0.1-4.9g/day: 1.07 (0.57-2.00) 5.0-14.9g/day: 0.83 (0.34-2.04) 15.0+g/day: 2.93 (1.55-5.54) *P*trend 0.01. Adjusted for age, BMI, study area, family history of breast cancer, walking, use of hormone, age at menarche, age at first birth, age at menopause and number of births.	Limitations ▪ 38% of current drinkers did not report level of alcohol intake ▪ Self administered questionnaire ▪ Few heavy drinkers in the cohort (74.5% were non-drinkers) ▪ Observational study susceptible to residual confounding Reported conclusions (by authors). Japanese women who consume at least a moderate amount of alcohol have an increased risk of breast cancer. Japanese women may be more susceptible to breast cancer risk than women of Western countries when consuming similar amounts of alcohol.

Table 14.2: Evidence tables for primary studies of alcohol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Suzuki et al. 2005) Sweden	Prospective population based cohort study Level III-2.	Study setting. Swedish Mammography Cohort established in 1987-1989 in Vastmanland County and 1988-1990 in Uppsala County. All women born between 1917 and 1948 in Vastmanland County and between 1914 and 1948 in Uppsala County were invited to mammography screening and completed a baseline questionnaire. Sample (n=51,847 including 1,284 cases) Mean age at entry 59 years BMI ≥ 30kg/m^2 11.6% Family history of breast cancer 8.6% 12+ years of education 9.0% Ever used HRT 43.7 Ever used oral contraceptives 46.4% Nulliparity 11.2%	Inclusion criteria Inclusion in Swedish Mammography Cohort as described under study setting. Exclusion criteria Women with missing or incorrect national identification numbers Women with missing data from key variables Moving out of study area Previous cancer diagnosis (excluding nonmelanoma skin cancer) Pre menopausal or perimenopausal at start of follow up Age 70+ years. Data collection Self reported average food and alcohol intake in six months before cohort entry. Outcome measures Histologically confirmed incident cases of invasive breast cancer were identified by linkage with the National and Regional Cancer Registries (March 1, 1987 through June 30, 2004). Dates of death obtained by linkage to the Swedish Death Register. Follow-up interval. Mean 8.3 year follow up.	<u>Adjusted relative risk (95% CI) for breast cancer in relation to alcohol consumption (g/day):</u> reference = no intake <median (3.4g/day): 1.08 (0.94-1.29) median-9.9g/d: 1.10 (0.94-1.29) 10.0+g/d: 1.43 (1.16-1.76) *P*trend 0.001 Adjusted for BMI, height, education, parity, age at first birth, age at menarche, age at menopause, type of menopause, use of oral contraceptives, use of HRT, family history of breast cancer, history of benign breast disease, quartiles of total energy intake, energy adjusted dietary fibre, and total fat intake. Results also presented by breast cancer receptor status.	Limitations ▪ 74% of eligible women were included in the original cohort (recruited 1987-1989) ▪ Self report data ▪ Residual confounding likely in this observational study both with known confounders (due to categorisation of these confounders) and unknown confounders ▪ Some potential misclassification in terms of inclusion is possible due to the arbitrariness of defining post menopausal status (26% were called postmenopausal simply on the basis of the 55 year cut off age) Comments ▪ All participants accounted for based on the exclusion criteria set out (22% of original sample were excluded from analysis). ▪ Swedish Cancer Registry estimated to be 98% complete. Reported conclusions (by authors). The observed association between risk of developing postmenopausal ER+ breast cancer and alcohol drinking, especially among those who use HRT, may be important, because the majority of breast tumours among postmenopausal women over express ER.

Table 14.2: Evidence tables for primary studies of alcohol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Suzuki et al. 2005) *continued*			Analysis Subjects entered into the study on the administration date of the FFQ-87 in Uppsala and FFQ-97 in Vastmanland if they were postmenopausal, the date of becoming postmenopausal during follow up, the date of bilateral oophorectomy or the women's 55th birthday for those with missing dates of menopause. Follow up was censored at date of death, date of migration out of the study area, date of diagnosis for any other type of cancer or the end of follow up (June 30 2004), whichever occurred first. Cox proportional hazards model used. Co-variates for inclusion in the model were selected *a priori*.		

Table 14.2: Evidence tables for primary studies of alcohol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Dumeaux et al. 2004) Norway	Prospective cohort study Level III-2.	Study setting. Between January 1991 and January 1997 women aged 30 to 70 years from the general Norwegian population were invited to participate in the prospective cohort. Sample (n=86,948, including 1,130 cases of breast cancer) Mean age at inclusion 45.3 years Mean age at menarche 13.3 years Mean age at first birth 23.8 years Mean parity 2.4 Mean BMI 23.6 kg/m^2 Ever used oral contraceptives 54.6% Family history of breast cancer 4.6% Postmenopausal 28.4% Ever used HRT 34.8%	Recruitment Women were sampled according to birth year from the national population register Exclusion criteria Women recruited in 1997 (alcohol intake not included in the questionnaire) Cancer present at baseline Data collection Information was collected by postal questionnaire with one to two reminders. Outcome measures Follow up information collected by linkage to the national cancer registry and to death certificates based on the unique national identification number. Analysis Cox proportional hazard model was used to investigate the simultaneous effect of oral contraceptive use, alcohol and breast cancer. Adjusted for *a priori* confounders.	<u>Adjusted relative risk (95% CI) for breast cancer in relation to alcohol consumption (g/day):</u> reference = no intake 0.1-4.9g/d: 1.24 (1.06-1.44) 5.0-9.9g/d: 1.35 (1.11-1.64) 10.0+g/d: 1.69 (1.32-2.15) *P*trend <0.0001 Adjusted for age, invitation to do breast screening, age at menarche, age at first birth and parity, family history of breast cancer in mother, menopausal status, HRT use and BMI. Negative interaction was observed with oral contraceptive use and alcohol intake in relation to the risk of breast cancer, implying that competitive responders must be present.	Limitations ▪ Among the 179,388 invited to participate, 102,443 were included in the overall NOWAC. Further exclusions resulted in the inclusion of 86,948 women. (major exclusions being included in the 1997 cohort and having prevalent cancer) ▪ Questionnaire was modified during the study period. ▪ Self administered questionnaire. ▪ Observational study susceptible to residual confounding. Comments ▪ Aim was to assess how oral contraceptives interact with alcohol on breast cancer risk ▪ National population register includes all residents who have stayed in Norway > 6 months ▪ National cancer registry is estimated to be "almost complete". ▪ A strength of the study is the lack of loss to follow up due to the use of linkage based data. Reported conclusions (by authors). Study findings in conjunction with biological data imply that alcohol and oral contraceptives have antagonistic effects on breast cancer risk through a common pathway. Whether the interactive effect differs according to menopausal status remains unclear and needs further investigation.

Table 14.2: Evidence tables for primary studies of alcohol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Horn-Ross et al. 2004) USA	Prospective cohort study Level III-2.	Study setting. Conducted using the California Teachers Study cohort. Cohort established in 1995-1996 when 133,479 active and retired female teachers and administrators returned a scannable questionnaire. Sample (n=103,460 including 1,742 with invasive breast cancer) Not presented	Exclusions Women not residing in California at baseline Diagnosed with breast cancer before completing the baseline questionnaire Inadequate completion of breast cancer or alcohol consumption data Aged 85+ years at baseline Data collection Number of drinks per week was assessed for three time periods: age 18-22 years, age 30-35 years, and the previous year. Outcome measures Annual linkage with the California Cancer Registry (CCR) is used to identify incident cancer cases. Analysis Follow up time calculated as the number of months between joining the cohort and either time of diagnosis of breast cancer *in situ* (not counted as a case), time of diagnosis of invasive breast cancer (case),estimated date of moving from California, date of death or 31 December, 2000, whichever came first. Relative risks (hazard ratio and 95% CI) were estimated using Cox proportional regression with time on study used as the timescale.	<u>Adjusted RR (95% CI) drinking pattern in the year before baseline and subsequent invasive breast cancer</u> (non drinkers as reference) 20+g/day: 1.28 (1.06-1.54) No statistically significant increased risk with daily consumption under 20g. Adjusted for age, race/ethnicity, caloric intake, family history of breast cancer, age at menarche, nulliparity/age at FFTP, physical activity, BMI and duration of oestrogen replacement therapy. Results also presented by menopausal status for drinking behaviour in the past year, at age 30-35 years and at age 18-22 years. Recent drinking was most clearly associated with increased risk of breast cancer. Results were also presented for change in consumption. <u>Effect modification</u> Increased risk associated with alcohol consumption in thin or normal weight women Increased risk associated with alcohol consumption in women without a family history of breast cancer. Increased risk associated with alcohol consumption in parous women	Limitations ▪ Excluded 21,153 women based on the exclusion criteria listed under methods (i.e. 17% of the original cohort) ▪ Self administered questionnaire ▪ Observational study susceptible to residual confounding ▪ Characteristics of the sample were unclear ▪ Measurement error may explain the lack of association between alcohol consumption in the younger age groups and risk of breast cancer Comments ▪ Primarily investigating the effect of age at drinking and drinking patterns and to identify effect modifiers in the relationship between alcohol and breast cancer ▪ The CCR uses a mandatory reporting system that covers the entire state of California and also includes interstate agreements with 13 other states for case sharing purposes. It is estimated to be over 97% complete. ▪ Results suggested it was the amount of alcohol consumed rather than the number of days on which it was consumed that was most important in determining risk. ▪ Both consistent and inconsistent results were identified between the effect modifying factors identified in this study and other studies Reported conclusions (by authors). Recent alcohol consumption equivalent to two or more drinks per day increases the risk of invasive breast cancer, with the greatest relative risks observed among heavy drinkers who are also postmenopausal and have a history of benign breast disease or who use HRT.

Table 14.2: Evidence tables for primary studies of alcohol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Horn-Ross et al. 2004) *continued*				Increased risk associated with alcohol consumption in physically active women Increased risk associated with alcohol consumption in women receiving oestrogen-progestogen therapy Note none of these interactions were statistically significant	

Table 14.2: Evidence tables for primary studies of alcohol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Mattisson et al. 2004) Sweden	Prospective cohort study Level III-2.	Study setting. Source population was, in 1991, all persons living in Malmo, Sweden and born during 1926-1945. Extended in 1995, to include all women born during 1923-1950 and all men born during 1923-1945. Sample at baseline Age (years): noncases 60.4, cases 59.4, *P*<0.01 Age at menarche (years): noncases 13.7, cases 13.6, *P*=0.54 Current hormone therapy (%): noncases 20.1, cases 31.9, *P*<0.01 Age at first child (years): ≤24, noncases 44.3, Cases 42.1 24-30, noncases 32.4, cases 32.2 >30, noncases 9.0, cases 10.2 No children, noncases 14.2, cases 15.5 *P*=0.74 Smoking status (%) Smoker, Noncases 25.9, cases 26.6 Ex-smoker, noncases 26.5, cases 29.8 Never smoker, noncases 47.6, cases 43.6 *P* = 0.28	Study population. Included women aged 50+ years. Excluded: People from the source population with inadequate Swedish language skills or mental incapacity. Prevalent cancer cases except cervical cancer *in situ* and non-malignant melanoma skin cancer Data collection Participants visited the screening centre twice. At first visit they were instructed about how to register meals and how to complete the diet questionnaire. Blood samples, blood pressure and anthropometric measurements were taken. At second visit, socioeconomic questionnaire was checked for completeness and dietary interview was conducted. National Swedish Cancer Registry provided data until December 1999. Cases were women with invasive breast cancer or breast cancer *in situ*. Food intake was converted to energy and nutrient intakes using a specifically designed nutrient database.	<u>Model comparing alcohol with risk of breast cancer (adjusted for total energy intake).</u> Reference: light drinkers (≤15g/day) Rate ratio (95% CI): Abstainers: 0.91 (0.58-1.41) 15-≤ 30 g/day: 0.88 (0.63-1.25) >30g/day: 1.77 (0.95-3.28) <u>Model comparing alcohol with risk of breast cancer (adjusted for non-alcohol energy intake).</u> Reference: light drinkers (≤15g/day) Rate ratio (95% CI): Abstainers: 0.92 (0.59-1.43) 15-≤ 30 g/day: 0.85 (0.60-1.20) >30g/day: 1.62 (0.87-3.00) Models adjusted for diet interviewer, method version, season of diet interview, age at baseline, change of dietary habits, height, waist, current hormone use, age at first child, age at menarche, leisure time physical activity, smoking habits and educational level. Exclusion of *in situ* cancer cases led to more significant p values for trend across fat quintiles in both energy adjustment models.	Limitations ▪ At baseline 28,098 of 74,138 had completed all parts ▪ Postmenopausal status subject to misclassification as it was based on the median natural menopause age in a subgroup of the source population ▪ Self reported data ▪ Residual confounding likely in this observational study both with known confounders (due to categorisation of these confounders) and unknown confounders Comments ▪ Aims: 1. is breast cancer risk associated with intakes of total alcohol, specific alcoholic beverages or total fat in postmenopausal women, 2. effects of total alcohol and fat intakes when adjusted for each other, 3. determine if the specific energy adjustment approach influences these associations. ▪ Cases were women with invasive breast cancer or breast cancer *in situ*. ▪ Low energy reporting was evaluated by comparing the total reported energy intake with the basal metabolic rate. ▪ Note reference group was light drinkers. Most studies use non-drinkers as the reference group. In this study, the use of non-drinkers as the reference group in the overall population would have resulted in higher estimated rate ratios. ▪ Well conducted study.

Table 14.2: Evidence tables for primary studies of alcohol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Mattisson et al. 2004) *continued*			Analysis Fat intake converted into two relative fat intake variables and five exposure categories were created. Total alcohol intake was converted into a four category variable. Two models of energy adjustment were developed, adjusting for total energy intake and non-alcohol energy intake. Student's t test and chi squared tests were used as appropriate. Cox regression was used to examine the associations between alcohol, fat and breast cancer. The models included known non-dietary risk factors and potential confounders. Follow-up interval: average 7.6 years		Reported conclusions (by authors). There were significant trends of increased breast cancer risk across quintiles of relative fat intake. Mutual adjustment did not affect risk estimates for total alcohol or relative fat intakes. The specific energy-adjustment approach did not influence associations differentially.

Table 14.2: Evidence tables for primary studies of alcohol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(McDonald et al. 2004) USA	Population based case control study Level III-2	Study setting. Women's contraceptive and reproductive experiences study conducted at five metropolitan sites in the USA. Sample Postmenopausal. Cases 33.8%, controls 34.1% (menopausal status was unknown in 20.0% of cases and 21.9% of controls) Family history of breast cancer. Cases 17.0%, controls 9.7% Current smoker. Cases 21.4%, controls 23.7% BMI ≥ 28.5 kg/m^2. Cases 21.4%, controls 23.7%. Ever used oral contraceptives. Cases 77.2%, controls 78.8%. Ever used HRT. Cases 38.0%, controls 41.3% Median age. Cases in 50-54 age group, controls in 45-59 age group.	Cases (n=4,575) Aged 35-64 Diagnosed with invasive breast cancer between July 1994 and April 1998 No preceding history of breast cancer Controls (n=4,682) Random digit dialling used. Selection designed to match case frequencies within strata of site, race and age group. Data collection Face to face interviews used. Analysis Conditional logistic regression models were fitted to the data. The log likelihood ratio test was used to determine whether to retain interaction terms in the models. Confounding variables to include in the model were selected *a priori*.	Note: Selected (significant) results presented <u>Association between number of drinks per week and breast cancer based on age of first alcohol use</u> (none as the reference category). Age group 45-54 <7: OR 1.1 (95% CI 0.9-1.2) 7+: OR 1.2 (95% CI 1.04-1.5) Age group 55-64 <7: OR 1.0 (95% CI 0.8-1.2) 7+: OR 1.4 (1.05-1.7) <u>Association between number of drinks per week and breast cancer two years before reference date</u> (none as the reference category). <7: OR 1.0 (95% CI 0.9-1.1) 7+: OR 1.2 (95% CI 1.01-1.3) Note reference date = date of diagnosis (cases) or date of telephone screening (controls) Estimates adjusted for study site, race, age group, menopausal status, age at menarche, age at menopause, number of term pregnancies, age at first term pregnancy, BMI, family history of breast cancer, use of HRT, use of oral contraceptives.	Limitations ▪ Participation rate: cases 76.5%, controls 64.7%. ▪ Women with missing values required in the models were excluded but it wasn't clear how many women this involved. ▪ Risk of recall bias – participants were asked to recall drinking history (including changes to drinking behaviour) from the time of first consuming alcohol. ▪ Self report data. ▪ Observational study susceptible to residual confounding. ▪ Interviewers were not blinded to case/control status. ▪ Affluent women may have been over-represented in the control group. This may have pushed the ORs toward 1.0. Comments ▪ Primary purpose of the study was to clarify the role of timing of exposure in the alcohol-breast cancer relationship. ▪ Validity and reliability studies examining the recall of alcohol history have produced reassuring results. Any under-reporting of alcohol intake by cases would have pushed the ORs toward 1.0. Reported conclusions (by authors). The effect of timing of alcohol exposure on breast cancer risk is complicated and will require additional study focussed on this issue. Further work is needed to explain how alcohol exposure, sex hormones, and tumour receptor status interact.

Table 14.2: Evidence tables for primary studies of alcohol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Petri et al. 2004) Denmark	Prospective cohort study Level III-2.	Study setting. Study population consisted of combined population based cohorts from various Danish studies. Sample (n=13,074) Mean age 53.1 years >14 cigarettes/day 20.3% Mean age at menopause 47.8 years Mean number of births 1.8 Mean BMI 24.7 kg/m^2 Physical activity (sedentary) 22.5%	Inclusion criteria Women aged 20+ years. Contributed with full information on determinants and covariates of interest. Data collection Self administered questionnaire Follow-up interval. Follow up time was the time from initial examination to date of breast cancer diagnosis, date of death, disappearance, emigration or end of follow up, whichever came first. Mean duration of follow up 6.1 years. Analysis Rate ratios estimated for pre and post menopausal women on the basis of quantity and type of alcohol intake. Log linear poison regression models were fitted. Cancer incidence rate was assumed to be constant in each 5 year age interval.	<u>Overall Association between number of drinks per week and breast cancer</u> (reference group 1-6 drinks per week). RR (95% CI) < 1: 0.91 (0.73-1.13) 7-13: 1.11 (0.85-1.45) 14-27: 1.10 (0.77-1.57) >27: 1.19 (0.58-2.41) Note 1 drink approximates 12g alcohol. Premenopausal women < 1: 1.17 (0.66-2.07) 7-13: 1.22 (0.66-2.25) 14-27: 0.86 (0.33-2.21) >27: 3.49 (1.36-8.99) Postmenopausal women < 1: 0.87 (0.69-1.10) 7-13: 1.09 (0.81-1.47) 14-27: 1.15 (0.78-1.69) >27: 0.57 (0.18-1.78) The only statistically significant result for type of drink was >6 drinks of spirits per week in the postmenopausal group aged 70+ years: RR 2.43 (95% CI 1.41-4.20) All data adjusted for age, cohort, parity and use of HRT.	Limitations ▪ Self administered questionnaire ▪ Observational study susceptible to residual confounding ▪ Cox regression may have been more appropriate ▪ No information on participation rate Comments ▪ Primary aim was to assess the influence of alcohol intake and type of beverage on breast cancer risk in relation to menopausal status. ▪ Used poisson regression rather than the more typical Cox regression (thus relying heavily on the assumption of a constant incidence rate in a 5 year interval). ▪ Note reference group was light drinkers. Most studies use non-drinkers as the reference group. In this study, the use of non-drinkers as the reference group in the overall population would have resulted in higher estimated rate ratios. Reported conclusions (by authors). Increasing risk of breast cancer among heavy drinking premenopausal women and among postmenopausal women who drank more than six drinks of spirits per week. More studies of the relation between breast cancer risk and heavy drinking in relation to menopausal status are warranted.

Table 14.2: Evidence tables for primary studies of alcohol (continued)

Authors Country	Study Design	Sample and Interventions	Methods	Results	Limitations and Conclusions
(Tjonneland et al. 2004) Denmark	Prospective cohort study Level III-2.	Study setting. Between December 1993 and May 1997, all 79,729 women aged 50-64 years living in specific municipality defined areas were invited to participate in the prospective study "Diet, cancer and health". Sample (n=29,875 including 423 cases of breast cancer) Median age at entry 57 years Median education 8-10 years Median BMI 18.5-25 kg/m^2 (14% had BMI > 30) Nulliparity 12% Median age at first child 20-24 years Previous benign breast surgery 13% Ever used HRT 51%	Inclusion criteria Born in Denmark Live in the greater Copenhagen or Aarhus areas Not registered as having cancer in the Danish Cancer Registry. Data collection Self-administered questionnaire. Alcohol intake over the past year recorded and over four different periods of life (age 20s, 30s, 40s and 50s up to 1 year before study entry. Follow-up interval. Follow up continued until diagnosis of any cancer (except nonmelanoma skin cancer), date of death, date of emigration or 31 December 2000, whichever came first. Median 4.7 years follow up. Analysis Cox proportional hazard model fitted with age as the time axis.	Rate ratio (95% CI) for each additional 10g/day of average daily alcohol intake, for different exposure periods. Analysis 1: adjusted for parity, number of births, age at first birth, previous benign breast surgery, school education, use of HRT, duration of HRT and BMI. 20s: 1.06 (0.93-1.20) 30s: 1.05 (0.96-1.14) 40s: 1.08 (1.01-1.15) 50s-baseline: 1.12 (1.05-1.19) Analysis 2: further adjusted for current alcohol intake 20s: 0.94 (0.79-1.11) 30s: 0.95 (0.84-1.06) 40s: 0.99 (0.90-1.08) 50s-baseline: 1.01 (0.91-1.13) Analysis 3: further mutually adjusted for the average alcohol intake in the other age periods 20s: 0.97 (0.79-1.20) 30s: 0.94 (0.79-1.12) 40s: 1.01 (0.88-1.16) 50s-baseline: 1.04 (0.90-1.19)	Limitations ▪ 37% of the women invited enrolled in the study. ▪ Self administered questionnaire. ▪ Observational study susceptible to residual confounding (although adjusted for all risk factors identified as significantly different between cases and non-cases at baseline). ▪ Retrospective collection of alcohol data with long periods of elapsed time for some of the exposure data – risk of misclassification. Any misclassification is likely to be non-differential thus diluting the estimated effect. This may explain lack of association in the young age groups. Comments ▪ Primarily investigated the influence of timing of alcohol consumption on risk of breast cancer. Reported conclusions (by authors). Results suggest that baseline intake of alcohol is a more important determinant of postmenopausal breast cancer risk than earlier lifetime exposure.