Cohort and Case Control Analyses of Breast Cancer Mortality: BreastScreen Aotearoa 1999-2011

by

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SUMMARY

SHORT LAY SUMMARY

BreastScreen Aotearoa (BSA) breast cancer mortality evaluation 1999-2011

Key Points:

The New Zealand (NZ) breast screening programme (BreastScreen Aotearoa) has reduced breast cancer mortality by a third in those screened.

This evaluation analysed data from the entire population of New Zealand women aged 45-69 years from the time the screening programme commenced in 1999 through to 2011. After adjusting for various factors, including recent screening participation rates,[1] the study found that, compared with women who were never screened, for screened women there has been a:

• 34% reduction in breast cancer mortality in NZ women

• 28% reduction in breast cancer mortality in Māori women (with projected 32% reduction at target screening coverage)

• 40% reduction in breast cancer mortality in Pacific women

Regular screening lowered the risk further. Compared to unscreened women, women who were screened regularly (at least 3 screens 30 months apart or less on average) had a 39% lower risk of death from breast cancer, and women who screened less regularly had a 31% lower risk.

For women with a screen-detected cancer, breast cancer mortality was 45% lower than for women whose cancers were detected outside the screening programme.

Among women who were diagnosed with breast cancer, prognostic indicators were more favourable (e.g. smaller tumours, less likely to have spread) for screened than for unscreened women, for regularly screened compared with irregularly screened women, and for women with screen-detected cancers than for those whose cancers were detected outside screening.

Conclusion:

These findings indicate:

• A reduction in breast cancer mortality from screening comparable to that observed in the original randomised trials of around 30-35%.

• A larger breast cancer mortality reduction with more regular screening, and from screen-detected than cancers detected outside of screening.

• More favourable indicators of malignancy and spread at diagnosis in screened women and for screen-detected cancers, consistent with the mortality evidence indicating a favourable screening effect.

• With the recent increases in screening participation, it is evident that Māori women will experience a breast cancer mortality reduction from screening comparable to that found for all NZ women.

[1] For 2012-13: 71% (All), 65% (Māori), 72% (Pacific), 72% (Other)

EXECUTIVE SUMMARY

INTRODUCTION

Population mammography screening programmes are based on evidence from a number of randomised trials conducted in the 1970s and 1980s on populations invited and not invited to screening. Meta-analyses of these trials have indicated reductions in breast cancer mortality of 20-30% in those invited to screening. The effect of actual screening on breast cancer mortality among screening participants from trial evidence is estimated to be a 35% reduction, compared to those not screening.

These trials determined efficacy, but effectiveness requires demonstration of mortality reduction in actual service conditions. The objective of population mammographic screening programmes is to reduce breast cancer mortality through earlier diagnosis (secondary prevention). A variety of study designs have been used to evaluate service mammography screening which indicate lower breast cancer mortality in screened populations compared to those unscreened or with lesser screening. These studies include cohort and case control designs which are undertaken here to evaluate the New Zealand population mammographic screening programme which commenced in 1999. Most cohort designs compare cohorts exposed or not exposed to screening (by time and place); however, this cohort analysis of the New Zealand BreastScreen programme is conducted entirely within a population within the screening epoch.

In this analysis, only actual screening mammograms through BreastScreen Aotearoa (BSA) are considered as exposure to screening.

OBJECTIVES

Research hypotheses are:

1. Breast cancer mortality is lower in ever-screened women compared to never-screened women.

2. Breast cancer mortality is lower in women with more compared to less regularity of screening as measured by: a composite measure of frequency and intervals between screens and other measures.

3. Women with screen-detected breast cancer have lower mortality than those with non-screen detected breast cancer.

4. Ever-screened women will have prognostic factors at diagnosis of breast cancer indicative of more favourable outcome than never screened women.

5. Māori and Pacific populations will also manifest lower breast cancer mortality in ever- compared to never-screened women, and in other analyses mentioned above.

METHODS

The quality and universality of record linkage through the National Health Index (NHI) which links individual person data from the screening services, cancer registry and death register provides the basis upon which cohort and case-control studies can be implemented.

An historical cohort offers a robust design to evaluate the effect of screening on mortality from breast cancer. For an inception cohort the assembly of denominator populations according to screening is complex because of changes in screening exposure over time, and never screened women (alive) without breast cancer can only be estimated in aggregate counts (by age group, ethnicity by period) by deduction of known populations from screening and/or cancer registry records from the total female (census derived) population. Further, there are potential disadvantages for subgroups which may leave New Zealand after diagnosis and die elsewhere.

The **inception cohort** comprises all women aged 45-69 years during 1999-2011 at screening inception and including women from these inception cohorts as they age. Women aged 45-49 years and 60-69 years were not offered BSA screening until 2004, and thus would remain unscreened by BSA in analyses until 2004. A screening inception cohort approach involves comparing an exposed group of ever-screened women, followed from the time of the first screen, with a corresponding cohort of never-screened women. Some of

the never-screened group will subsequently become screened, and, if cancer free, these women would be censored from that particular cohort and would form part of an ever-screened cohort from the time they first screened. The main advantage of a screening inception cohort approach is that **lead time bias** does not affect the estimates of any breast cancer mortality differences found between screened and unscreened women.

Using incident cancers only, **prognostic indicators** at diagnosis of breast cancer are compared between different screening exposure and ethnic groups; these indicators include: grade of tumour, extent of disease (spread), multiple tumours, and maximum tumour size.

An additional **case-control study** is also undertaken because it was anticipated that results for Pacific women from the cohort studies would be affected by out-migration of some women after diagnosis with breast cancer so that their subsequent death would not be registered in New Zealand (**attrition bias**), and as a means of comparative validation of results of cohort studies.

Both inception cohort and case control studies of service screening, which involve comparison to the never screened, are subject to **screening selection bias**, since those who do not participate in screening when offered, have been found to have higher breast cancer mortality than unscreened women not offered screening. This inflates estimates of mortality reduction from screening compared to the never screened. The excess breast cancer mortality reported in the literature and used in this report is a relative risk (RR) of 1.17 from the Swedish service studies. Adjustment for screening selection bias, which also incorporates screening coverage, indicates the extent of breast cancer mortality in a population offered mammography screening compared to a population not offered mammography screening.

Analyses of the total population are adjusted for age and ethnic groups, and subgroup analyses are undertaken for Māori, Pacific and Other populations (age adjusted).

RESULTS

1. EVER SCREENED AND NEVER SCREENED WOMEN

In the **NZ population 1999-2011** in the **inception cohort,** adjusted for age and ethnic group, and also adjusted for screening selection bias, the mortality reduction was 29% (95% CI: 20-38) at average screening coverage of 64% for the period. For recent coverage of 71% (2012-13) the estimated mortality reduction is **34% (95% CI: 25-43)**.

The **Other** group (non-Māori, non-Pacific) manifested 29% (95% CI: 16-41) lower breast cancer mortality (age adjusted) in ever- compared to never-screened women in the **inception cohort**, adjusted for screening selection bias at average coverage of 66% for the period 2001-11. For recent coverage of 72% (2012-13) this estimated mortality reduction is **33% (95% CI: 19-45)**.

In **Māori** the ever screened had a 17% (95% CI: 7-25) lower breast cancer mortality compared to never screened (age adjusted) in the **inception cohort** adjusted for screening selection bias at average coverage of 48% for the period 2001-11. For recent coverage of 65% (2012-13) the estimated mortality reduction is **28% (95% CI: 18-38)**, and for target screening coverage (70%) the projected mortality reduction would be **32% (21-41).**

For **Pacific** ethnicity the mortality differential in ever and never screened was larger in the inception cohort analysis, but this finding may be affected by differential under-enumeration of deaths from out-migration. In **Pacific women** (1999-2011) from the **case control study** those who were ever screened manifested a 22% (95% CI: 15-28) lower breast cancer mortality compared with never screened (age adjusted), adjusted for screening selection bias at average screening coverage of 49% for the period. For recent coverage of 72% (2012-13) the estimated mortality reduction is **40% (95% CI: 34-46)**. Mortality reduction in Pacific women may also be affected by higher baseline mortality in the unscreened compared to other sub-groups.

2. SCREENING REGULARITY

Breast cancer mortality is investigated in relation to a composite measure of screening regularity incorporating frequency and length of interval between screens. Regular screeners are defined as those screened ≥3 times with ≤30 months mean screening interval. Irregular screeners are those who have ever screened, but do not qualify as regular screeners.

In the **NZ population**, in the **inception cohort,** compared to never-screened women (adjusted for age and ethnic group) the mortality reduction in **irregular screeners** was 26% (95% CI: 17-35) when also adjusted for screening selection bias at prevalent screening coverage 2001-11 (64%); this was **31% (95%CI: 21-40)** at recent screening coverage (71%). In **regular screeners** the breast cancer mortality reduction was estimated as 33% (95% CI: 19-46) at the average coverage for 2001-11 of 64%, and **39% (95%CI: 22-52)** at current screening coverage (71%).

In the **Other** group (non-Māori, non-Pacific), in the **inception cohort,** compared to never-screened women (adjusted for age), when also adjusted for screening selection bias, the mortality reduction in Other **irregular screeners** was 26% (95% CI: 13-37) at prevalent screening coverage 2001-11 (66%), and **29% (95%CI: 16-41)** at recent screening coverage (72%). In Other **regular screeners** the breast cancer mortality reduction was estimated to be 34% (95% CI: 13-50) at prevalent screening coverage 2001-11 (66%), and **38% (95%CI: 16-55)** at recent screening coverage (72%).

In **Māori** the findings of the **inception cohort study** and **case-control study** are inconsistent for reduction of mortality in irregular and regular screeners, compared with never screeners, and some estimates are not significantly different to zero.

For **Pacific** ethnicity the mortality differentials in the **inception cohort study** compared to never screened were larger (and not plausible), and may be affected by differential under-enumeration of deaths from out-migration. Among **Pacific** women from the **case-control study,** results indicate that after adjusting for screening selection bias, based on screening participation over the study period (49%), Pacific women who screened regularly were estimated to have 33% (95% CI: 25-40) lower breast cancer mortality (statistically significant). After adjusting for screening selection bias based on 2012-13 screening participation (72%), Pacific women who **screened regularly**, were estimated to have **53% (95% CI: 43-61)** lower breast cancer mortality (statistically significant) than never screening. Less regularly screened Pacific women were estimated to be 20% (95% CI: 13-27) less likely to die from breast cancer than never-screened Pacific women, after adjusting for screening selection bias, with screening participation over the study period (49%). For 2012-13 screening participation (72%) in Pacific women who **screened less regularly**, breast cancer mortality was estimated to be **36% (95% CI: 29-43)** lower than never screening (statistically significant). Mortality reduction in Pacific women may also be affected by higher baseline mortality in the unscreened compared to other sub-groups.

3. SCREEN DETECTED COMPARED TO NON-SCREEN DETECTED BREAST CANCER

For ever screened **NZ women**, in the **inception cohort,** breast cancer mortality in those with a **screen-detected cancer** was **45% (95% CI: 31-57)** lower than in similar ever-screened women whose cancer was detected outside screening, adjusted for age an ethnic groups.

In ever-screened **Māori** women, in the **inception cohort,** breast cancer mortality in those with a screen-detected cancer was **56% (95% CI: 23-75)** lower than in ever-screened Māori women whose cancer was non-screen detected (age adjusted).

For **Pacific** ethnicity the mortality differential between screen and non-screened detected breast cancer was not statistically significant, and may be affected by differential under-enumeration of deaths from out-migration, although the point estimate appears comparable to other groups.

4. PROGNOSTIC INDICATORS

From data on diagnosed breast cancers, women who were **ever screened** had more favourable prognostic indicators that those **never screened** with respect to: grade of tumour (differentiation on histology, 30% in ever-screened women versus 18% in never-screened women); extent of spread (localised, 63% in ever-screened women, 46% in never-screened women); and maximum tumour size (average 18 mm in ever-screened women and 24 mm in never-screened women). Differences between prognostic indicators were all statistically significant for all NZ women, and for Māori, Pacific and Other (non-Māori, non-Pacific) women.

From data on diagnosed breast cancers, women whose cancers were **screen detected** had more favourable prognostic indicators that those whose cancers were **non-screen detected** (detected outside of screening) with respect to: grade of tumour (differentiation on histology, 35% for screen-detected versus 21% for non-screen detected); extent of spread (localised, 69% for screen-detected, 50% for non-screen detected); and maximum tumour size (average 16 mm for screen-detected and 23 mm for non-screen detected).

CONCLUSION

This report relates analyses of breast cancer mortality in relation to service mammography screening within the screening epoch using cohort analyses in all, Māori and Other (non- Māori, non-Pacific) women, and a case-control analysis especially for Pacific women because of probable differential under-recording of deaths from out-migration.

Results from the inception cohort and case-control studies involving comparisons with never-screened were **adjusted for screening selection bias** including screening coverages for 2000-2011, 2012-13 and target (70%).

Lower breast cancer mortality was demonstrated in relation to service mammographic screening for ever-compared to never-screened NZ women, including all ethnicities, of an expected magnitude in relation to trial data. Compared to never-screened women, breast cancer mortality reduction in screened women was 34% for all NZ women, 28% in Māori women (with a projected 32% reduction at target screening coverage), and 40% in Pacific women.

A 'dose-response' effect was apparent with generally **lower breast cancer mortality with greater screening regularity**. Compared to unscreened women, a 39% mortality reduction applied to women who were screened regularly (at least 3 screens with an average interval of 30 months or less), and a mortality reduction of 31% for less regularly screened women.

For women with a **screen-detected cancer**, breast cancer mortality was 45% lower than for women whose cancers were detected outside the screening programme.

Prognostic factors at diagnosis (tumour grade, extent of spread, multiple tumours, and maximum size), revealed more favourable indicators for all ever- compared to never-screened NZ women across all ethnic groups, with similar findings for screen-detected compared to non-screen detected breast cancer.

CHAPTER 1: BACKGROUND AND INTRODUCTION

1.1. Evidence for screening mammography reducing breast cancer mortality

The evidence for breast cancer mortality reductions being associated with screening mammography is based on a number of randomised trials conducted in the 1970s and 1980s on populations invited and not invited to screening.[1,2] Screening recommendations have been based on the results of such trials from Sweden,[3,4] Edinburgh,[5] New York[6] and Canada.[7] Meta-analyses of these trials have suggested reductions in breast cancer mortality of 24-29%[8,9] and 20-30%[1,2] in those invited to screening. Other meta-analyses which exclude several studies because of possible randomisation bias have failed to show an effect of mammography screening on breast cancer mortality.[10–13] However, this result is due almost entirely to a negative finding from the Canadian breast screening trial.[14] Evidence also exists for a somewhat smaller breast cancer mortality reduction in younger 40-49 year women from annual screening mammography.[15]

A review by the International Agency for Research on Cancer (IARC) produced a meta-analysis which indicated a pooled relative risk (RR) of 0.75 (i.e., 25% breast cancer mortality reduction) for invitation to mammography screening in women aged 50-69 years.[16]

Randomised trials based on invitation to screening (as an intention-to-treat analysis) will tend to under-estimate the benefit of screening because of several factors including non-compliance in the intervention group and screening in the control group. The effect of actual screening on breast cancer mortality among screening participants is estimated to be a 35% reduction compared to those not screening.[16] However, this effect may be biased by selection into screening, in that those who screen may also have lower prevalence of risk factors for breast cancer mortality; or the converse: selection into screening may be influenced by perceived higher risk of breast cancer, as reported in a Dutch study, for example.[17]

Service studies of mammography screening employing a variety of methodologies in the United Kingdom,[18–21] Holland,[22,23] Finland,[24] Sweden[1,2,25,26] and Australia[27–31] have indicated lower mortality associated with screening compared to non-screened populations, although not all results reached statistical significance. Australian studies have shown significant breast cancer mortality reductions associated with screening mammography using different study designs and analytical approaches.[27–29,31]

Numerous study design options are available to assess breast cancer mortality in relation to participation in the BreastScreen Aotearoa (BSA) programme. The purpose of population-based mammography screening programmes is to reduce mortality from breast cancer, and breast cancer mortality benefits associated with established screening programmes, including that of New Zealand, need to be evaluated to determine whether this purpose is being achieved in the real-world setting. In the context of an established evidenced-based programme, however, it is not possible or necessary to conduct a randomised controlled trial of mammography screening.

Evaluation of the New Zealand (NZ) mammography screening programme is necessarily based on observational study designs. Feasible study designs are considered to be:

- an aggregate study of mammography screening participation and subsequent breast cancer mortality similar to that conducted in NSW[27] and at small area level, such as that conducted as part of the 2009 evaluation of BreastScreen Australia;[29, 31]
- a case-control study of breast cancer mortality in which individual screening histories in all breast cancer deaths (cases) diagnosed during screening are compared to those in a control group of women who are still alive, similar to the South Australian[28] and Western Australian[30] studies as well as numerous US and European studies.[32–36]
- an historical or retrospective cohort study, including the total female population in the screening target age range, comparing breast cancer mortality of individuals between those with different screening histories;

- a prospective cohort study where exposures (screening) and outcomes (breast cancer mortality) of individuals are not known until a given time has elapsed from the initiation of the cohort;
- and a quasi-experimental design, where individuals exposed quasi randomly to the study variable of interest (screening) are followed over time or space and subsequent outcomes (breast cancer mortality) are compared in relation to the exposure (screening).[37]

Given existing health service and health data arrangements in NZ, and following discussions between the investigators and staff of the NZ Ministry of Health, it was considered that the most desirable approach for evaluation of the effect on breast cancer mortality of BreastScreen Aotearoa would be through a retrospective population-based cohort study and a nested population-based case-control study. These studies reinforce and complement each other, as discussed below.

1.2. Retrospective population-based cohort and case-control studies of BreastScreen Aotearoa

Given the quality and universality of the master National Health Index (NHI) linkage key in NZ, an historical population cohort study of individuals is feasible and provides the strongest observational study design and largest numbers to assess the effectiveness of the NZ mammography screening programme. Individual-level screening exposure and breast cancer incidence and mortality outcome data are already available. A population cohort study offers advantages over a case-control design, in that it would circumvent questions around appropriateness of controls (see below). It likely would produce more credible results, and as a co-benefit showcase the greater opportunities that exist in NZ for effective service evaluations than in many countries, including Australia, that lack an equivalent record linkage environment. The main disadvantage of an historic population cohort design is loss to follow-up, or attrition, especially from out-migration, and possibilities of inaccuracies in data linkage. However, the procedure in NZ for linkage is well established and likely to provide reliable results with only a small proportion of mismatches expected.

Cumulative mortality is the most direct and understandable method for analysis and in general is not subject to lead or length time bias. Whereas survival analysis of breast cancer cases can be adjusted for competing causes of death and other factors, controlling for lead time bias due to screening is difficult. Although gains in case survival might be expected to be due to mortality reduction from treatment at an earlier stage of diagnosis due to screening, a part of the extended survival from earlier diagnosis would be lead-time bias. That is, time from diagnosis from screening mammography versus clinical diagnosis is part of the survival time for those with screen-detected cancer, but does not contribute to the survival time of those with non-screen detected cancer. Consequently, this study will focus on evaluating breast cancer mortality reduction from BSA screening and will not examine survival.

In temporal or spatial comparisons of whole populations exposed and not exposed to service screening, breast cancer mortality differences are not affected by lead time bias because time of diagnosis is ignored or, is classified into deaths from cancers diagnosed before versus after the introduction of service screening. In the latter so-called incidence-based mortality studies, cumulated breast cancer mortality rates for equivalent times before and after screening, or in areas exposed versus not exposed to screening, are compared. Exposure to screening may be measured as a binary variable (yes/no), or as recorded population-level screening participation rates and related ecologically to cumulated breast cancer mortality rates.

By contrast, cohort studies of individuals in a specific population, and only during the epoch of service screening with universal availability, require estimating denominator populations of those exposed versus unexposed to screening subject to change over time as, for example, never-screened individuals become ever-screened individuals. Consequently, ‘snap-shots’ of those ever and never exposed to screening at a given time point serve to define exposure cohorts. Breast cancers diagnosed over a set subsequent period, for example, for the year after the time point, are classified as ever or never-screened at the beginning of the period, and cumulated mortality to the end of follow-up period is then estimated and compared. The numerator in each cohort is the number of breast cancer deaths occurring over the follow-up period

multiplied by the number of years exposed/not exposed to screening, and the denominator is essentially the cohort population multiplied by the number of years of exposure/non exposure to screening.

A disadvantage of population cohort studies is that deaths can be missed when some sub-groups leave the cohort, or are mismatched in linkage, and 'alive status' is falsely assumed when evidence of death is absent. Where possible, dates of last contact with health services as a marker of 'alive status' enables sensitivity analyses to be undertaken with alternative endpoints. In the case of New Zealand, Pacific women may be significantly affected by cohort attrition because of return to their country of origin.

An historical cohort offers a robust design to evaluate the effect of screening on mortality from breast cancer, however, there are potential disadvantages for subgroups which may leave New Zealand after diagnosis and die elsewhere. Further, for an inception cohort the assembly of denominator populations according to screening is complex because of changes in screening exposure over time, and never screened women (alive) without breast cancer can only be estimated in aggregate counts (by age group, ethnicity by period) by deduction of known populations with NHI from the total female (census derived) population. An inception cohort design is the most robust observational study type, as subsequent breast cancer mortality is examined without regard to when the breast cancer was diagnosed. However, the inception cohort study design is also the most complex to operationalise as it is based on populations with screening exposure that changes over time.

1.2.1. Inception cohort study

For the inception cohort the study population comprises all women aged 45-69 years during 1999-2011 at screening inception: up to 2004, BSA targeted women aged 50-64 years, and thereafter women aged 45-69 years. For 1999-2003 relatively few women aged 45-49 and 65-69 years were screened by BSA. Nonetheless, these women form groups with some exposure to screening and are treated as such. A screening inception cohort approach involves comparing a group of ever-screened women followed from the time of the first screen, or from the time of first eligibility to screen in never-screened women. Some of the never-screened group will subsequently become screened, and, if cancer free, these women would be censored from the never-screened cohort and form part of an ever-screened cohort from the time they first screened. The main advantage of a screening inception cohort approach is that lead-time bias does not affect the estimates of any breast cancer mortality differences found between screened and unscreened women. Similar analyses can also be made according to frequency and regularity of screening.

The main potential weakness of any observational cohort study is loss to follow-up (such as from out-migration) and consequent attrition bias relating to outcomes (e.g. mortality), which could especially affect Pacific women. A further weakness of the screening inception cohort approach is its operationalisation because some never-screened women in a given year will become screened during the remaining study period. Some of these women subsequently will be diagnosed with breast cancer and up to the time of diagnosis will have a history of being never-screened and ever-screened depending on and when they were first eligible to be screened, when they first screened, and when they were diagnosed with breast cancer. The approach used to avoid this complexity was to limit the follow-up time for breast cancer mortality to that occurring in the following year only. That is, for all women in a given year, times of exposure/non exposure to screening since the commencement of the screening programme are estimated, and breast cancer mortality occurring in these women over the following year is compared. This process is repeated successively for each year and the analysis is treated statistically as a repeated measures analysis. The time of the breast cancer diagnosis is ignored except that in those women diagnosed with breast cancer their screening status at the time of diagnosis remains fixed thereafter. Post-diagnosis mammography is ignored.

1.2.2. Case control study

A nested case control study is also undertaken as a means of cross-validation of the results of the inception cohort study, and because it was anticipated that results for Pacific women from the cohort study would be affected by out-migration of some women after diagnosis with breast cancer so that their subsequent death

would not be registered in New Zealand. Differential ascertainment bias is the likely explanation for any implausible results obtained for Pacific women from the cohort method. In the case-control study, cases are breast cancer deaths, and age- and ethnicity-matched controls are women alive for the whole study period, using the 'last updated' indicator (contact with health services) for all screened women and women diagnosed with breast cancer. The main advantage of the case-control study is that it minimises bias from loss to follow-up (attrition bias); the difficulties of this approach relate to the appropriateness and representativeness of both cases (breast cancer deaths) and matched controls. Nonetheless, the case-control analysis is important in the assessment of the effects of population mammographic screening on Pacific women in New Zealand.

1.2.3. Screening selection bias

Both cohort and case-control studies of service screening are subject to screening selection bias, since those who do not participate in screening when it is available, have been found in many screening settings to have higher breast cancer mortality than unscreened women not offered screening. This inflates estimates of mortality reduction from screening compared to a population not offered screening when the unexposed comparison group is women not screening when screening is available. Excess breast cancer mortality reported in the literature in non-participants offered screening, compared to unscreened women not offered screening, range from RR=1.36 from the Swedish trials, to RR=1.17 from the Swedish service studies. Adjustment for screening selection bias in analyses in this Report uses the excess RR=1.17 from the Swedish service studies, with screening coverage derived from BreastScreen Aotearoa participation data for 1999-2011.

1.2.4. Prognostic indicators

Prognostic indicators at diagnosis of breast cancer are compared between those who have ever screened and never screened using cancer cases only. These indicators include grade of tumour (degree of malignancy from histopathology), extent of disease (spread), multiple tumours, and maximum tumour size.[53] The purpose of examining these indicators is to demonstrate the plausibility of any findings of breast cancer mortality reduction associated with screening mammography. It would be expected that if screening confers lower breast cancer mortality than not screening then this should be reflected in worse prognostic indicators for non-screened women diagnosed with breast cancer.

1.2.5. Subgroup analyses

Separate analyses for Māori, Pacific, and Other women are conducted. While analyses restricted to Māori women should involve sufficient numbers to provide evidence of BSA effects, separate analyses for Pacific women will be more affected by small numbers. Besides stratification by ethnicity, BSA effects on breast cancer mortality for ethnic sub-groups can be derived using interaction terms in multiple regression models, although statistical power may still be insufficient. There are also added complications that deaths may be missed more often in Pacific women if they are more likely to out-migrate following a diagnosis of breast cancer.

Māori women manifest higher population mortality from breast cancer than other NZ women (SMR in 2002-2006 was 1.73).[38,39] From January 2007 to December 2009 biennial screening coverage was also lower for Māori women (53%) compared to non-Māori/non-Pacific women (68%),[40] although the most recent figures for July 2012 to June 2013 show 65% screening for Māori women and 72% for other women.[41]

1.3. Hypotheses

The main hypotheses for testing are that participation in mammography screening reduces breast cancer mortality, and that there is a larger reduction in breast cancer mortality with greater exposure to screening ('dose-response'). Analyses will be conducted separately for the total population, and for Māori, Pacific women and Others.

Hypothesis 1: That mortality from breast cancer in New Zealand women ever exposed to screening mammography is significantly lower than in women never exposed to screening mammography. This hypothesis is to answer the question of whether women who have ever had at least one screening mammogram through BSA have lower breast cancer mortality compared to women who have never been recorded as having a BSA mammogram.

Hypothesis 2: In ever-screened women higher frequency of, and smaller time intervals between, screening mammograms is associated with lower breast cancer mortality.

Hypothesis 2 is operationalised as follows:

> **Hypothesis 2a: In ever-screened women, a longer time interval from the last screen to diagnosis of breast cancer is significantly associated with higher breast cancer mortality.** This hypothesis is to answer the question of whether breast cancer mortality is higher in screened women with a longer elapsed time from their last screening mammogram to a breast cancer diagnosis compared to women with shorter elapsed times.
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> **Hypothesis 2b: In ever-screened women, a longer average time interval between screening mammograms is significantly associated with higher breast cancer mortality.** This hypothesis is to answer the question whether breast cancer mortality in women with shorter intervals between screening mammograms prior to a cancer diagnosis is lower than in women with longer intervals.
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> **Hypothesis 2c: In ever-screened women, a greater frequency of screening mammography is associated significantly with lower breast cancer mortality.** This hypothesis is to answer whether breast cancer mortality is lower in screened women who have more screening mammograms prior to their breast cancer diagnosis than women who have lesser numbers of screening mammograms.
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> **Hypothesis 2d: In ever-screened women, those screened 3 or more times previously with a mean screening interval of ≤ 30 months had significantly lower breast cancer mortality than ever-screened women who screened less frequently.** This hypothesis answers the question of whether women who have screened more frequently over shorter screening intervals have lower breast cancer mortality than women who have screened less frequently and at longer intervals.

Hypothesis 3: Women with screen-detected breast cancer have lower breast cancer mortality than women with non-screen detected cancer. This hypothesis is to answer the question of whether breast cancer mortality in women with a history of screening mammography is lower than in women without a screening history by separating screen-detected and non-screen detected breast cancers mortality in order to assess whether this is similar in groups with similar lead time effects. Hypothesis 3 is operationalised as:

> **Hypothesis 3a: Breast cancer mortality in women with screen-detected cancer is significantly lower than in women with non-screen detected breast cancer.** This hypothesis is to answer the question of whether breast cancer mortality is lower in women whose cancer was detected at a screening episode than outside of screening where the cancer is most likely to have become clinically manifest (symptoms, palpable lump, etc.).
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> **Hypothesis 3b: Breast cancer mortality in ever-screened women whose breast cancer is not screen detected is lower than in corresponding never-screened women.** This hypothesis is to answer the question of whether past exposure to screening mammography confers lower breast cancer mortality to women whose cancer was detected outside of screening compared to women with no prior record of BSA screening. This comparison is between women diagnosed with breast cancer outside of screening and therefore without mammographic lead-time bias that favours screen-detected cancer cases since the comparison is between never- and ever-screened women who had non-screen detected cancer only. However, such a mortality difference may also reflect screening selection bias which would need to be adjusted for. After adjusting for screening selection bias this

would answer the question: does a mortality benefit found from exposure to screening mammography remain when lead-time bias in the ever-screened group is absent?

Hypothesis 4: Breast cancers diagnosed in ever-screened women will have prognostic factors indicative of better recurrence and survival outcomes than those diagnosed in never-screened women. The principal hypothesised mechanism for screening mammography reducing breast cancer mortality is through detection of cancer at an earlier stage and smaller tumour size, allowing more effective treatment.

Hypothesis 5: Despite higher breast cancer mortality in Māori and Pacific women, those who have ever attended screening mammography will have significantly lower breast cancer mortality compared to never-screened Māori and Pacific women. This hypothesis answers the question that if exposure to screening mammography is associated with lower breast in the whole population, then is breast cancer mortality also lower in Māori and Pacific women who have ever screened compared to Māori and Pacific women who have never screened?

CHAPTER 2: METHODS

2.1. INCEPTION COHORT STUDY

2.1.1. Study design

Population exposure to screening and breast cancer mortality outcome

This retrospective total population study utilises exposure to the study factor (screening) that has already been recorded, and the outcome factors as death from breast cancer, death from another cause, or alive during the study period. From 1999 to 2003 the BreastScreen Aotearoa (BSA) screening target age group was women aged 50-64 years; from July 2004 45-49 and 65-69 year women were added to the target population. For this analysis, the study population comprises all women aged 45-69 years during 1999-2011 at screening inception and follows them as they age up to 2011.

These women comprise those: (1) diagnosed with breast cancer, who in turn were: 1a. diagnosed before the advent of BSA screening in 1999 (and excluded); or 1b. diagnosed after the advent of BSA screening, with the latter comprising those diagnosed through BSA screening and those diagnosed outside of screening; (2) not diagnosed with breast cancer who had either been screened by BSA or not.

While this study is a cohort design, it is evident that only outcomes of breast cancers diagnosed after the advent of screening are of relevance since screening has no influence on the course of cancers diagnosed prior to screening. A screening inception cohort approach involves comparing an exposed group of ever-screened women, followed from the time of the first screen, with a corresponding cohort of never-screened women. Some of the never-screened group will subsequently become screened, and, if cancer free, these women would be censored from that particular cohort and would form part of an ever-screened cohort from the time they first screened, rather than from the time of a cancer diagnosis.

The main advantage of a screening inception cohort approach is that lead-time bias does not affect the estimates of any breast cancer mortality differences found between screened and unscreened women. This is because the follow-up time is defined from the time of first screen and takes no account of when or how the cancer was diagnosed.

From the above, not all members of the cohort are individuals that can be followed up. Women who have never attended BSA, and have not been diagnosed with or died of breast cancer, are known only in aggregate from population statistics. Women who have never screened are derived from subtraction of women who have ever attended BSA from the corresponding total population. The annual counts of these women (by age and ethnicity) from aggregate population statistics incorporate effects of migration and deaths, and age and ethnicity are the only variables that are adjusted for when comparing breast cancer mortality in never- and ever-screened women.

Screening exposure in this evaluation is that recorded by BSA only. The extent of non-BSA mammography for screening purposes in New Zealand is unknown. Such private mammography is not subsidised or provided without charge and is paid for by the individual or their insurance company (if they are insured). Anecdotal information is that such screening is not frequent.

In this cohort approach, comparisons of breast cancer mortality risk as ratios of mortality are made according to: (1) whether there was a history of participation in BSA (exposure versus non-exposure to screening); and (2) for BSA participants, the extent of participation in BSA or screening regularity; for example, whether screening frequency conformed to screening recommendations, compared to lesser screening or never screening.

2.1.2. Sample assembly

The study population includes all women resident in NZ in the target age groups for the period of the study during 1999-2011, and requires numerator and denominator information for the study period. An indication

of the possible detectable effect sizes, for the period 2000-09 and assuming breast cancer mortality in ≥45 year women of 80 per 100,000, with 80% power and 0.05 significance level, is in Table 1.1.

Table 1.1: Minimum detectable breast cancer mortality reductions with corresponding follow-up times of New Zealand women aged 50-69 years exposed to screening, by ethnicity, and all women

Years cumulated	Population				Mortality reduction (%) at p<0.05			
	Māori (45%)†	Pacific (50%)†	Other (68%)†	All (64%)†	Māori	Pacific	Other	All
2009 (1)	19,598	8,555	265,987	296,749	55.8	81.1	26.8	23.5
2009-08 (2)	38,234	16,765	524,865	584,797	41.2	61.0	19.4	17.0
2009-07 (3)	56,061	24,608	777,002	864,685	34.6	51.5	16.1	14.0
2009-06 (4)	73,055	32,133	1,022,376	1,136,426	30.5	45.7	14.1	12.3
2009-05 (5)	86,756	38,208	1,217,076	1,352,486	28.1	42.2	13.0	11.3
2009-04 (6)	99,864	44,068	1,406,780	1,562,586	26.3	39.6	12.1	10.5
2009-03 (7)	112,365	49,688	1,591,303	1,766,490	24.9	37.4	11.4	<10
2009-02 (8)	124,304	54,414	1,767,912	1,960,776	23.7	35.9	10.8	<10
2009-01 (9)	134,391	58,689	1,922,722	2,130,714	22.9	34.6	10.4	<10
2009-00 (10)	143,268	62,404	2,062,825	2,283,951	22.2	33.7	10.0	<10

† Biennial screening participation rate January 2007-December 2009[40]

As is evident from the table, the sample size calculations indicate sufficient numbers to investigate the hypotheses using 10 years of data, and sufficient numbers overall for calculations using 5 years of data, but statistically significant findings are the least likely for Pacific women.

The National Health Index (NHI) number has been used for more than 20 years in NZ for those who access health and disability services; it is estimated that 95% of the population have a NHI number and it is now allocated at birth.[42] However, NHI records exceed the census population (estimated as 4.4 million in 2012) by around half a million, said to be mainly due to: outmigration, deaths occurring prior to 1988, and duplicates. The NHI number is valuable for record linkage, but NHI records cannot be used as a population register.

As previously indicated, individual screening, cancer and death data were linked using the National Health Index (NHI). Population denominators were obtained by 5-year age group, by Māori, Pacific and Other ethnicity, as estimated by Statistics New Zealand. Details of the data sources and assembly are in the Appendix.

2.1.3. Prioritised populations and ethnicity classification

Prioritised populations

Māori are the indigenous population of New Zealand. The Māori population is relatively youthful, comprising around 15% of the total population, but 11% of New Zealand women aged 45 to 69 years in 2013.[49] Health inequalities between Māori and non-Māori women are evident across many conditions, influenced by differential access to the living conditions for good health and to appropriate health care.[38,39] Disparities in breast cancer are substantial. For example, the breast cancer registration rate for Māori women was 66% higher than for non-Māori during 2005 to 2007, and the breast cancer mortality rate was 84% higher.[49] Māori women are also an under-screened population.[49] BreastScreen Aotearoa recognises the Treaty of Waitangi as the founding document of New Zealand and is committed to reducing inequalities in health.[50] Māori women are therefore a priority population for BSA and this report.

Pacific women (7% of the total New Zealand population, 5% of women aged 45 to 69 years) also have a relatively disadvantaged socioeconomic profile and are at greater risk of developing breast cancer. Pacific women are therefore a priority group for BreastScreen Aotearoa.[50]

Ethnicity classification

When a woman attends a breast screening episode, she is asked to record her ethnicity (BSA ethnicity). In addition, each woman attending BSA has an NHI with ethnicity recorded. Ethnicity on cancer registrations is

automatically populated from the NHI or death registration, and if an ethnic group appears on at least 20% of a person's hospital discharge records, it is also assigned to the cancer registration.[51] Ethnicity on death registrations has been found to be a reasonable match with the Population Census (98% concordant).[51]

In this study ethnicity was primarily designated from the NHI and BSA records. Where there was conflicting ethnicity status from these sources, any mention of Māori or Pacific ethnicity from any source (screening, cancer registration, death registration or NHI) classified that woman as Māori or Pacific respectively.

In accordance with the Ministry of Health's ethnicity data protocols,[52] the 'prioritisation' method was used whereby a woman was classified as Māori if any one of their recorded ethnic groups was Māori. Otherwise, if any ethnic group was nominated as Pacific they were classified as Pacific. All others were classified as 'Other' (Māori>Pacific>Other).

2.1.4. Population denominators

Denominator data for this study comprise both aggregate and individual information. Female census populations by 5-year age group, by Māori, Pacific and remainder (Other) serve as denominators for calculating population screening and breast cancer mortality rates. Inter-Censual populations are obtained from Statistics NZ or estimated as required. Denominator populations are segmented into those who have never screened through BSA and those ever screened (through BSA), by subtraction of the number of women who have ever screened from the corresponding census-derived denominator populations.

The women ever screened through BSA (by period, age group, ethnicity) were obtained through BSA records, after ensuring adequate de-duplication, and then further characterised by BSA screening history. Furthermore, analysis of a subset of the NZ population who have ever attended BSA is performed using numerators and denominators only from this group. Although ethnicity designation is available from the BSA register, Cancer Registry, mortality registration, the Census and the NHI, the most appropriate sources are the BSA and NHI for individual data, and from the census for aggregate data. The reason for the latter is that not all subjects will have died, been to BSA or were diagnosed with cancer. All subjects from BSA would also have an NHI with ethnicity recorded, and aggregate female populations can be classified by ethnicity from the Census if they have never attended BSA. A source of bias in ethnicity recording in the NHI stems from the frequency a person uses secondary health care. Those with higher usage would tend to be less well and will have a higher probability of accurate recording of ethnicity on the NHI, as opposed to healthier people who predominantly encounter primary care only. There may be instances of individuals with conflicting ethnicity status from NHI and BSA sources. In these instances any mention of Māori or Pacific ethnicity from any source (viz. screening, cancer registration, mortality or NHI data) then classifies that woman as Māori or Pacific, respectively, with priority given to Māori then Pacific, as outlined above.

With regard to breast cancer mortality in screen-detected breast cancer cases versus non-screen detected cases, the denominator populations for screen-detected cancers is the cumulated number of women ever screened up to the year of diagnosis, and the denominator for non-screen detected breast cancer mortality is the remaining population.

2.1.5. Numerators: measures of outcome

BSA screening participation, breast cancer incidence and breast cancer mortality originate from individual (de-identified) mammography screening and cancer registry records and from death registrations. These records are linked together via the NHI number. Linkage of breast cancer registrations to breast cancer deaths using the NHI allows for incidence-based mortality analyses in relation to date of BSA mammography screening episodes.

Dead/alive status of all women was established from matching data against vital registration records via the NHI. Breast cancer as cause of death is established through death registration and from NZ Cancer Registry. BSA and NZ Cancer Registry records were linked against all death records to the end of 2011, the latest year of occurrence for which cause of death was available. Persons are assumed to be alive if not documented to

be dead. The date of last contact with health services is added to the data file records as a marker of 'alive status'.

The cancer status of women is established through linkage via the NHI with the BSA database and the NZ Cancer Registry. This enables prognostic indicators to be used for supplementary analyses. Knowledge of date of diagnosis of breast cancer minimises false association of cancer diagnosis with screening since women diagnosed with breast cancer prior to the availability of BSA screening in 1999, and who subsequently participate in screening, could otherwise be misclassified as being exposed to screening in relation to their cancer diagnosis. Women diagnosed with breast cancer prior to 1999 are excluded from analyses, and women diagnosed with breast cancer after the advent of screening, but prior to their first screen, are classified as never screened. The inception cohort study design of breast cancer mortality with respect to screening focusses only on breast cancer mortality from incident breast cancers diagnosed after the advent of screening mammography.

2.1.6. Measures of exposure to screening

The mammography screening history of all women in the population cohort is established using the NHI linkage key to extract screening information from BSA records. Dates of BSA screening episodes and results from screening mammograms are added to matching cohort records, along with other information relevant to risk of breast cancer death (prognostic indicators), to the extent that this information is available. Some breast cancer prognostic indicators are available only for cases of BSA-detected cancers, and not available from breast cancer cases detected outside of BSA.

2.1.7. Statistical analyses

The main analytical advantage of a cohort study is that denominators and numerators exist for both comparison groups (e.g. screened and unscreened women), so that breast cancer mortality rates can be compared directly. Mantel-Haenszel chi-square statistics and Poisson and/or negative binomial regression is used to estimate relative risk of death from breast cancer in women in the cohort, adjusting for age and other potential confounders, effect modifiers or biases, and accounting for repeated measures. The study factors are based on whether a woman in the cohort was recorded on the BSA register or not, with times calculated since the last screen to the period of interest (i.e. diagnosis year or screening inception year), and frequency of screening. The effect of BSA screening (frequency and intervals between screens) on breast cancer mortality are examined separately for Māori, Pacific, and Other women.

2.1.8. Potential bias

Bias occurs when the sample is unrepresentative of the population under study (selection bias) and/or when inaccuracies occur in the measurement of exposure (screening), or outcome (breast cancer mortality), or other relevant variable (measurement bias). Also, screening selection bias is an issue to be addressed, particularly if breast cancer mortality in relation to screening offered to a whole population is being compared with that in a whole population not offered screening.

2.1.8.1. Selection bias

In a study that compares breast cancer mortality between those who screen with BSA versus those who do not, selection bias may occur if those who screen or do not screen with BSA possess characteristics which render them more or less susceptible to breast cancer mortality. For example, women who screen with BSA and develop breast cancer may have less co-morbidity or have better access or adherence to treatment than those who do not screen with BSA and subsequently develop breast cancer. Selection bias is thought to stem partly from pro-active health behaviours, such as screening, being more prevalent in healthy populations at lower risk of the disease. However, selection bias may also occur in populations at higher risk of the disease, such as those with a family history of the disease, or in those aware that their fertility pattern may put them at higher risk. However, segments of the population with higher risk of incidence may also manifest lower mortality because of earlier diagnosis and better access and/or response to treatment. Additionally, a

population screening programme has effects beyond those which occur in attenders. For example, women who do not participate in the BSA programme may be prompted to seek private sector mammography, or may practice breast examination, or be more alert to breast changes (and so present earlier as clinical cases) as a consequence of the existence of the programme. Further, a mammography screening programme may improve referral and treatment practices which affect the prognosis of all women with breast cancer, including those who never attend the screening programme.

Screening selection bias

To evaluate the programme it is necessary to consider not only breast cancer mortality in screened versus unscreened populations but also to assess whether a mortality benefit attributable to screening occurs in the post-screening epoch compared to the pre-screening epoch or in populations with screening available versus not available. Screening selection bias is a consequence of the changed environment attributable to a screening programme, and is evident when the estimated relative benefit from screening in a whole population compared to the pre-screening epoch, or with a whole population not offered screening, is estimated only from those exposed to screening versus those not exposed to screening during the screening epoch (when screening is offered to the whole population). For the present evaluation, screening selection bias is a potential issue because mortality differences between screened and unscreened groups are considered from cancers diagnosed in the screening epoch only. In the absence of a randomised controlled trial, adjusting for screening selection bias allows estimation of the screening benefit in the screening epoch compared to breast cancer mortality in the absence of screening. It is possible that differences exist between women who screen, compared to those who do not screen, contribute to the risk of breast cancer mortality irrespective of screening. However, the extent that breast cancer mortality differs in populations who do not screen when screening is available from those who do screen is due to factors unrelated to screening is difficult to estimate empirically.

The question that is directly answerable is, what is the breast cancer mortality in women who screen if available, compared to that in women who do not screen when available? In order to answer the different question of what is the difference in breast cancer mortality in a population of women with screening available compared to a population of women with screening not available, adjustment for screening selection bias is then necessary if the data available relate only to the screening epoch where women taking up screening versus not taking up screening is the only comparison possible. In order to answer this question, the approach employed by Duffy *et al.,* is based on the original field trials,[43] which found higher breast cancer mortality in women who were offered screening but did not avail themselves of it, compared to women who were not offered screening and were unscreened. These adjustments were used in the South Australian screening evaluation,[28] and are also employed in this analysis to mitigate this potential source of bias. Nonetheless, the direction of the bias may also be variable, minor or in the opposite to that assumed from the trial data, as two Dutch evaluations have shown,[44,45] and as Duffy *et al.* also illustrate.[43]

In order to adjust for screening selection bias in this cohort analyses, an estimate from the literature with respect to Swedish service studies is employed to modify the RR obtained from analyses of ever screeners, and those screeners in various categories of screening regularity, compared to never screeners (referent category RR=1.00). Estimates for excess breast cancer mortality in those who do not take up screening when offered from service studies in Sweden is a RR=1.17[46] and a RR=1.36 from the Swedish trials[46] The RR of 1.17 from Swedish service studies is used in this analysis as the most comparable and appropriate figure.

2.1.8.2. Measurement bias

Measurement or information bias occurs when study subjects are systematically misclassified with respect to study variables, either exposure or outcome variables.[47] If the bias is non-differential then in most cases findings of association would be biased toward the null. Differential measurement bias, when an outcome (or study) variable is measured differently according to whether it is associated with the study (or outcome) variable, is more problematic, and important to minimise.[47]

Bias in the outcome variable breast cancer mortality, will occur if mismatching occurs in the data linkage, with either the deaths not linked to individuals in the cohort or mistakenly linked to individuals still alive. Differential measurement bias with respect to screening and breast cancer mortality may occur if the chance of linking mortality records with records of screened women differs significantly from the chance of linking mortality records with unscreened women diagnosed with breast cancer. For this evaluation, all deaths are linked with the NZ cancer registry and all breast cancers are linked to the BreastScreen register. Cancer cause of death is determined by the New Zealand cancer registry without regard to screening exposure or screen-detection status. The death linkage thus is not dependent on whether the breast cancer diagnosis originated from a screening episode. A potential source of bias stems from death certificate-only (DCO) notifications to the cancer registry. These occur in a small proportion of cancers (1-3%), and unscreened women would be expected to be over-represented in DCO notifications if breast cancer is detected on average later in unscreened women. However, since the time of diagnosis is unknown, DCO breast cancer cases are excluded from this evaluation.

Attrition bias from out-migration can under-estimate breast cancer mortality, and potentially more so in migrant groups than others. This is expected to more likely occur in Pacific women than in Māori and the remaining (Other) population. Further, this bias may be differential with greater or lesser out-migration occurring in relation to prior screening status.

Bias can affect the exposure variable (screening) with inadequate linkage of screening data with the cohort. Screening outside of BSA is more an issue of confounding if the aim is to evaluate screening by BSA rather than any screening mammography.

Another issue for consideration is the possibility of over-diagnosis[48] adding artefactually to survival following breast cancer diagnosis in screened women versus unscreened women. Over-diagnosis may be regarded as an extreme form of **length time bias** in which the detected cancer is very slow growing, indolent or destined to regress. However, this issue is circumvented through examination of breast cancer mortality over follow-up time from first screening in the screening-inception cohort analyses, rather than time following diagnosis.

Ascertainment bias. If over-diagnosis of breast cancer has become prevalent as a result of the NZ screening programme, then this may bias breast cancer mortality against screening. A diagnosis of breast cancer confers an increased chance of death being erroneously attributed to the disease since people can die with breast cancer and not of it. However, this is more likely if cancer cause of death is assigned by, for example, the Cancer Register with knowledge of screen-detected status of the cancer, rather than by civil death registration or by the Cancer Registry without knowledge of screening status. Differences in cause of death between both sources according to screen-detected status of the cancer can inform the extent of this bias introduced by over-diagnosis.

Screening epoch. Early in a screening programme prevalent breast cancers detected by screening confer a bias against screening, even though breast cancer mortality overall is reduced from the earlier diagnosis of prevalent cancers from screening compared to before screening. However, when compared to an established screening programme, where the majority of screen-detected cancers are incident cancers detected at the screening interval, breast cancer mortality is hypothesised to be higher early in the newly established programme because of the worse prognosis (e.g. stage, tumour sizes, etc.) from the higher proportion of prevalent cancers. Since prevalent versus incident breast cancer cases are known from screening data, analysis of breast cancer mortality in cancers detected at prevalent compared to incident screens provides estimates of the extent of differences in outcomes from cancers detected at an initial compared with a subsequent screen. Comparison of outcomes in non-screen detected cancers in screened women versus never-screened women highlights differences between screening exposure versus no screening exposure, unaffected by lead-time bias.

2.1.9. Potential Confounding

Confounding occurs when variables other than the study factor (screening) influence the outcome (breast cancer mortality), and are differentially distributed across exposure (screening) groups.

Age is an important risk factor for breast cancer incidence, mortality and survival, and is a source of confounding of associations between other putative risk factors or study factors (screening) for these outcomes. Age is the easiest potential confounder to control for in regression and other analyses. Other confounding issues to consider in the analysis include **ethnicity**, socio-economic status (SES) and geographic and other factors as potential markers for to access and adherence to treatment. These factors are inter-related, proxies for other unmeasured confounders, and are also of interest for sub-group analyses. Individual information on age and ethnicity are employed to control for these factors, to the extent possible.

Mammography **screening may occur outside of BSA** and could cause confounding by contributing to breast cancer mortality reduction if the aim is to evaluate BSA programme effects; or is a measurement bias issue if the aim is to evaluate any screening. Without relevant information on the extent of private mammography, these effects are difficult to estimate.

Treatment improvements coinciding with screening regularity can confound any association between screening and breast cancer mortality. Year of diagnosis may be incorporated in modelling breast cancer mortality and screening to control for underlying breast cancer mortality changes related to treatment. However, the advent of BSA (1999) occurred after the major breast cancer treatment improvements were introduced from the late 1980s, and thus treatment improvements are unlikely to substantially confound the relation of screening and breast cancer mortality in the case of New Zealand.

Higher rates of screening in women on **hormone replacement therapy (HRT)** have been observed in some studies. If higher breast cancer mortality is also associated with HRT use, then HRT use may bias against screening if not accounted for. While data on HRT use may be available on screened women (from the screening service), it is not routinely available in unscreened women, except from aggregate data from population surveys that include both HRT use and screening history. If HRT data are available in screened women, it is possible to account for HRT use in sub-analyses of these women with respect to screening regularity; and if a HRT effect can be estimated from this source, then it may be used as the basis for correcting effects found when comparing breast cancer mortality in screened versus never-screened women. However, if HRT data are not available, then the estimates of breast cancer mortality reduction attributable to screening will be conservative if HRT use is more prevalent in ever-screened women. It may be possible to use survey data to estimate the prevalence of HRT in screened versus unscreened women, but these data are not usable at an individual level.

A source of bias is over-control of prognostic indicators with breast cancer mortality as the outcome. The principal hypothesised effect of screening on breast cancer mortality is through the intermediary mechanism of improved prognostic indicators in screened versus unscreened women diagnosed with cancer. Separate analyses of prognostic and mortality outcomes in relation to screening exposure provide an indication of the extent of the mediation of screening and breast cancer mortality by prognostic indicators. It would be expected that any breast cancer mortality benefit from screening should be associated with better prognostic indicators for screened women diagnosed with breast cancer.

In summary, the data available for this evaluation offer at a whole-population level an unprecedented opportunity to address many of the issues that potentially can undermine a valid service study of screening mammography and breast cancer mortality.

2.1.10. Screening inception cohort

Using a screening inception cohort approach avoids the issue of lead time affecting estimates of breast cancer mortality in relation to screening exposure. This is because survival or person years (or days) in screened

women is defined from the time of first screen or first eligibility to screen, not from the time of cancer diagnosis.

Three broad approaches to analysing screening with respect to breast cancer mortality in an inception cohort are:

1. Examine breast cancer mortality outcomes in the whole population after screening became available in relation to cohorts of ever- versus never-screened women
2. Examine breast cancer mortality outcomes in screened women in relation to indicators of screening regularity
3. Examine breast cancer mortality in regularly versus irregularly versus never-screened women

All women aged ≥45 years are included in the study and are classified at any given time as either ever or never screened. Breast cancer mortality is then compared in the two groups; and within screened women among those less screened versus more screened, as defined above. Breast cancer can be diagnosed at any age ≥45 years.

An issue with this approach is that with increasing time from the commencement of the screening programme, the population of ever-screened women increases, absolutely and proportionally, and the population of never-screened women decreases correspondingly. For example, the estimated denominator population of never-screened women aged ≥45 years at the beginning of 2011 was 327,623 (38% of the total ≥45 year population) compared to 580,494 at the beginning of 2000 (88% of the ≥45 year population); ever screened women in 2011 numbered 543,247 (62%) compared to 75,566 (12%) at the beginning of 2000. This would favour screening artefactually if breast cancer deaths occurring in a given year are analysed with respect to a denominator population in the year of death later in the study period than earlier. Mortality rates from x cancers in never-screened women diagnosed after 1999 and who die in 2009 are higher than if the same number of x never-screened women died of breast cancer in 2001, as the denominator of never-screened women in 2009 is lower than in 2001. While it would not be expected that the number of breast cancer deaths in 2001 from diagnoses cumulated from 1999 would be as high as those in 2009 (as the latter would be cumulated from diagnoses over 1999- 2009), it remains that for a given number of deaths in unscreened women, the mortality rate would be higher for these occurring in 2009 than 2001.

A person-years approach was utilised to minimise the effect mentioned above. The person years offset is defined as the relevant population *x* years exposed/not exposed to screening. For those never-screened, person years was defined as *(year of interest-1999)x(never-screened population in the year of interest).* The never-screened denominator population was calculated by subtracting the number of women ever screened as at the beginning of the year from the denominator (aggregate) population for that year. The above person-years formula is applied to never-screened women old enough in a given year to have commenced screening in 1999. In younger women, the person years was estimated according to the median age of the 5-year age group. For instance, for the year 2008, the number of 50-54 year never-screened women (median age 52 years) would be multiplied by 7 (i.e., 52 minus 45) rather than 9 (2008 minus 1999) to produce the person-years for this age group and year.

In women last screened in the year *yyyy*, not diagnosed with breast cancer and still alive are aged *+a* years from *yyyy* to the *yyyy+a* year of interest. Person years for the ever-screened is comprised of those who first screened in the year prior to the year of interest, plus those who had first screened the year before, and the year before that, and so on back to 1999. These were also aged +1 year for each year after their initial screen up to the year prior to the year of interest, so the person years for the year of interest is a sum of those who had screened for the first time in the prior year, plus those who had screened the first time in the year before x2 (aged +1 year), plus those who had screened the first time the year before x3 (aged+2 years), and so on to 1999.

The log of these (person years+1) was then used as the offset in Poisson and negative binomial regression modelling.

Some examples of person year contributions for individuals as of 2009 are:

a. Aged 50 in 2009, never screened: 52-45=7 person years unscreened only (from 5-year age group denominator population).
b. Aged 65 in 2009, never screened: 2009-1999=10 person years unscreened only (the same for 65-69 year women, from 5-year denominator population).
c. Aged 50 in 2009, screened once in 2004: 2009-2004=5 person years screened only.
d. Aged 50 in 2009 screened in 2004, 2006 and 2008: 2009-2004=5 person years screened only.
e. Aged 65 in 2009, screened once in 2000: 2009-2000=9 person years screened; 1 person year unscreened (the same unscreened PYs from 65-69 year denominator population)
f. Aged 65 in 2009, screened in 2001, 2003 and 2005: 2009-2001=8 person years screened; 2 person years unscreened (the same unscreened PYs from 65-69 year denominator population).

Note that evident differences in frequency of screening do not influence the time a person was never exposed or ever exposed to screening.

Breast cancer mortality for a given year, 2005 for example, by ever- and never- screened status, is then used as the outcome measure for the 2004 cohorts of ever- and never-screened women. Breast cancer mortality in each yearly cohort is modelled as a repeat measures basis, repeating over each year. Mortality in a given cohort of ever- and never-screened women as at the end of a given year is measured for the following year only, so that the ever- and never-screened cohorts under comparison are well defined. This avoids the problem of changes within each cohort, viz. from never- to ever-screened status, that occurs when mortality in the index cohort is followed indefinitely. This also avoids changes to screening status that occur during the year of mortality follow-up; and as population denominators are annual estimates, it was not feasible to produce populations fractionated over the year and by screening status coinciding with each date of death.

The above approach is also adopted for estimating breast cancer mortality differences between ever- and never-screened populations when comparing breast cancer mortality in regularly versus irregularly versus never-screened women. For the analysis of regular screening with respect to breast cancer mortality occurring in a given year, the regular screening criterion was applied to women for the year prior to the year of death. That is, for the year prior to the given year of breast cancer mortality, a regular screener was someone whose average screening interval was ≤30 months and who had screened more than 3 times up to and including the year prior to the year of death (non-breast cancer cases) or diagnosis (breast cancer cases).

2.1.11. Analyses

Four broad analyses were undertaken. The first compared breast cancer mortality in women ever exposed to screening versus never exposed to screening. The second compares breast cancer mortality among screened women with respect to regularity of screening or screening regularity. The third compares breast cancer mortality in those regularly versus less-regularly screened versus never screened. The fourth analysis compares breast cancer mortality in women whose breast cancer was detected at screening versus women whose cancer was not detected from a screening episode. This latter analysis is conducted for all women diagnosed with breast cancer in the study period with regard to their exposure to ever- or never-screening irrespective of when they were diagnosed. Statistical analysis was by multiple negative binomial or Poisson regression of counts of breast cancer mortality offset by the log of person years, as specified above.

2.1.11.1 Correction for screening selection bias

The purpose of this adjustment is to provide estimates of breast cancer mortality reduction from screening on an intention-to-treat basis, to replicate as closely as possible the results from the trials of screening mammography. The method proposed by Duffy *et al*. is used to correct for possible *a priori* breast cancer mortality risk in the never-screened women who were offered screening.[42,45] This correction relies on empirical estimates from randomised controlled trials[42] and service studies[45] of breast cancer mortality relative risk in women not taking up screening when offered, compared to women not offered screening (D_r);

an estimate of population-based screening participation (*p*); and the relative risk estimates of never- versus ever-screening derived from the Poisson or negative binomial modelling employed here (RR_{der}). The resulting adjusted relative risk estimate is an intention-to-treat estimate and represents the relative risk in a population where screening is available or offered compared to a population where screening is unavailable or not offered.[42]

The adjusted relative risk is:

$$RR_{adj} = D_r(pRR_{der} + 1 - p)$$

The variance for *RRadj* is calculated from:

$$V\{ln(RR_{adj})\} = V\{ln(D_r)\} + \frac{p^2(RR_{der})^2 V\{ln(RR_{der})\}}{(pRR_{der}+1-p)^2}$$

The variance of $ln(D_r)$, $V\{ln(D_r)\}$, is estimated to be 0.0014995, derived from the 95% confidence interval reported for the overall estimate of Dr by the Swedish Organized Service Screening Evaluation Group,[45] and $V\{ln(RR_{der})\}$ is provided directly by the regression outputs, the standard error of the regression estimate squared.

The standard error is then:

$$SE[ln(RR_{adj})] = \sqrt{V\{ln(RRadj)\}}$$

The upper and lower 95% confidence intervals of $ln(RR_{adj})$ are:

$$ln(RR_{adj}) \pm 1.96SE[ln(RR_{adj})]$$

These are exponentiated to produce the upper and lower 95% confidence intervals of RR_{adj}, as in:

$$exp[ln(RR_{adj}) \pm 1{:}96\sqrt{V\{ln(RRadj)\}}\,]$$

In the case of New Zealand there are no reliable contemporaneous data on breast cancer mortality risk in a population not offered screening (and unscreened) versus in a population not undertaking a screening mammogram if offered. While risk of breast cancer mortality in those who have never screened can be derived from the data available for the present evaluation, risk of breast cancer mortality in a whole population not offered screening mammography is not readily available for New Zealand, especially since the present study encompasses only the screening epoch. The BSA mammography screening programme commenced in 1999, following significant improvements in breast cancer treatment during the early- to-mid 1990s. Mortality risk in a population not offered screening could be approximated by breast cancer mortality in the whole New Zealand population prior to screening, but only from mortality cumulated from cases diagnosed during an equivalent period to the study period which is limited because the NZ cancer registry did not include pathology notification until 1996.

The alternative is to use the range of known estimates of relative risk of breast cancer mortality in those who do not undertake screening when offered, compared to those not offered screening (and unscreened). From Randomised Controlled Trials in Sweden this was estimated as RR=1.36 for Sweden.[42] Another study, based on service screening in Sweden estimated the RR to be 1.17.[45] Conversely, the extent that the relative risk of breast cancer mortality in non-compliers would need to exceed that in a population not offered screening, for screening to have no effect on breast cancer mortality, can be estimated.

For this report we provide unadjusted estimates of mortality decline from screening in screened versus unscreened women, and estimate mortality decline from screening in relation to a population not offered screening based on RR=1.17, where the RR reflects the excess mortality from screening selection bias (from Swedish Service studies). Standard errors from this study are also used as the basis for estimating 95% confidence intervals. For these adjusted estimates we use mean recorded participation rates for 2001-11 (64% overall, 48% in Māori women, 49% in Pacific women and 66% in other non-Māori, non-Pacific women) for the study period, screening participation for the most recent period 2010-12 (71% overall, 65% in Māori

women, 72% in Pacific women and 72% in other non-Māori, non-Pacific women), and screening participation at target of 70%.[49]

2.2. CASE CONTROL STUDY

2.2.1. Introduction and rationale

An additional case control study was also undertaken as a means of cross-validation of the results of the inception cohort study, and because it was anticipated that results for Pacific women from the cohort studies would be affected by out migration of some women after diagnosis with breast cancer so that their subsequent death would not be registered in New Zealand. The latter situation did probably occur and differential ascertainment bias is the likely explanation for the implausible results obtained for Pacific women from the cohort method. Thus the case control analysis is important in the assessment of the effects of population mammographic screening on Pacific women in New Zealand.

A case-control study design is a cost-effective means for assessing associations between risk factors and rare outcomes, such as death from breast cancer. Additionally, a case-control study can largely overcome attrition bias (loss to follow-up from out migration, for example) that may affect cohort studies. The case-control design here is population-based, regarded as the highest quality case-control design, and nested within the 1999-2011 NZ cohort study as the sampling frame. While a well-designed case-control study should give similar results to a historic cohort study, there are often questions about appropriateness of chosen controls and potential for recall bias, although this latter bias will not be an issue in the case-control study proposed here, as information on the cases (deaths from breast cancer) with respect to exposure to screening is not collected any differently to non-cases.

A BreastScreen South Australia (SA) evaluation of mammography,[28] using a case-control design, found a similar statistically significant screening effect to the Australian national evaluation (aggregate cohort design).[31] As in SA, the NZ analysis will be by screening participation, rather than invitation to screen, since the latter data are not available. Such an approach may introduce screening participation selection bias that will need to be addressed (previously described in detail for the historic cohort study).

The South Australian study,[28] conducted by one of the investigators (DR), used a sample of 491 breast cancer deaths in 45-80 year old women from South Australia and compared their BreastScreen participation to 1,473 randomly selected live population controls (three per death), randomly selected from the State Electoral Roll, matched on date of birth (to control for age confounding). The study found the odds ratio (OR) of breast cancer mortality in BreastScreen participants to be 0.59 compared to non-participants (OR=1.0) - a mortality reduction of 41%. The protective benefit of screening was still evident in women who last screened ≥3 years before their diagnosis (OR=0.70). There was evidence of a dose-response relationship: women who screened more frequently before their diagnosis (screening 30 months or less before the diagnosis, and two or more prior screens no more than 30 months apart) had an OR of 0.47 of dying from breast cancer, whereas in the remaining BreastScreen participants the OR was 0.64 (compared to non-participants). These figures indicate the magnitude of breast cancer mortality benefits from screening participation to be expected in evaluating BreastScreen Aotearoa (BSA).

The two main purposes of the case-control study are to cross-validate the previous BSA cohort study results and to counter bias stemming from possible loss to follow-up that can affect cohort studies. Notably, not all breast cancer deaths or live controls (non-cases) are required in the case-control study; thus the effects of the tendency for attrition from the cohort from out-migration that leads may artefactually lower mortality are minimised. This enables more reliable estimates of breast cancer mortality in women in relation to their BSA screening exposure. Previous results from the cohort study appear to show a relatively large (an implausible) reduction in breast cancer mortality from screening in Pacific women, despite higher breast cancer mortality in these women compared to all NZ women.[55,56]

A possible scenario for such differential bias could be that ever-screened Pacific women may be more likely to have the means to out-migrate than never-screened Pacific women. This introduces a bias in favour of screening with respect to breast cancer mortality. Thus in the case of Pacific women especially, it is not tenable to assume that a death not recorded in New Zealand is equivalent to being alive, or that unrecorded deaths are equally distributed according to screening exposure. While breast cancer mortality in Pacific women overall is higher than non-Māori, non-Pacific (Other) women, the mortality difference between never-and ever-screened Pacific women might also be higher than in the remaining (Other) population.

The magnitude of the mortality reduction from cohort study likely reflects under-recording of breast cancer mortality in screened Pacific women who may have out-migrated, particularly to their country of origin, after diagnosis of breast cancer. However, an effect of under-ascertainment of deaths on results of analyses of screening participation and breast cancer mortality carries with it the implication that there exists differential under-recording of breast cancer mortality according to screening status. Findings from the cohort study for Pacific women imply screening participation is associated with a higher likelihood of under-recording of mortality in Pacific women diagnosed with breast cancer, and thus a higher likelihood of out-migration than unscreened women. The case-control study is not affected by such differential under-ascertainment of deaths if the living controls can be positively ascertained to be still alive. The availability of the 'last updated' indicator in the demographic details of all screened women, and women diagnosed with breast cancer, allows selection of controls from these data sources to be limited to those still alive at the end of the study period. Those not screened and not diagnosed with breast cancer form the remaining control population which is ascertained by deducting known alive screened or breast cancer controls from the NZ female population (by age group and ethnicity) from population estimates produced by Statistics New Zealand from censuses and interpolations.

In this analysis, only screening mammograms through BreastScreen Aotearoa are considered. Comparisons will be made of the results of the case-control study with findings from the cohort analyses for all New Zealand Women, and for Māori, Pacific and non-Māori and non-Pacific women. Comparison of prognostic indicators for diagnosed breast cancer in relation to mammography screening participation and regularity are contained in the analyses of diagnosed cancers.

The quality and universality of record linkage through the National Health Index (NHI) which links individual person data from the screening services, cancer registry and death register provides the basis upon which both cohort and case-control studies can be implemented.

2.2.2. Comparison of cohort and case control methods

Whereas an **historical cohort** offers a robust design to evaluate the effect of screening on mortality from breast cancer, there are, however, potential disadvantages for subgroups which may leave New Zealand after diagnosis and die elsewhere. Further, for an **inception cohort** the assembly of denominator populations according to screening is complex because of changes in screening exposure over time, and never screened women (alive) without breast cancer can only be estimated in aggregate counts (by age group, ethnicity by period) from deduction of known populations with NHI from the total female (census derived) population. The advantage is that lead time bias does not affect the estimates of any breast cancer mortality differences found between screened and unscreened women in the inception cohort method. **Incidence cohorts** consist of those diagnosed with breast cancer in a given year classified as screened or unscreened at diagnosis, and cumulated mortality rates are compared with the corresponding unscreened and screened populations. The chief disadvantage of this approach is that potential mammographic lead- time bias requires adjustment.

In the context of a population-based study, a **case-control** analysis of screening mammography is most useful when a segment of the population is more likely to be lost to follow-up than the remaining population, which can produce biased estimates if, for example, the loss to follow-up is different between the exposure groups of interest. In the case of New Zealand, despite Pacific women having higher breast cancer mortality than the non-Māori, non-Pacific population,[55,56] the estimated effect of screening on breast cancer mortality in Pacific

women from the cohort analysis appears implausibly large. This suggests that some Pacific women may have artefactually lower breast cancer mortality from under-recording of mortality due to out-migration to the country of origin following cancer diagnosis and treatment, and that out-migration is more common in ever-screened than never-screened women.

A case-control analysis should provide more plausible estimates of the extent of mortality benefit in Pacific women from screening than the cohort analysis.

2.2.3. Data sources

2.2.3.1. Cases: breast cancer deaths

Cases comprise women who have died from breast cancer in New Zealand 1999-2011 from incident breast cancer from 1999. Cases of breast cancer death are determined by the New Zealand Cancer Registry (NZCR) using information on registered cancers linked to death data. Deaths from breast cancer are coded by NZCR according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM), sixth edition, to classify sites and topography.[57] Breast cancers are coded in ICD-10-AM as C50.0 to C50.9. For this report, only breast cancer deaths from breast cancers diagnosed from 1999 onwards are used. This prevents breast cancer mortality emanating from cases diagnosed prior to the advent of screening mammography in New Zealand (1999) contaminating the analysis

2.2.3.2. Controls

The data available make it possible to sample controls known to be alive for case-control studies. Individuals who have been recorded as screening or were diagnosed with breast cancer, have a 'last updated' date flag on their demography table that indicates the last time they were in contact with the health system and therefore known to be alive at the time. These women, matched for age and ethnicity, would be the basis of assembling controls among screened or women diagnosed with cancer.

All such women known to be still alive by the end of the study period (31 December 2011) are used as part of the controls. The remaining controls comprise those not screened and not diagnosed with cancer that nonetheless are enumerated in the population. In short, living controls come from:

1. Those ever-screened or diagnosed with cancer in the population known to be alive at the time of death of a given case.

2. Those never-screened and counted in the population at the time of death of a given case.

At a given time (i.e. year), the never-screened population without breast cancer, is derived by subtracting those known to be ever-screened (and still alive) at the time from the overall population from census derived data for that time. The only information available on never-screened women not diagnosed with, or dying from, breast cancer, is: 5-year age group, ethnicity and year.

A case control study at a whole-population level involves a strata-matched analysis, matched on year of death (or diagnosis), age group at diagnosis and ethnicity. Using controls known to be alive for whole the study period ensures that mortality differentials that may emanate from attrition bias are minimised.

Screening exposure for cases (breast cancer deaths), such as ever-screened or never-screened women, is relevant only at time of diagnosis of breast cancer, not at the time of death from breast cancer. Correspondingly, screening exposure in controls also needs to be measured at the same time as when cases are diagnosed, not when they died. Thus control populations are defined in relation to the case at the time (e.g. year) of diagnosis.

2.2.4. Analysis

2.2.4.1. Analytic design

Analyses confined to screened women, or those diagnosed with cancer, are exclusively of individuals and use more information than analyses also utilising data on residual unscreened populations without breast cancer (obtained by subtraction from census derived populations by age and ethnic group by period). Living controls come from all screened women or diagnosed breast cancers known to be still alive at the time of a breast cancer death, matched on ethnicity and age and year at diagnosis. The ever- or never-screened status of each woman before breast cancer diagnosis is known, and the controls are known to be alive up to the date of death of a case by their 'last updated' date flag.

Within screened women, more information is known at an individual level. In particular, screening status changes can be tracked to enable valid classification of screening exposure in controls prior to breast cancer diagnosis in cases of breast cancer death at a given time. All available records were used, and the 'last updated' flag used to classify controls validly as alive. Over the whole study period the same individuals will be in different screening exposure categories at different times.

Given the size of the population and data available, controls for this study are restricted to those known to be alive by the end of the study period. Cases with the longest follow-up time from diagnosis to death (i.e. diagnosed in 1999, died in 2011) are matched with controls of the same age and still alive in 2011.

Lesser information is available on unscreened women without breast cancer obtained by deduction by age group, ethnicity and period from census derived NZ populations. However, such controls by ethnicity are alive and within a 5 year age group at particular periods.

As this is a case-control study with the endpoint being death from breast cancer examined against retrospective information on exposure to screening in cases versus controls at the time of diagnosis, time from cancer diagnosis to cancer death is not used in this analysis. In cases of breast cancer mortality, the relevant exposure factor is screening prior to cancer diagnosis regardless of when the breast cancer death occurs. Thus lead-time bias is not a factor that influences this analysis and does not require adjustment.

2.2.4.2. Adjustment for screening selection bias

Adjustment for screening selection bias is as for the inception cohort (p.24 of this report).

2.2.4.3. Statistical analysis

Statistical analyses were performed by conditional logistic regression using PROC GENMOD in SAS© software, with a logit link function and a binary distribution, with strata matching by age and ethnicity.

Repeated measures analysis was employed in the statistical modelling since strata matching and repeated measures analyses produce the same standard errors, which are larger than in a naïve analysis.

As in the cohort study, screening selection bias is controlled for in this case-control study when the never-screened are included in the analyses.[43] A relative risk of 1.17 is employed for breast cancer mortality in those declining to screen when offered, compared to a population not offered screening.[46] In adjusting for screening selection bias for the period 2001-11, mean screening participation rates of 64% are used for the whole population, 45% for Māori, 49% for Pacific and 68% for Other women.[41] Adjustment for screening selection bias for the most recent period 2012-13 uses mean screening participation rates of 71% for the whole population, 65% for Māori, 72% for Pacific and 72% for Other women.[41] Analogous to the cohort analysis, estimates of ever-screening compared to never-screening are first derived from logistic regression modelling and then adjusted for screening selection bias.

2.2.5. Hypotheses for testing in the case-control study

The hypotheses (H) for testing in the case control study are:

H1: That mortality from breast cancer in New Zealand women ever exposed to screening mammography is significantly lower than in women never exposed to screening mammography.

H2: In ever-screened women higher frequency of, and smaller time intervals between, screening mammograms is associated with lower breast cancer mortality H2 is operationalised as follows: in ever-screened women, those screened 3 or more times previously with a mean screening interval of ≤30 months had significantly lower breast cancer mortality than ever-screened women who screened less frequently.

H3: Women with screen-detected breast cancer have lower breast cancer mortality than women with non-screen detected cancer. H3 is operationalised as follows:

> **H3a:** Breast cancer mortality in women with screen-detected cancer is significantly lower than in women with non-screen detected breast cancer.
>
> **H3b:** Breast cancer mortality in ever-screened women whose breast cancer is not screen detected is lower than in corresponding never-screened women.

H4: Despite higher breast cancer mortality in Māori and Pacific women, those who have ever attended screening mammography will have significantly lower breast cancer mortality compared to never-screened Māori and Pacific women.

Appendix for Chapter 2: Methods

A.1. Data Sources and Assembly

The steps involved in assembling the data were as follows:

1. Verification of BSA NHI data accuracy
2. Resolution of BSA NHI data discrepancies and the extraction, cleaning and processing of BSA evaluation data
3. Construction of the evaluation cohort
4. Data exaction from the NZ Cancer Registry and NZ Mortality Data Collection
5. Creation of the four evaluation datasets and supply of supporting information

A.2. Verification of BSA NHI data accuracy

In preparation for BSA data being matched via National Health Index (NHI) against NZ Cancer Registry and Mortality Collections data for the mortality evaluation dataset, the National Screening Unit (NSU) collaborated with the New Zealand Ministry of Health Identity Data Management Team to help verify the level of accurateness of BSA NHIs.

NSU supplied the Identity Data Management Team with an extract of all BSA NHIs with corresponding name(s), date of birth and address details of all women screened by BSA during the evaluation period (1 January 1999 to 31 December 2011). This initial extract contained 600,256 BSA NHIs. These data were all derived from screening client records held by BSA Lead Providers with the most recent screening episode for that NHI within in the specified period.

Address fields, whilst not critical for the matching process, were used during manual matching (clerical review) for records not successfully linked via automated matching.

Originally, 39,914 BSA NHIs were unable to be linked due to one or more discrepancies. However, following further investigations of unmatched records by the Identity Data Management team, this figure reduced to 31,867 BSA NHIs with discrepancies.

The 31,867 NHIs with discrepancies were then categorised under one or more of the following:

- Different NHI Match: 721 BSA NHIs were matched to a different NHI in the NHI database. For these records, the Identity Data Management Team supplied the NSU what they believed to be the correct NHI. The NSU found 224 of the supplied NHIs were already in the BSA database.
- Suspect Auto-merges: 17,853 BSA NHIs were found to have no exact match of gender and date of birth or the address details had a different domicile code compared with that held in the NHI database. It is believed that these records were the result of a past auto merge exercise to merge duplicate records in the NHI database.
- Unmatched: 79 BSA NHIs were not found in the NHI database and their details were not able to be matched to another NHI within the NHI database.
- Secondary NHI: 5,762 BSA NHIs were found to be the secondary NHI rather than the primary NHI. For these records, the Identity Data Management Team supplied the NSU the corresponding primary NHIs. The NSU found 2,475 of the supplied primary NHIs were already in the BSA database.
- Potential Overlays: 8,503 BSA NHIs were identified as being potentially overlaid (overwritten) in the past with another person's information due the use of an incorrect NHI.

A.3. Resolution of BSA NHI data discrepancies and the extraction, cleaning and processing of BSA evaluation data

Based on the authors' feedback, the NSU re-extracted BSA NHIs and required data fields for all women screened by BSA from 1 January 1999 to 31 December 2011 and applied the following BSA NHI discrepancy resolutions:

Different NHI Match: NSU updated the 721 BSA NHIs in the BSA mortality evaluation dataset to reflect what the Identity Data Management Team indicated the correct NHI should be. For the 224 records where the correct NHI already contained screening records in the BSA database, NSU merged both sets of records and deleted duplicate data. Where the NSU found that the two sets of screening data were for different women, the two NHIs and corresponding screening records were kept separate. All records associated with being incorrect NHIs were identified in the BSA mortality evaluation dataset as 'different NHI match' records.

Suspect auto-merge: NSU included the 17,853 suspect auto-merge records in the BSA mortality evaluation dataset. These records were identified in the BSA mortality evaluation dataset as 'suspect auto-merge' records. This was done to allow sensitivity analyses with and without the suspect auto-merge records to evaluate the effect of their inclusion or exclusion in the evaluation.

Unmatched NHIs: NSU included the 79 unmatched records and were identified in the BSA mortality evaluation dataset as 'unmatched NHI' records. This to allow the sensitivity analyses with and without the unmatched records to evaluate the effect of their inclusion or exclusion in the evaluation.

Secondary NHIs: NSU updated the 5,762 secondary NHIs to primary NHIs. Where the primary NHI (2,475 records) already contained screening records in the BSA database, NSU merged both sets of records and de-duplicated the data. Where the NSU found that the two sets of screening data were for different women, the two NHIs and corresponding screening records were kept separate. All records associated with being 'secondary NHI' records were identified in the BSA mortality evaluation dataset as 'secondary NHI' records.

Potential Overlays: NSU included the 31,867 potential overlay records in the BSA mortality evaluation dataset. These records were identified as 'potential overlay' records. This was to allow sensitivity analyses with and without the potential overlay records to evaluate the effect of their inclusion or exclusion in the evaluation.

A 'change reason' field was added to the evaluation dataset to indicate where an NHI and associated screening episode data had been modified for the evaluation dataset.

The resulting BSA mortality evaluation dataset contained the following information for 597,459 women screened by BSA during the evaluation period:

NHI, date of birth, ethnic group, gender, date and screening episode number for each screen an individual has with BSA, corresponding final clinical decision by the radiologist, final definitive diagnosis from any assessment, information on non-completed assessments, the code of the BSA Lead Provider for each screen, and the District Health Board (DHB) the woman was domiciled to at the time her screen.

Obviously, not all the above variables were used in the analyses presented in this evaluation report.

Originally only NHI demographic details held by National Collections for each BSA screened woman were to be used in the analysis. Following Ministry of Health Identity Data Management Team investigations suggesting that a number of BSA NHIs could possibly have been affected by past NHI merging and overlaying (overwriting) with another person's information, date of birth, gender and ethnicity fields for BSA screened

women were used to help identify any discrepancies following the BSA NHI match with Cancer Registry and Mortality Data Collection data. The matching against NZ Cancer Registry and NZ Mortality Collections was performed by the Ministry of Health Analytical Team.

To ensure the confidentiality of BSA screened women, no names or addresses were sent to Analytical Services or the evaluators. To further protect confidentiality, Analytical Services replaced all NHIs with an encrypted NHI and added a master encrypted NHI number.

A.4. Construction of the evaluation cohort

Analytical Services built the evaluation cohort from all master encrypted NHIs that met one of the following conditions:

- Were supplied in the mortality evaluation dataset of BSA screened women
- Had any breast cancer registration (ICD-10 codes C50, D05, D24 or D48.6) 1 January 1999 to 31 December 2011, and sex = Female
- Have a death registration from 1 January 1999 to 31 December 2011 with any clinical code indicating breast cancer (ICD-10 codes C50, D05, D24 or D48.6), and sex = Female

For each of the encrypted NHIs, Analytical Services extracted the following fields from the NHI database: master encrypted NHI, date of birth, sex, ethnicity 1, ethnicity 2, ethnicity 3, prioritised ethnic group code, domicile code, DHB of domicile code, date of death, last updated date.

A.5. Data extraction from the NZ Cancer Registry and the NZ Mortality Data Collection

The BSA mortality evaluation dataset provided by NSU was used by Analytical Services to extract all breast cancer registrations and all deaths of women screened by BSA from 1 January 1999 to 31 December 2011. From the NZ Cancer Registry, breast cancer registrations (ICD-10 codes C50, D05, D24 or D48.6) from 1 January 1999 to 31 December 2011 were extracted with the following fields:[53]

master encrypted NHI, event encrypted NHI, year of diagnosis, site code (ICD-10), date of diagnosis, age at diagnosis, date of birth, sex, domicile code, DHB of domicile, ethnicity 1, ethnicity 2, ethnicity 3, prioritised ethnic group code, morphology code, basis of diagnosis, laboratory code, cancer notes, extent of disease, laterality, grade of tumour code, positive nodes, nodes tested flag, total nodes sampled, smoking History flag, TNM-M, TNM-N, TNM-T, ER status, Her2 status, Her2 test type, histopathology code, lymphovascular invasion flag, multi-centric or multifocal tumour flag, positive sentinel nodes, PR status, resection margin, sentinel nodes sampled, size of tumour, and multiple tumours flag.

From the Mortality Data Collection, Analytical Services extracted all deaths from 1 January 1999 to 31 December 2011 along with the following fields:

master Encrypted NHI, event Encrypted NHI, registration year, country of birth, date of birth, death type, age at death, sex, prioritised ethnicity, ethnicity 1, ethnicity 2, ethnicity 3, domicile code, DHB of domicile, years in New Zealand, death date, underlying cause of death (diagnosis Type “D”), other relevant diseases present (B1) (Diagnosis Type “F”), other contributing causes (B2) (e.g. medical misadventure) (Diagnosis Type “G”), cancer as a non-contributing cause of death (Diagnosis Type “C”), certifier of death, post mortem indicator, death information source, and clinical notes.

Again, not all the above variables were used in the analyses for this report. As there were multiple ethnicity fields, a person was classified according to the prioritised ethnicity field accordingly as Māori, Pacific or

'Other'. If codes for Māori or Pacific appeared in any of the remaining ethnicity fields but not in the prioritised ethnicity field they were re-classified as Māori or Pacific accordingly. If a code for both Pacific and Māori was present in any of the remaining fields, then the person was classified as Pacific.

A.6. Creation of the four evaluation datasets and supply of supporting information

As a result of the above data extractions, Analytical Services created four evaluation datasets as follows:

- BSA screening data for women screened 1 January 1999 to 31 December 2011
- BSA demographic data for women screened 1 January 1999 to 31 December 2011
- Cancer registration data 1 January 1999 to 31 December 2011
- Mortality collection data 1 January 1999 to 31 December 2011 (registration year)

The datasets were password-protected and sent to the evaluators in a secure manner. Separately, the NSU supplied the evaluators the following information:

- The BSA mortality evaluation data specification document
- The NZ Cancer Registry Data Dictionary
- The NZ Mortality Collection Data Dictionary
- BSA codes for the data fields plus mapping of BSA Data Management Manual fields and codes to evaluation fields and codes
- Business rules for created field Final Assessment Outcome
- Population denominators for total, Māori and Pacific females by five year age groupings for the years 1999 to 2011.

CHAPTER 3: RESULTS

3.1. INCEPTION COHORT STUDY

3.1.1. Screening inception cohort

This section analyses breast cancer mortality in all women. Never- and ever-screened women are compared first, then regularity of screening in screened women is examined. For the analysis of breast cancer mortality in ever- and never- screened women, person years exposed to screening or to never screening is used as the basis for the offset in the Poisson/negative binomial regression modelling. This approach is detailed in the Methods section. This differs from an incidence cohort approach because it minimises the effect of artefactually longer times in screen-detected cancers, due to lead time from diagnosis to death or to the end of the study expected in screened women, which can bias results based on cancer case cohorts defined by time of diagnosis rather than time of first screening mammogram.

A detailed breakdown of breast cancer deaths by year of death by the ever- and never- screened population at the beginning of each year shows the extent of breast cancer mortality difference between the ever- and never-screened populations (Tables 3.2a, 3.2b).

Table 3.2a: Cohort populations and person years of ever- and never-screened women by breast cancer mortality and year of death from breast cancers diagnosed in 2000-2011, all New Zealand women aged 45-69 years.

Year of Death	Ever-screened			Never-screened		
	Population†	Person years	Breast Cancer deaths	Population†	Person years	Breast Cancer deaths
All						
2000	75,562	75,562	5	580,494	580,494	112
2001	154,117	229,612	17	516,246	1,032,492	193
2002	189,075	418,150	27	503,245	1,376,937	244
2003	216,368	633,114	45	492,249	1,696,190	264
2004	240,501	871,106	64	485,611	2,006,453	279
2005	264,539	1,132,195	69	479,766	2,301,812	336
2006	306,023	1,432,983	79	456,778	2,560,596	315
2007	359,385	1,785,670	97	430,703	2,750,229	331
2008	408,896	2,185,630	95	401,855	2,877,408	350
2009	453,086	2,627,404	120	378,058	2,982,745	377
2010	497,697	3,110,437	132	352,890	3,062,181	340
2011	542,234	3,635,261	123	327,623	3,113,051	370
2000-11	3,707,483	18,137,124	873	5,405,518	26,340,588	3,511

† As at the beginning of year

Thus from above the breast cancer mortality 2000-11 is 23.5 per 100,000 for ever screened and 65.0 per 100,000 for never screened. The unadjusted mortality reduction from screening is thus 64%. The breast cancer mortality age 45-69 years 2000-11 was 48.1 per 100,000.

Table 3.2b: Cohort populations and person years of ever- and never-screened women by ethnicity, breast cancer mortality and year of death from breast cancers diagnosed in 2000-2011, women aged 45-69 years

Year of Death	Ever-screened			Never-screened		
	Population†	Person years	Breast Cancer deaths	Population†	Person years	Breast Cancer deaths
Māori						
2000	4,771	4,771	1	43,509	43,509	11
2001	10,350	15,111	2	40,178	80,356	17
2002	13,040	28,075	2	39,968	104,943	32
2003	15,214	43,049	5	38,323	122,590	27
2004	17,373	59,995	10	38,824	145,685	31
2005	19,375	78800	7	39,750	170,480	32
2006	22,998	100,955	6	39,182	193,789	43
2007	27,588	127,478	13	37,143	203,269	40
2008	33,018	159,176	16	34,828	209,405	41
2009	38,338	195,714	10	32,563	211,670	41
2010	43,868	237,329	25	29,841	211,087	42
2011	49,369	284,125	19	27,007	207,834	35
2000-11	295,302	1,334,578	116	441,116	1,904,617	392
Pacific						
2000	1,552	1,552	0	15,518	15,518	2
2001	3,214	4,766	2	14,911	29,822	10
2002	4,180	8,924	1	16,730	44,642	10
2003	5,227	14,101	1	16,418	54,244	9
2004	6,279	20,293	4	16,321	63,728	16
2005	7,244	27,418	2	16,356	73,256	10
2006	8,248	35,521	3	16,425	83,355	18
2007	10,319	45,614	0	16,307	91,476	17
2008	13,137	58,390	2	14,511	90,566	14
2009	15,907	73,898	4	13,003	88,469	20
2010	18,635	92,003	6	11,376	84,211	26
2011	21,830	113,205	5	9,477	76,769	20
2000-11	115,772	495,685	30	177,353	796,056	172
Other (non-Māori, non-Pacific)						
2000	69,239	69,239	4	521,467	521,467	99
2001	140,553	209,735	13	461,157	922,314	166
2002	171,855	381,151	24	446,547	1,227,352	202
2003	195,927	575,964	39	437,508	1,519,356	228
2004	216,849	790,818	50	430,466	1,797,040	232
2005	237,920	1,025,977	60	423,660	2,058,076	294
2006	274,777	1,296,507	70	401,171	2,283,452	254
2007	321,478	1,612,578	84	377,253	2,455,484	274
2008	362,741	1,968,064	77	352,516	2,577,437	295
2009	398,841	2,357,792	106	332,492	2,682,606	316
2010	435,194	2,781,105	101	311,673	2,766,883	272
2011	471,035	3,237,931	99	291,139	2,828,448	315
2000-11	3,296,409	16,306,861	727	4,787,049	23,639,915	2,947

† As at the beginning of year

3.1.2. Ever- compared to never screened women

3.1.2.1. 1999-2011

All New Zealand women

The breast cancer mortality differences between ever- and never-screened women in Tables 3.2a and 3.2b - for example, 873 deaths from 18 million person years versus 3,511 deaths from 26 million person years - are reflected in the estimated breast cancer mortality reduction of 62% overall, in ever- compared to never-screened women after adjusting for age and ethnicity (Table 3.3). Adjusted for screening selection bias employing an estimated relative risk in women not participating in screening compared to women not offered screening of 1.17, and based on the recorded mean screening participation rate for 2001-11 of 64%, the estimated mortality reduction is 29%. That is, the breast cancer mortality reduction attributable to screening is 29%, in a population offered screening compared to breast cancer mortality in a contemporaneous population not offered screening. For there to be no mortality reduction from screening mammography, the relative risk of breast cancer mortality in women never screened (the referent category) compared to a whole population of women not offered screening would need to be 1.66. Based on recorded screening rates for 2012-13 (71%), the mortality reduction is estimated as 34%, similar to that for the target screening participation rate of 70%.[49]

Table 3.3: Relative risk[†] of breast cancer mortality in ever- and never-screened New Zealand women, 1999-2011

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Never screened			**1.00**	
Ever screened	**-0.9685 (0.1273)**	**<.0001**	**0.38 (0.30-0.49)**	**-62 (-70 to -51)**
Ever screened (adj)[a]	-	-	**0.71 (0.62-0.80)**	**-29 (-38 to -20)**
Ever screened (adj)[b]	-	-	**0.66 (0.57-0.75)**	**-34 (-43 to -25)**
Ever screened (adj)[c]	-	-	**0.66 (0.58-0.76)**	**-34 (-42 to -24)**
Variables adjusted				
Age at death (yr):				
60-64			1.00	
45-49	-0.0628 (0.0512)	0.2198	0.94 (0.85-1.04)	-6 (-15 to +4)
50-54	-0.2660 (0.0742)	0.0003	0.77 (0.66-0.89)	-23 (-34 to -11)
55-59	-0.1378 (0.0582)	0.0179	0.87 (0.78-0.98)	-13 (-22 to -2)
65-69	-0.0608 (0.0336)	0.0704	0.94 (0.88-1.01)	-6 (-12 to +1)
70-74	-0.1211 (0.0625)	0.0526	0.89 (0.78-1.00)	-11 (-22 to 0)
75-79	-0.0676 (0.0846)	0.4242	0.93 (0.79-1.10)	-7 (-21 to +10)
80-84	-0.0072 (0.1587)	0.9637	0.99 (0.73-1.36)	-1 (-27 to +36)
85+	0.5230 (0.1082)	<.0001	1.69 (1.36-2.09)	69 (36 to 109)
Ethnicity:				
Other			1.00	
Māori	0.5130 (0.0475)	<.0001	1.67 (1.52-1.83)	67 (52 to 83)
Pacific	0.4668 (0.0606)		1.59 (1.42-1.80)	59 (42 to 80)
Intercept	-8.8737 (0.0784)	<.0001		

[†] From negative binomial regression model adjusted for repeat measures, screening inception cohort

[a] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and mean screening participation rate of 64% for 2001-11

[b] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and recorded screening participation rate of 71% for 2012-13

[c] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and target screening participation rate of 70%

Māori women

In Māori women the estimated breast cancer mortality in those ever screened was 60% lower than in never-screened Māori women (Table 3.4). Based on an estimated relative risk in non-screeners compared to women not offered screening of 1.17 and for mean screening participation of 48% for 2001-11, the estimated mortality reduction in Māori women with screening available is 17% compared to estimated breast mortality occurring in the same population if screening were not offered. If there were no screening effect, the relative risk of breast cancer mortality for 2001-11 in Māori women never screened compared to Māori women not offered screening would need to be 1.40. Based on the recorded 2012-13 screening participation rate for Māori women of 65%, the estimated breast cancer mortality reduction is 28%, and would be 32% if the screening target participation rate of 70% were achieved.

Table 3.4: Relative risk[†] of breast cancer mortality in ever- and never-screened Māori New Zealand women, 1999-2011

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Never screened			**1.00**	
Ever screened	**-0.9105 (0.1387)**	**<.0001**	**0.40 (0.31-0.53)**	**-60 (-69 to -47)**
Ever screened (adj)[a]			**0.83 (0.75-0.93)**	**-17 (-25 to -7)**
Ever screened (adj)[b]			**0.72 (0.62-0.82)**	**-28 (-38 to -18)**
Ever screened (adj)[c]			**0.68 (0.59-0.79)**	**-32 (-41 to -21)**
Variables adjusted				
Age at death (yr):				
60-64			1.00	
45-49	-0.0645 (0.0468)	0.1687	0.94 (0.86-1.03)	-6 (-14 to +3)
50-54	-0.2001 (0.0367)	<.0001	0.82 (0.76-0.88)	-18 (-24 to -12)
55-59	-0.0396 (0.0096)	<.0001	0.96 (0.94-0.98)	-4 (-6 to -2)
65-69	-0.1461 (0.0117)	<.0001	0.86 (0.84-0.88)	-14 (-16 to -12)
70-74	-0.0807 (0.0402)	0.0445	0.92 (0.85-1.00)	-8 (-15 to 0)
75-79	-0.3029 (0.0597)	<.0001	0.74 (0.66-0.83)	-26 (-34 to -17)
80-84	-0.5200 (0.0605)	<.0001	0.59 (0.53-0.67)	-41 (-47 to -33)
85+	0.2041 (0.0604)	0.0007	1.23 (1.09-1.38)	23 (9 to 38)
Intercept	-8.3641 (0.0605)	<.0001	-	-

[†] From Poisson regression model adjusted for repeat measures and over-dispersion, screening inception cohort

[a] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and mean screening participation rate of 48% for 2001-11

[b] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and recorded screening participation rate of 65% for 2012-13

[c] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and target screening participation rate of 70%

Pacific women

In Pacific women, the estimated breast cancer mortality reduction in those ever-screened was 74% compared to never-screened women (Table 3.5). Using the estimated relative risk in women never screened compared to women not offered screening of 1.17 and the mean screening participation rate of 49% for 2001-11, the adjusted mortality reduction in Pacific women offered screening is 24% (compared to a contemporaneous population of Pacific women not offered screening). If there were no screening effect, the relative risk of breast cancer mortality in Pacific women participating in screening compared to Pacific women not offered screening would need to be 1.57 for 2001-11. Based on reported screening participation for 2012-13 of 72%, the estimated mortality reduction in Pacific women is 45%, and 43% if Pacific women screened at the target participation rate of 70% (lower than that recorded for 2012-13).

It should be noted that these estimates of breast cancer mortality reduction in Pacific women associated with screening may reflect under-recording of breast cancer mortality in screened compared to unscreened Pacific women, from possible differential out-migration to Pacific countries of origin to die.

Table 3.5: Relative risk[†] of breast cancer mortality in ever- and never-screened Pacific Zealand women, 1999-2011

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Never screened			**1.00**	
Ever screened	**-1.3301 (0.1472)**	**<.0001**	**0.26 (0.20-0.35)**	**-74 (-80 to -65)**
Ever screened (adj)[a]			**0.76 (0.68-0.86)**	**-24 (-32 to -14)**
Ever screened (adj)[b]			**0.55 (0.48-0.63)**	**-45 (-52 to -37)**
Ever screened (adj)[c]			**0.57 (0.50-0.65)**	**-43 (-50 to -35)**
Variables adjusted				
Age at death (yr):				
60-64			1.00	
45-49	-0.2394 (0.0375)	<.0001	0.79 (0.73-0.85)	-21 (-27 to -15)
50-54	-0.2395 (0.0311)	<.0001	0.79 (0.74-0.84)	-21 (-26 to -16)
55-59	-0.3056 (0.0092)	<.0001	0.74 (0.72-0.75)	-26 (-28 to -25)
65-69	-0.2698 (0.0125)	<.0001	0.76 (0.75-0.78)	-24 (-25 to -22)
70-74	-0.5166 (0.0353)	<.0001	0.60 (0.56-0.64)	-40 (-44 to -36)
75-79	-0.1578 (0.0467)	0.0007	0.85 (0.78-0.94)	-15 (-22 to -6)
80-84	-0.8420 (0.0472)	<.0001	0.43 (0.39-0.47)	-57 (-61 to -53)
85+	0.0005 (0.0472)	0.9911	1.00 (0.91-1.10)	0 (-9 to +10)
Intercept	-8.1746 (0.0473)	<.0001	-	-

[†] From Poisson regression model adjusted for repeat measures and over-dispersion, screening inception cohort

[a] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and mean screening participation rate of 49% for 2001-11

[b] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and recorded screening participation rate of 72% for 2012-13

[c] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and target screening participation rate of 70%

Other (non-Māori, non-Pacific) women

In Other (non-Māori, non-Pacific) women, the estimated breast cancer mortality reduction was 60% in ever- compared to never-screened women (Table 3.6). Using the estimated relative risk in non-screeners compared to women not offered screening of 1.17, and mean screening participation of 66% for 2001-11, the estimated mortality reduction in Other women with screening available is 29% compared to the estimated breast cancer mortality risk in this population if screening were not available. If there were no screening effect, the relative risk of breast cancer mortality (for 2001-11) in Other women not participating in screening compared to Other women not offered screening would need to be 1.65. Based on reported 2012-13 screening participation of 72% in Other women offered screening, the estimated breast cancer mortality reduction was 33% compared to that in Other women not offered screening. If Other women screened at the target rate of 70% (lower than for 2012-13), the corresponding breast cancer mortality reduction is estimated as 32%.

Table 3.6: Relative risk[†] of breast cancer mortality in ever- and never-screened Other (non-Māori, non-Pacific) New Zealand women, 1999-2011

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Never screened			**1.00**	
Ever screened	**-0.9181 (0.1882)**	**<.0001**	**0.40 (0.28-0.58)**	**-60 (-72 to -42)**
Ever screened (adj)[a]			**0.71 (0.59-0.84)**	**-29 (-41 to -16)**
Ever screened (adj)[b]			**0.67 (0.55-0.81)**	**-33 (-45 to -19)**
Ever screened (adj)[c]			**0.68 (0.56-0.82)**	**-32 (-44 to -18)**
Variables adjusted				
Age at death (yr):				
60-64			1.00	
45-49	-0.0189 (0.0626)	0.7626	0.98 (0.87-1.11)	-2 (-13 to +11)
50-54	-0.3275 (0.0244)	<.0001	0.72 (0.69-0.76)	-28 (-31 to -24)
55-59	-0.1672 (0.0025)	<.0001	0.85 (0.84-0.85)	-15 (-16 to -15)
65-69	-0.0053 (0.0125)	0.6749	0.99 (0.97-1.02)	-1 (-3 to +2)
70-74	-0.0530 (0.0583)	0.3636	0.95 (0.85-1.06)	-5 (-15 to +6)
75-79	0.0247 (0.1038)	0.8120	1.03 (0.84-1.26)	3 (-16 to +26)
80-84	0.2138 (0.1100)	0.0519	1.24 (1.00-1.54)	24 (0 to 54)
85+	0.6720 (0.1100)	<.0001	1.96 (1.58-2.43)	96 (58 to 143)
Intercept	-8.9241 (0.1100)	<.0001	-	-

[†] From Poisson regression model adjusted for repeat measures and over-dispersion, screening inception cohort

[a] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and mean screening participation rate of 66% for 2001-11

[b] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and recorded screening participation rate of 72% for 2012-13

[c] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and target screening participation rate of 70%

3.1.2.2. All New Zealand women by period

Mortality reduction by period can be arranged by **year of death** from cancers incident since 1999. Corresponding with period, the estimated mortality reduction in ever-screened compared to never-screened women showed a progressive increase, from 56% during 1999-2004 to 66% by 2010-11 (for all NZ women) (Table 3.7). The corresponding estimates of mortality decline by period after adjustment for screening selection bias were 24%, 27% and 37% for RR=1.17 and recorded screening participation of 63%, 63% and 70% for each period respectively. These estimates can reflect increasing selection effects among women who have never screened.

Table 3.7: Relative risk[†] of breast cancer mortality in ever- and never- screened New Zealand women, by period, 2000-2011

Period	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
2000-04	-0.8112 (0.1641)	<.0001	0.44 (0.32-0.61)	-56 (-68 to -39)
2000-04 (adj)[a]	-	-	0.76 (0.67-0.88)	-24 (-33 to -12)
2005-09	-0.9186 (0.1489)	<.0001	0.40 (0.30-0.53)	-60 (-70 to -47)
2005-09(adj)[a]	-	-	0.73 (0.66-0.82)	-27 (-34 to -18)
2010-11	-1.0924 (0.1941)	<.0001	0.34 (0.23-0.49)	-66 (-77 to -51)
2010-11(adj)[a]			0.63 (0.53-0.75)	-37 (-47 to -25)

[†] From negative binomial regression model adjusted for repeat measures, screening inception cohort

[a] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17, with recorded screening participation rates of 63%, 63% and 70% for 2001-04, 2005-2009, 2010-2011, respectively

Māori women by period

In Māori women, the relative breast cancer mortality difference between ever- and never-screened women did not increase consistently over the 3 periods (55%, 61% and 57%, Table 3.8), although the mortality difference increased more consistently with time when adjusted for screening selection bias. In relation to a similar population not offered screening breast cancer mortality reduction increased from 11% to 25% over 2000-2011.

Table 3.8: Relative risk[†] of breast cancer mortality in ever- and never- screened New Zealand Māori women, by period, 2000-2011/13

Period	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
2000-04	-0.7960 (0.1411)	<.0001	0.45 (0.34-0.59)	-55 (-66 to -41)
2000-04 (adj)[a]	-	-	0.89 (0.80-0.98)	-11 (-20 to -2)
2005-09	-0.9294 (0.1235)	<.0001	0.39 (0.31-0.50)	-61 (-69 to -50)
2005-09(adj)[a]	-	-	0.83 (0.76-0.92)	-17 (-24 to -8)
2010-11	-0.8399 (0.3204)	0.0088	0.43 (0.23-0.81)	-57 (-77 to -19)
2010+ (adj)[a]			0.75 (0.57-0.99)	-25 (-43 to -1)

[†] From negative binomial regression model adjusted for repeat measures, screening inception cohort

[a] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17, with recorded screening participation rates of 44%, 47% and 63% in Māori women for 2001-04, 2005-2009, 2010-2011, respectively

Pacific women by period

In Pacific women, small numbers precluded a period breakdown of breast cancer mortality differences by ever- and never-screened status, so it is not possible to make any statements regarding possible trends in these differences (Table 3.9)

Table 3.9: Relative risk[†] of breast cancer mortality in ever- and never- screened New Zealand Pacific women, by period, 2000-2011

Period	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
2000-04	[Model failed to converge]	-	-	-
2000-04 (adj)[a]	-	-	-	-
2005-09	-1.5091 (0.2706)	<.0001	0.22 (0.13-0.38)	-78 (-87 to -62)
2005-09(adj)[a]	-	-	0.72 (0.64-0.81)	-28 (-36 to -19)
2010-11	[Model failed to converge]	-	-	-
2010+ (adj)[a]	-	-	-	-

[†] From negative binomial regression model adjusted for repeat measures, screening inception cohort

[a] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17, with recorded screening participation rates in Pacific women of 43%, 49% and 65% for 2001-04, 2005-2009, 2010-2011, respectively

Other women by period

In Other (non-Māori, non-Pacific) women, the breast cancer mortality differences between ever- and never-screened women were largely unchanged (58%) over the 3 periods (Table 3.10). Due to increased screening participation during 2010-11, the breast cancer mortality reduction in relation to a similar population of women not offered screening (after adjusting for screening selection bias) increased to 32% (from 27%).

Table 3.10: Relative risk[†] of breast cancer mortality in ever- and never- screened Other (non-Māori, non-Pacific) New Zealand women, by period, 1999-2011/13

Period	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
2000-04	-0.8591 (0.2091)	<.0001	0.42 (0.28-0.64)	-58 (-72 to -36)
2000-04 (adj)[a]	-	-	0.73 (0.60-0.89)	-27 (-40 to -11)
2005-09	-0.8733 (0.1872)	<.0001	0.42 (0.29-0.60)	-58 (-71 to -40)
2005-09(adj)[a]	-	-	0.73 (0.61-0.87)	-27 (-39 to -13)
2010-11	-0.8980 (0.3671)	0.0144	0.41 (0.20-0.84)	-59 (-80 to -16)
2010+ (adj)[a]			0.68 (0.47-0.98)	-32 (-53 to -2)

[†] From negative binomial regression model adjusted for repeat measures, screening inception cohort

[a] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17, with recorded screening participation rates in Other women of 65%, 65% and 71% for 2001-04, 2005-2009, 2010-2011, respectively

It should be noted that observed changes with time in relative risk of breast cancer mortality for never compared to ever-screened can reflect changing screening selection effects. That is, with increases over time in screening population coverage, the remaining never-screened group may have correspondingly different absolute breast cancer mortality which contributes to the secular changes in relative risk of breast cancer mortality in the ever-screened group.

3.1.3. Regularity of screening in screened women

3.1.3.1. Regularity indicator: Screened ≥ 3 times with a mean screening interval of ≤ 30 months

The indicator of regularity of screening in this analysis is screened at least 3 times with a mean screening interval of 30 months or less. Age at first screen, to indicate earlier or later exposure to screening, is controlled for, along with ethnicity. Breast cancer mortality in relation to screening is also analysed separately

by ethnic group. Age at first screen is used in the models to minimise the chance of bias in the age estimates due to higher likelihood of diagnosis of breast cancer at a younger age in screened versus unscreened women, from lead time.

As a result of non-converging Hessian matrices in negative binomial regression models of screening in Māori and Pacific women, Poisson regression models with adjustment for over-dispersion were used. Model coefficients and standard errors in the non-Hessian matrix converging negative binomial models were identical to those from the unadjusted (for over-dispersion) Poisson models. Over-dispersion adjusted Poisson models produce identical regression estimates with standard errors inflated by (*model deviance) / (model degrees of freedom)* to adjust for over-dispersion. Note also that the period of interest for this analysis is limited by adequate numbers of women who became regular screeners, which was from 2003 overall, and from 2004 for Māori and Pacific women. Also, for repeat measures analysis, individual strata measured repeatedly (age group and ethnicity, for each year) need to have offset populations for both regular and non-regular screeners.

3.1.3.1.1. Comparison of regular and irregular screening in ever-screened women

All New Zealand screened women: regularity of screening

Women who had screened three or more times with an average screening interval of 30 months or less were estimated to have 81% lower breast cancer mortality risk than women who screened less often or regularly which was statistically significant (Table 3.11).

Table 3.11: Relative risk[†] of breast cancer mortality, ever-screened New Zealand women, breast cancers diagnosed 2003-2011

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Not screened regularly			**1.00**	
Screened regularly[‡]	**-1.6799 (0.0855)**	**<.0001**	**0.19 (0.16-0.22)**	**-81 (-84 to -78)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-2.6626 (0.1620)	<.0001	0.07 (0.05-0.10)	-93 (-95 to -90)
50-54	-0.3302 (0.0894)	0.0002	0.72 (0.60-0.86)	-28 (-40 to -14)
55-59	0.1288 (0.0968)	0.1832	1.14 (0.94-1.38)	14 (-6 to +38)
65-69	-1.1712 (0.2616)	<.0001	0.31 (0.19-0.52)	-69 (-81 to -48)
Ethnicity:				
Other			1.00	
Māori	0.1962 (0.1033)	0.0574	1.22 (0.99-1.49)	22 (-1 to +49)
Pacific	-0.4486 (0.1931)	0.0202	0.64 (0.44-0.93)	-36 (-56 to -7)
Intercept	-5.1789 (0.0699)	<.0001	-	-

[†] From negative binomial regression model adjusted for repeat measures, screening inception cohort

[‡] Screened ≥3 times and ≤30 months mean screening interval

Māori women: regularity of screening

In screened Māori women, regular screening was associated with 4% higher breast cancer mortality compared to less frequent screening, which was not statistically significant (Table 3.12). This was the result of a cluster of breast cancer deaths occurring among 70-74 year regularly screened Māori women in 2008, 2010 and 2011 (6 altogether from a regularly screened population of 125 Māori 70-74 year women cumulated over 2008, 2010 and 2011).

Table 3.12: Relative risk[†] of breast cancer mortality, ever-screened New Zealand Māori women, breast cancers diagnosed 2004-2011

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Not screened regularly			**1.00**	
Screened regularly[‡]	**0.0348 (0.5963)**	**0.9535**	**1.04 (0.32-3.33)**	**4 (-68 to +233)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-1.1666 (0.2016)	<.0001	0.31 (0.21-0.46)	-69 (-79 to -54)
50-54	-0.1650 (0.0945)	0.0808	0.85 (0.70-1.02)	-15 (-30 to +2)
55-59	0.2292 (0.0007)	<.0001	1.26 (1.26-1.26)	26 (26 to 26)
65-69	0.1567 (0.0373)	<.0001	1.17 (1.09-1.26)	17 (9 to 26)
70-74	1.8214 (0.1895)	<.0001	6.18 (4.26-8.96)	518 (326 to 796)
75-79	2.1847 (0.2356)	<.0001	8.89 (5.60-14.1)	789 (460 to 1310)
Intercept	-9.5080 (0.2356)	<.0001	-	-

[†] From negative binomial regression model adjusted for repeat measures, screening inception cohort

[‡] Screened ≥3 times ≤30 months mean screening interval

Pacific women: regularity of screening

In screened Pacific women regular screening mammography was associated with an 86% reduction in breast cancer mortality compared to women who screened less frequently which was statistically significant (Table 3.13). However, this estimate of breast cancer mortality reduction may be inflated by differential under-recording of mortality in Pacific women.

Table 3.13: Relative risk[†] of breast cancer mortality, ever-screened New Zealand Pacific women breast cancers diagnosed 2004-2011

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Not screened regularly			**1.00**	
Screened regularly[‡]	**-1.9397 (0-.8462)**	**0.0219**	**0.14 (0.03-0.75)**	**-86 (-97 to -25)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-0.0559 (0.0501)	0.2645	0.95 (0.86-1.04)	-5 (-14 to +4)
50-54	0.1940 (0.0298)	<.0001	1.21 (1.15-1.29)	21 (15 to 29)
55-59	-0.0188 (0.0045)	<.0001	0.98 (0.97-0.99)	-2 (-3 to -1)
65-69	0.3096 (0.0103)	<.0001	1.36 (1.34-1.39)	36 (34 to 39)
70-74	-0.8084 (0.0528)	<.0001	0.45 (0.40-0.49)	-55 (-60 to -51)
Intercept	-9.6196 (0.0545)	<.0001	-	-

[†] From negative binomial regression model adjusted for repeat measures, screening inception cohort

[‡] Screened ≥3 times ≤30 months mean screening interval

Other women: regularity of screening

For the remaining (Other) non-Māori, non-Pacific population, regular mammographic screening was associated with a non-significant 25% reduction in breast cancer mortality compared to women screening less frequently (Table 3.14).

Table 3.14: Relative risk[†] of breast cancer mortality, ever-screened New Zealand non-Māori, non-Pacific, breast cancers diagnosed 2003-2011

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Not screened regularly			**1.00**	
Screened regularly[‡]	**-0.2884 (0.3196)**	**0.3669**	**0.75 (0.40-1.40)**	**-25 (-60 to +40)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-1.0029 (0.1134)	<.0001	0.37 (0.29-0.46)	-63 (-71 to -54)
50-54	-0.6112 (0.0534)	<.0001	0.54 (0.49-0.60)	-46 (-51 to -40)
55-59	-0.3837 (0.0066)	<.0001	0.68 (0.67-0.69)	-32 (-33 to -31)
65-69	0.2632 (0.0161)	<.0001	1.30 (1.26-1.34)	30 (26 to 34)
70-74	1.0119 (0.1022)	<.0001	2.75 (2.25-3.36)	175 (125 to 236)
75-79	1.9097 (0.1378)	<.0001	6.75 (5.15-8.84)	575 (415 to 784)
Intercept	-9.7778 (0.1378)	<.0001	-	-

[†] From negative binomial regression model adjusted for repeat measures, screening inception cohort

[‡] Screened ≥3 times ≤30 months mean screening interval

3.1.3.1.2. Comparison of regular, irregular and never screened women

All New Zealand women

Here we compare in single models the risk of breast cancer death between regular, irregular and never screeners. Compared to never-screened women, breast cancer mortality was estimated to be 58% lower in irregularly screened women, and 67% lower in regularly screened women (Table 3.15). These results are statistically significant. After adjustment for screening selection bias, the mortality benefit in women with screening available and assumed to screen less regularly, compared to women not offered screening, was 26% using the RR=1.17 for the relative risk of breast cancer mortality in unscreened women offered screening, compared to unscreened women not offered screening, and using the mean recorded screening participation rate of 64% for 2001-11. That is, the estimate of breast cancer mortality reduction attributable to screening when compared to the same population not offered screening is 26%. Based on the most recent screening rate for 2012-13 (71%), the mortality reduction is estimated to be 31% and similar to that for the screening participation target of 70%.

The adjusted mortality benefit attributable to regular screening is 33%, based on recorded average screening for 2001-11, compared to the same population not offered screening. The corresponding estimate based on 2012-13 screening is 39%, similar to that (38%) for the 70% target screening participation rate.

Table 3.15: Relative risk[†] of breast cancer mortality in regularly, irregularly, and never-screened New Zealand women, breast cancers diagnosed 2003-2011[a]

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Never screened			**1.00**	
Irregular screening	**-0.8685 (0.1117)**	**<.0001**	**0.42 (0.34-0.52)**	**-58 (-66 to -48)**
Irregular screening (adj)[a]	**-**	**-**	**0.74 (0.65-0.83)**	**-26 (-35 to -17)**
Irregular screening (adj)[b]	**-**	**-**	**0.69 (0.60-0.79)**	**-31 (-40 to -21)**
Irregular screening (adj)[c]	**-**	**-**	**0.69 (0.61-0.79)**	**-31 (-39 to -21)**
Regularly screening [‡]	**-1.1231 (0.2622)**	**<.0001**	**0.33 (0.19-0.54)**	**-67 (-81 to -46)**
Regular screening (adj)[a]	**-**	**-**	**0.67 (0.55-0.82)**	**-33 (-45 to -18)**
Regular screening (adj)[b]	-	-	**0.61 (0.48-0.78)**	**-39 (-52 to -22)**
Regular screening (adj)[c]	-	-	**0.62 (0.49-0.78)**	**-38 (-51 to -22)**
Variables adjusted				
Age at death (yr):				
60-64			1.00	
45-49	0.1149 (0.0696)	0.0987	1.12 (0.98-1.29)	12 (-2 to +29)
50-54	-0.2360 (0.0736)	0.0013	0.79 (0.68-0.91)	-21 (-32 to -9)
55-59	-0.1400 (0.0328)	<.0001	0.87 (0.82-0.93)	-13 (-18 to -7)
65-69	0.0006 (0.0654)	0.9924	1.00 (0.88-1.14)	0 (-12 to +14)
70-74	-0.1312 (0.0750)	0.0802	0.88 (0.76-1.02)	-12 (-24 to +2)
75-79	-0.2142 (0.0863)	0.0131	0.81 (0.68-0.96)	-19 (-32 to -4)
Ethnicity:				
Other			1.00	
Māori	0.5925 (0.0409)	<.0001	1.81 (1.67-1.96)	81 (67 to 96)
Pacific	0.5550 (0.0586)	<.0001	1.74 (1.55-1.95)	74 (55 to 95)
Intercept	-8.9849 (0.0932)	<.0001	-	-

[†] From negative binomial regression model adjusted for repeat measures, screening inception cohort

[‡] Screened ≥3 times ≤30 months mean screening interval

[a] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and mean recorded screening participation rate of 64% for 2001-11

[b] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and recorded screening participation rate of 71% for 2012-13

[c] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and target screening participation rate of 70%

Māori women

In Māori women, those who screen irregularly had 57% lower breast cancer mortality than never-screened Māori women (statistically significant), and those regularly screened had 58% lower breast cancer mortality compared to the never-screened (also significant) (Table 3.16). After adjustment for screening selection bias, using estimated RR=1.17 for the breast cancer mortality differential between unscreened women offered compared to women not offered screening, and based on mean screening participation of 48% for 2001-11, the estimated breast cancer mortality benefit attributable to irregular and regular screening compared to the same population not offered screening was 15% and 16%, respectively. However, the 95% confidence limits for the latter estimate covered zero, due mainly to low numbers. Based on observed screening rates for 2012-13 (65%), the breast cancer mortality reduction is estimated to be 26% in women with screening available and assumed to be irregularly screened compared to women not offered screening; and 27% in women with screening available and assumed to be regularly screening. If Māori women screened at 70% participation, it is estimated that the breast cancer mortality reduction would be 30% and 31% in women

offered screening and assumed to be irregularly and regularly screened respectively, compared to women not offered screening.

Table 3.16: Relative risk[†] of breast cancer mortality in regularly, irregularly and never-screened Māori New Zealand women, breast cancers diagnosed 2004-2011

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Never screened			**1.00**	
Irregular screening	**-0.8414 (0.1698)**	**<.0001**	**0.43 (0.31-0.60)**	**-57 (-69 to -40)**
Irregular screening (adj)[a]			**0.85 (0.75-0.96)**	**-15 (-25 to -4)**
Irregular screening (adj)[b]			**0.74 (0.63-0.87)**	**-26 (-37 to -13)**
Irregular screening (adj)[c]			**0.70 (0.59-0.85)**	**-30 (-41 to -15)**
Screened regularly[‡]	**-0.8732 (0.4085)**	**0.0326**	**0.42 (0.19-0.93)**	**-58 (-81 to -7)**
Regular screening (adj)[a]	**-**	**-**	**0.84 (0.67-1.07)**	**-16 (-33 to +7)**
Regular screening (adj)[b]			**0.73 (0.51-1.04)**	**-27 (-49 to +4)**
Regular screening (adj)[c]			**0.69 (0.46-1.04)**	**-31 (-54 to +4)**
Variables adjusted				
Age at death (yr):				
60-64			1.00	
45-49	0.1467 (0.0682)	0.0314	1.16 (1.01-1.32)	16 (1 to 32)
50-54	-0.0282 (0.0584)	0.6290	0.97 (0.87-1.09)	-3 (-13 to +9)
55-59	0.0048 (0.0164)	0.7710	1.00 (0.97-1.04)	0 (-3 to +4)
65-69	-0.0678 (0.0171)	<.0001	0.93 (0.90-0.97)	-7 (-10 to -3)
70-74	0.0851 (0.0666)	0.2012	1.09 (0.96-1.24)	9 (-4 to +24)
75-79	-0.1701 (0.0847)	0.0445	0.84 (0.71-1.00)	-16 (-29 to 0)
Intercept	-8.5238 (0.0855)	<.0001	-	-

[†] From Poisson regression model adjusted for repeat measures and over-dispersion, screening inception cohort

[‡] Screened ≥3 times ≤30 months mean screening interval

[a] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and mean recorded screening participation rate of 48% for 2001-11

[b] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and recorded screening participation rate of 65% for 2012-13

[c] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and target screening participation rate of 70%

Pacific women

Findings in Pacific women are not plausible and reflect probable differential under-recording of breast cancer mortality in Pacific women (Table 3.17). In Pacific women, those who screened regularly had an estimated 71% lower breast cancer mortality than in never-screened Pacific women, and an estimate of 96% lower breast cancer mortality reduction in regularly screened compared to never-screened Pacific women. The mortality benefit in Pacific women offered screening and assumed to be screening less regularly compared to Pacific women not offered screening, after adjusting for screening selection bias was 24%, using RR=1.17 and mean 49% screening participation for 2001-11 in Pacific women. The corresponding adjusted breast cancer mortality benefit attributable to regular screening compared to the same population of Pacific women not offered screening was 38%. However, it is evident that with higher screening rates achieved in Pacific women in 2012-13, and in relation to the screening target of 70%, implausible breast cancer mortality reductions result after adjusting for screening selection bias.

Table 3.17: Relative risk[†] of breast cancer mortality in regularly, irregularly and never-screened Pacific New Zealand women, breast cancers diagnosed 2004-2011

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Never screened			**1.00**	
Irregular screening	**-1.2394 (0.1887)**	**<.0001**	**0.29 (0.20-0.42)**	**-71 (-80 to -58)**
Irregular screening (adj)[a]			**0.76 (0.68-0.85)**	**-24 (-32 to -15)**
Irregular screening (adj)[b]			**0.57 (0.48-0.68)**	**-43 (-52 to -32)**
Irregular screening (adj)[c]			**0.59 (0.50-0.69)**	**-41 (-50 to -31)**
Screened regularly[‡]	**-3.1608 (0.8596)**	**0.0002**	**0.04 (0.01-0.23)**	**-96 (-99 to -77)**
Regular screening (adj)[a]	**-**	**-**	**0.62 (0.56-0.68)**	**-38 (-44 to -32)**
Regular screening (adj)[b]			**0.36 (0.30-0.43)**	**-64 (-70 to -57)**
Regular screening (adj)[c]			**0.39 (0.33-0.46)**	**-61 (-67 to -54)**
Variables adjusted				
Age at death (yr):				
60-64			1.00	
45-49	-0.1745 (0.2404)	0.4679	0.84 (0.52-1.35)	-16 (-48 to +35)
50-54	-0.3094 (0.2204)	0.1604	0.73 (0.48-1.13)	-27 (-52 to +13)
55-59	-0.2536 (0.2304)	0.2711	0.78 (0.49-1.22)	-22 (-51 to +22)
65-69	-0.3933 (0.2645)	0.1371	0.67 (0.40-1.13)	-33 (-60 to +13)
70-74	-0.6157 (0.2722)	0.0237	0.54 (0.32-0.92)	-46 (-68 to -8)
75-79	-0.4234 (0.2751)	0.1238	0.65 (0.38-1.12)	-35 (-62 to +12)
Intercept	-8.1258 (0.1740)	<.0001	-	-

[†] From Poisson regression model adjusted for repeat measures and over-dispersion, screening inception cohort

[‡] Screened ≥3 times ≤30 months mean screening interval

[a] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and mean recorded screening participation rate of 49% for 2001-11

[b] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and recorded screening participation rate of 72% for 2012-13

[c] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and target screening participation rate of 70%

Other women

For the remaining non-Māori, non-Pacific population, women who screened irregularly had an estimated 56% lower breast cancer mortality than in corresponding never-screened women (Table 3.18). Breast cancer mortality in those regularly screened was 66% lower than in the never-screened. After adjustment for screening selection bias, using the estimate of screening selection bias of RR=1.17 and a mean screening participation rate of 66% for 2001-11, the estimated breast cancer mortality benefit in Other women offered screening and assumed to be irregular screeners, compared to Other women not offered screening, was 26%. The corresponding adjusted mortality reduction attributable to regular screening was 34%. These estimates were 29% and 38% respectively with recorded 2012-13 screening participation of 72%, and similar in relation to the screening target of 70%.

Table 3.18: Relative risk[†] of breast cancer mortality in regularly, irregularly and never-screened Other (non-Māori, non-Pacific) New Zealand women, breast cancers diagnosed 2003-2011

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Never screened			**1.00**	
Irregular screening	**-0.8114 (0.1572)**	**<.0001**	**0.44 (0.33-0.60)**	**-56 (-67 to -40)**
Irregular screening (adj)[a]			**0.74 (0.63-0.87)**	**-26 (-37 to -13)**
Irregular screening (adj)[b]			**0.71 (0.59-0.84)**	**-29 (-41 to -16)**
Irregular screening (adj)[c]			**0.71 (0.60-0.85)**	**-29 (-40 to -15)**
Screened regularly[‡]	**-1.0784 (0.3397)**	**0.0015**	**0.34 (0.17-0.66)**	**-66 (-83 to -34)**
Regular screening (adj)[a]	-	-	**0.66 (0.50-0.87)**	**-34 (-50 to -13)**
Regular screening (adj)[b]			**0.62 (0.45-0.84)**	**-38 (-55 to -16)**
Regular screening (adj)[c]			**0.63 (0.46-0.85)**	**-37 (-54 to -15)**
Variables adjusted				
Age at death (yr):				
60-64			1.00	
45-49	0.1875 (0.0846)	0.0267	1.21 (1.02-1.42)	21 (2 to 42)
50-54	-0.3041 (0.0496)	<.0001	0.74 (0.67-0.81)	-26 (-33 to -19)
55-59	-0.1659 (0.0064)	<.0001	0.85 (0.84-0.86)	-15 (-16 to -14)
65-69	0.0908 (0.0165)	<.0001	1.10 (1.06-1.13)	10 (6 to 13)
70-74	-0.0626 (0.0872)	0.4732	0.94 (0.79-1.11)	-6 (-21 to +11)
75-79	-0.1556 (0.1268)	0.2200	0.86 (0.67-1.10)	-14 (-33 to +10)
Intercept	-9.0222 (0.1312)	<.0001	-	-

[†] From Poisson regression model adjusted for repeat measures and over-dispersion, screening inception cohort

[‡] Screened ≥3 times ≤30 months mean screening interval

[a] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and mean recorded screening participation rate of 66% for 2001-11

[b] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and recorded screening participation rate of 72% for 2012-13

[c] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and target screening participation rate of 70%

3.1.4. Screen-detected cancer versus non-screen detected cancer

In this section we consider breast cancer mortality outcomes in screened women whose cancer was screen detected versus not screen detected. The analysis necessarily is of women diagnosed with breast cancer since screen-detected versus non-screen detected outcomes are not relevant to those not diagnosed with breast cancer. Age at first screen is the age variable controlled for, and time from first screen in ever-screened women, and time from first eligibility for screening in never-screened women defines the offset person-year denominators.

Breast cancer mortality outcomes can be compared by whether the cancer was detected at a screening episode or not, at an initial screen versus subsequent screen and at an initial screen compared with that detected in never-screened women. The possible comparisons of breast cancer mortality outcomes from among breast cancer cases include:

1. Screen-detected versus non-screen detected (in ever-screened women)
2. Screen-detected at initial screen versus subsequent screen (in ever-screened women)
3. Screen-detected versus non-screen detected in women who screened once only (initial screeners, ever-screened women)
4. Screen detected versus non-screen detected in women who screened more than once (subsequent screeners, ever-screened women)
5. Non-screen detected in ever-screened versus in never-screened women

6. Non-screen detected following initial screen versus non-screen detected following a subsequent screen (in ever-screened women)
7. Non-screen detected following once-only (initial) screen versus in never-screened women

The hypothesis implicit in comparison 1 is that breast cancer mortality is expected to be lower in screen-detected breast cancer cases because mammography detects the cancer before symptoms manifest or the cancer becomes clinically apparent.

For comparison 2 (screen-detected cancer at initial screen versus subsequent screen), cancers detected in subsequent screened women should on average be smaller, and more likely detectable mammographically than clinically, compared to initial screeners. Therefore the mortality benefit from this comparison comes from having a screening history where any changes occurring are detected within, on average a screening interval rather than over a longer period or lifetime of no prior screening.

Any mortality benefit found in screen-detected cancer cases from comparison 1 should be attenuated in comparison 4 (screen-detected versus non-screen detected cancer in subsequent screened women), since prevalent cancers detected from initial screens are excluded and only outcomes from incident cancers arising between mammographic screens are being compared. Non-screen detected cancers in these women may arise either from interval cancers or from a longer interval between the last screen and the cancer diagnosis.

Comparison 5 examines the possible mortality benefit from having a screening history, despite not having the cancer detected by a screening mammogram. This comparison allows partial assessment of the contribution of length time bias to any mortality reduction associated with screening mammography when comparing regular versus irregular screening. This is because if length time bias were contributing significantly to an observed breast cancer mortality benefit from screening, then there should not be a significant breast cancer mortality benefit from non-screen detected cancers in screened women who screen regularly versus non-regularly. That is, if a regular screener who presents with symptoms whose cancer is detected outside the screening cycle – i.e., typically the most recent (negative) screen was 2 years or less prior to the diagnosis – the cancer would be expected to be faster growing than in the irregular screener with a longer interval to the previous (negative) screen. Length bias in this case favours the irregular screener, and if, despite this, a mortality benefit is found to favour the regular screener with non-screen detected cancer, then the benefit of screening becomes apparent.

Comparison 7 examines the possible mortality benefit from a cancer in detected women with a history of multiple screens compared with a single screen only, despite the cancer in both groups being detected outside of screening.

For ever-screened women diagnosed with breast cancer, those with cancer detected at screening had 45% lower breast cancer mortality than those with cancer detected outside screening (Table 3.19).

Table 3.19: Breast cancer mortality by screen-detected status in ever-screened New Zealand women[2]

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Not screen detected			**1.00**	
Screen detected‡	**-0.6032 (0.1207)**	**<.0001**	**0.55 (0.43-0.69)**	**-45 (-57 to -31)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-0.2232 (0.2589)	0.3886	0.80 (0.48-1.33)	-20 (-52 to +33)
50-54	-0.1671 (0.1503)	0.2663	0.85 (0.63-1.14)	-15 (-37 to +14)
55-59	-0.1517 (0.1651)	0.3582	0.86 (0.62-1.19)	-14 (-38 to +19)
65-69	0.0585 (0.5295)	0.9121	1.06 (0.38-2.99)	6 (-62 to +199)
Ethnicity:				
Other			1.00	
Māori	0.3964 (0.1715)	0.0208	1.49 (1.06-2.08)	49 (6 to 108)
Pacific	0.6154 (0.3194)	0.0540	1.85 (0.99-3.46)	85 (-1 to +246)
Intercept	-9.5973 (0.1211)	<.0001	-	-

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

Māori women

In ever-screened Māori women with breast cancer, those with screen-detected cancer had 56% lower breast cancer mortality than corresponding women with non-screen detected breast cancer (Table 3.20).

Table 3.20: Breast cancer mortality by screen-detected status in ever-screened New Zealand Māori women[3]

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Not screen detected			**1.00**	
Screen detected	**-0.8297 (0.2874)**	**0.0039**	**0.44 (0.25-0.77)**	**-56 (-75 to -23)**
Variables adjusted				
Age at first screen (yr):				
60-64	0.0000	-	1.00	-
45-49	-0.2576 (0.7088)	0.7162	0.77 (0.19-3.10)	-23 (-81 to +210)
50-54	0.2067 (0.4015)	0.6067	1.23 (0.56-2.70)	23 (-44 to +170)
55-59	0.0049 (0.4486)	0.9913	1.00 (0.42-2.42)	0 (-58 to +142)
65-69	0.6992 (0.9366)	0.4554	2.01 (0.32-12.6)	101 (-68 to +1162)
Intercept	-9.3300 (0.3540)	<.0001	-	-

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

Pacific women

[2] Relative risk of breast cancer mortality by screen-detected status, ever-screened New Zealand women aged 45-69 years at first screening mammogram and subsequently diagnosed with breast cancer, 1999-2011

[3] New Zealand Māori women, relative risk of breast cancer mortality by screen-detected status in women ever-screened, aged 45-69 years at first screening mammogram and subsequently diagnosed with breast cancer, 1999-2011

In ever-screened Pacific women, those with screen-detected cancer had 42% lower breast cancer mortality than corresponding women with non-screen detected breast cancer (Table 3.21). However, this was not statistically significant.

Table 3.21: Breast cancer mortality by screen detected status in ever-screened New Zealand Pacific women[4]

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Not screen detected			**1.00**	
Screen detected	**-0.5389 (0.4671)**	**0.2486**	**0.58 (0.23-1.46)**	**-42 (-77 to +46)**
Variables adjusted				
Age at first screen (yr):				
60-64	0.0000	-	1.00	-
45-49	0.1390 (0.7714)	0.8570	1.15 (0.25-5.21)	15 (-75 to +421)
50-54	-0.4268 (0.6098)	0.4840	0.65 (0.20-2.16)	-35 (-80 to +116)
55-59	-0.2795 (0.6556)	0.6699	0.76 (0.21-2.73)	-24 (-79 to +173)
65-69			Excluded due to small numbers	
Intercept	-8.8830 (0.4808)	<.0001	-8.8830 (0.4808)	<.0001

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

Other women

In remaining (Other) non-Māori, non-Pacific women, those with screen-detected cancer were 43% less likely to die from breast cancer than corresponding screened women with non-screen detected breast cancer (Table 3.22).

Table 3.22: Breast cancer mortality by screen-detected status in ever-screened Other (non-Māori, non-Pacific) women[5]

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Not screen detected			**1.00**	
Screen detected	**-0.5668 (0.2535)**	**0.0254**	**0.57 (0.35-0.93)**	**-43 (-65 to -7)**
Variables adjusted				
Age at first screen (yr):				
60-64	0.0000	-	1.00	-
45-49	-0.2367 (0.5425)	0.6626	0.79 (0.27-2.29)	-21 (-73 to +129)
50-54	-0.2143 (0.3119)	0.4921	0.81 (0.44-1.49)	-19 (-56 to +49)
55-59	-0.1675 (0.3409)	0.6232	0.85 (0.43-1.65)	-15 (-57 to +65)
65-69	0.0326 (1.1808)	0.9780	1.03 (0.10-10.5)	3 (-90 to +945)
Intercept	-9.5894 (0.2437)	<.0001	-	-

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

The results above may be affected by length bias, in that screen-detected cancers would likely be slower-growing cancers than non-screen detected cancers, despite the comparison being within ever-screened women. Analysis of screening frequency and regularity by screen-detected versus non-screen detected status

[4] New Zealand Pacific women, relative risk of breast cancer mortality by screen detected status in women ever-screened, aged 45-69 years at first screening mammogram and subsequently diagnosed with breast cancer, 1999-2011

[5] Other (non-Māori, non-Pacific) women, relative risk of breast cancer mortality by screen-detected status in ever-screened women, aged 45-69 years at first screening mammogram and subsequently diagnosed with breast cancer, 1999-2011

would shed light on the extent that length bias contributes to breast cancer mortality reduction in regular versus non-regular screeners.

3.1.4.1. Regularity of screening in screen-detected and non-screen detected breast cancer

Screen detected breast cancer

In those with screen-detected breast cancer, regular screening was associated with 59% lower breast cancer mortality compared to corresponding women not screening regularly (Table 3.23).

Table 3.23: Breast cancer mortality by screening regularity, ever-screened New Zealand women with screen-detected breast cancer[6]

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Not screened regularly			**1.00**	
Screened regularly‡	**-0.8956 (0.1035)**	**<.0001**	**0.41 (0.33-0.50)**	**-59 (-67 to -50)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-1.3405 (0.1987)	<.0001	0.26 (0.18-0.39)	-74 (-82 to -61
50-54	-0.2602 (0.1148)	0.0234	0.77 (0.62-0.97)	-23 (-38 to -3)
55-59	-0.0938 (0.1224)	0.4435	0.91 (0.72-1.16)	-9 (-28 to +16
65-69	-0.9312 (0.3656)	0.0109	0.39 (0.19-0.81)	-61 (-81 to -19)
Ethnicity:				
Other				
Māori	-0.0070 (0.1312)	0.9574	0.99 (0.77-1.28)	-1 (-23 to +28)
Pacific	0.1406 (0.2165)	0.5161	1.15 (0.75 -1.76)	15 (-25 to +76)
Intercept	-2.5255 (0.0926)	<.0001	-	-

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

‡ Screened ≥3 times ≤30 months mean screening interval

These results are not directly comparable to those for all women (cf. Table 3.11), as the comparison here is not of regular versus irregular screening in all screened women, but within screened women diagnosed with cancer through screening only. Similarly, the results for screening regularity in screened women with non-screen detected cancer are not comparable to those for all women.

Non-screen detected breast cancer

In screened women with non-screen detected breast cancer, those who screened regularly had 79% lower breast cancer mortality than those who screened less regularly, which was a somewhat greater reduction than in women with screen-detected cancer (Table 3.24, cf. Table 3.23).

[6] Relative risk of breast cancer mortality by screening regularity, ever-screened New Zealand women aged 45-69 years at first screening mammogram with screen-detected breast cancer, 1999-2011

Table 3.24: Breast cancer mortality by screening regularity, ever-screened New Zealand women with non-screen detected breast cancer[7]

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Not screened regularly			**1.00**	
Screened regularly‡	**-1.5750 (0.1193)**	**<.0001**	**0.21 (0.16-0.26)**	**-79 (-84 to -74)**
Variables adjusted				
Age at first screen (yr):				
60-64	-0.0375 (0.2047)	0.8548	0.96 (0.64-1.44)	-4 (-36 to +44)
45-49	0.6775 (0.1188)	<.0001	1.97 (1.56-2.49)	97 (56 to 149)
50-54	0.7525 (0.1327)	<.0001	2.12 (1.64-2.75)	112 (64 to 175)
55-59	-0.4710 (0.4660)	0.3122	0.62 (0.25-1.56)	-38 (-75 to +56)
65-69	-0.0375 (0.2047)	0.8548	0.96 (0.64-1.44)	-4 (-36 to +44)
Ethnicity:				
Other	0.0000	-	1.00	-
Māori	0.2150 (0.1363)	0.1147	1.24 (0.95-1.62)	24 (-5 to +62)
Pacific	0.3839 (0.2783)	0.1678	1.47 (0.85-2.53)	47 (-15 to +153)
Intercept	-9.5782 (0.0923)	<.0001	-	-

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

‡ Screened ≥3 times ≤30 months mean screening interval

These analyses of regular screening in women with screen-detected and non-screen detected breast cancer indicate that length bias contributes little to mortality benefit from screening mammography. In particular, if lower mortality from screening mammography were due to length bias, then in screened women with non-screen detected cancer no significant mortality benefit would be expected from regular screening versus non-regular screening, which is not the case here.

3.1.4.2. Screen-detected cancer in initial versus subsequent screened women

Women whose cancer was detected at a subsequent screen had 62% lower breast cancer mortality than women with breast cancer detected at their initial screening mammogram (Table 3.25). In this analysis the risk of breast cancer mortality in Māori and Pacific women is very similar to the remaining population.

[7] Relative risk of breast cancer mortality by screening frequency, ever-screened New Zealand women aged 45-69 years at first screening mammogram with non-screen detected breast cancer, 1999-2011

Table 3.25: Relative risk† of breast cancer mortality in women with screen-detected breast cancer by cancer detected at subsequent versus initial screen, ever-screened New Zealand women aged 45-69 years at first screening mammogram, 1999-2011

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Detected at initial‡ screen			**1.00**	
Detected at subsequent screen	**-0.9710 (0.1179)**	**<.0001**	**0.38 (0.30-0.48)**	**-62 (-70 to -52)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-1.4218 (0.2555)	<.0001	0.24 (0.15-0.40)	-76 (-85 to -60)
50-54	-0.2694 (0.1480)	0.0688	0.76 (0.57-1.02)	-24 (-43 to +2)
55-59	-0.1460 (0.1588)	0.3577	0.86 (0.63-1.18)	-14 (-37 to +18)
65-69	-1.1529 (0.4702)	0.0142	0.32 (0.13-0.79)	-68 (-87 to -21)
Ethnicity:				
Other			1.00	
Māori	-0.0459 (0.1716)	0.7892	0.96 (0.68-1.34)	-4 (-32 to +34)
Pacific	0.0210 (0.2864)	0.9415	1.02 (0.58-1.79)	2 (-42 to +79)
Intercept	-2.2141 (0.1275)	<.0001	-	-

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

‡ Women who have had two or more screening mammograms

Screen-detected versus non-screen detected cancer in initially screened women

In women with cancer who had a single screen only before the cancer was detected, those whose cancer was screen detected had 52% lower risk of breast cancer mortality than corresponding women whose cancer was not screen detected (Table 3.26). In this analysis, breast cancer mortality in Māori and Pacific women was higher than the remaining population, but not significantly so.

Table 3.26: Relative risk† of breast cancer mortality from screen-detected versus non-screen detected cancer in women with a single screening mammogram only prior to breast cancer diagnosis, ever-screened New Zealand women aged 45-69 years at first screening mammogram, 1999-2011

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Not screen detected at initial‡ screen			**1.00**	
Detected at initial screen	**-0.7240 (0.1033)**	**<.0001**	**0.48 (0.40-0.59)**	**-52 (-60 to -41)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-1.1632 (0.1988)	<.0001	0.31 (0.21-0.46)	-69 (-79 to -54)
50-54	0.1254 (0.1306)	0.3370	1.13 (0.88-1.46)	13 (-12 to +46)
55-59	0.2807(0.1449)	0.0527	1.32 (1.00-1.76)	32 (0 to 76)
65-69	-1.0525 (0.3657)	0.0040	0.35 (0.17-0.71)	-65 (-83 to -29)
Ethnicity:				
Other			1.00	
Māori	0.1364 (0.1408)	0.3325	1.15 (0.87-1.51)	15 (-13 to +51)
Pacific	0.1949 (0.2276)	0.3918	1.22 (0.78-1.90)	22 (-22 to +90)
Intercept	-1.8116 (0.1101)	<.0001	-	-

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

‡ Women who have had a single screening mammogram only prior to diagnosis

Screen-detected versus non-screen detected cancer in subsequent screened women

In women who had two or more screening mammograms prior to a breast cancer diagnosis, those whose breast cancer was screen detected had 64% lower risk of breast cancer mortality than corresponding women whose breast cancer was not screen detected (Table 3.27).

Table 3.27: Relative risk[†] of breast cancer mortality from screen-detected versus non-screen detected cancer in women with more than one screening mammogram (subsequent screeners) prior to breast cancer diagnosis, ever-screened New Zealand women aged 45-69 years at first screening mammogram, 1999-2011

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Not detected at subsequent[‡] screen			**1.00**	
Detected at subsequent screen	**-1.0329 (0.1062)**	**<.0001**	**0.36 (0.29-0.44)**	**-64 (-71 to -56)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-1.2732 (0.2861)	<.0001	0.28 (0.16-0.49)	-72 (-84 to -51)
50-54	-0.3312 (0.1323)	0.0123	0.72 (0.55-0.93)	-28 (-45 to -7)
55-59	-0.2113 (0.1436)	0.1411	0.81 (0.61-1.07)	-19 (-39 to +7)
65-69	-0.6486 (0.7849)	0.4086	0.52 (0.11-2.43)	-48 (-89 to +143)
Ethnicity:				
Other			1.00	
Māori	0.1726 (0.1683)	0.3052	1.19 (0.85-1.65)	19 (-15 to +65)
Pacific	-0.1693 (0.4199)	0.6868	0.84 (0.37-1.92)	-16 (-63 to +92)
Intercept	-2.1296 (0.1110)	<.0001	-	-

[†] From Poisson regression model adjusted for over-dispersion, screening inception cohort

[‡] Women who have had two or more screening mammograms

Non-screen detected in initial versus subsequent screeners

In women with non-screen detected breast cancer, those who had two or more screens prior to cancer detection had 47% lower risk of breast cancer mortality than those who had only one screening mammogram prior to the breast cancer diagnosis (Table 3.28). In this analysis Māori and Pacific women had higher breast cancer mortality than the remaining population, and Māori breast cancer mortality was significantly higher.

Table 3.28: Relative risk[†] of breast cancer mortality from non-screen detected cancer in women with one only versus more than one screening mammogram prior to breast cancer diagnosis, ever-screened New Zealand women aged 45-69 years at first screening mammogram, 1999-2011

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Not screen detected, women with initial screen only			**1.00**	
Not screen detected, women with subsequent screen[‡]	**-0.6288 (0.1031)**	**<.0001**	**0.53 (0.44-0.65)**	**-47 (-56 to -35)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-1.1277 (0.2230)	<.0001	0.32 (0.21-0.50)	-68 (-79 to -50)
50-54	0.0150 (0.1269)	0.9060	1.02 (0.79-1.30)	2 (-21 to +30)
55-59	0.1587 (0.1416)	0.2622	1.17 (0.89-1.55)	17 (-11 to +55)
65-69	-1.1199 (0.5075)	0.0273	0.33 (0.12-0.88)	-67 (-88 to -12)
Ethnicity:				
Other			1.00	
Māori	0.3282 (0.1473)	0.0259	1.39 (1.04-1.85)	39 (4 to 85)
Pacific	0.2100 (0.3029)	0.4880	1.23 (0.68-2.23)	23 (-32 to +123)
Intercept	-1.7734 (0.1109)	<.0001	-	-

[†] From Poisson regression model adjusted for over-dispersion, screening inception cohort

[‡] Women who have had two or more screening mammograms

3.1.5. Screening frequency (total mammograms)

It is of interest to know the extent that frequency of screening, independently of its regularity, predicts lower breast cancer mortality. This analysis also shows whether a dose-response relationship exists between

screening mammography and lower breast cancer mortality. To aid interpretation, we have also categorised screening frequency into 1, 2-3, and ≥4 screens.

3.1.5.1. Ever-screened New Zealand women

All New Zealand women

For all New Zealand women, the total number of screening mammograms was significantly associated with lower breast cancer mortality, by 48% per additional screen (Table 3.29).

Table 3.29: Breast cancer mortality by total mammograms, ever-screened New Zealand women, 1999-2011[8]

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Total number of mammograms	**-0.6589 (0.0316)**	**<.0001**	**0.52 (0.49-0.55)**	**-48 (-51 to -45)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-2.9177 (0.1791)	<.0001	0.05 (0.04-0.08)	-95 (-96 to -92)
50-54	-0.2944 (0.0975)	0.0025	0.74 (0.62-0.90)	-26 (-38 to -10)
55-59	0.2074 (0.1057)	0.0497	1.23 (1.00-1.51)	23 (0 to 51)
65-69	-1.4885 (0.2894)	<.0001	0.23 (0.13-0.40)	-77 (-87 to -60)
Ethnicity:				
Other			1.00	
Māori	0.1016 (0.1138)	0.3719	1.11 (0.89-1.38)	11 (-11 to +38)
Pacific	-0.5959 (0.2131)	0.0052	0.55 (0.36-0.84)	-45 (-64 to -16)
Intercept	-4.0422 (0.0966)	<.0001	-	-

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

‡ Total number of screening mammograms each woman has had

Compared with one screen only, having had 2-3 screens was associated with a breast cancer mortality risk reduction of 55%, and ≥4 screens a 94% reduction, indicating a strong positive dose-response relationship between screening frequency and breast cancer mortality reduction (Table 3.30). It should be borne in mind that in these comparisons relative reductions are with regard to a baseline comparison group of singly-screened women in whom a higher proportion of screen-detected cancers would have been prevalent rather than incident cases.

[8] Relative risk† of breast cancer mortality by screening frequency, ever-screened New Zealand women aged 45-69 years at first screening mammogram with non-screen detected breast cancer, 1999-2011

Table 3.30: Breast cancer mortality by category of screening frequency, ever-screened New Zealand women, 1999-2011[9]

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Screening frequency‡				
1 screen only			**1.00**	
2-3 screens	**-0.7951 (0.3217)**	**0.0134**	**0.45 (0.24-0.85)**	**-55 (-76 to -15)**
≥4 screens	**-2.8080 (0.5161)**	**<.0001**	**0.06 (0.02-0.17)**	**-94 (-98 to -83)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-2.8040 (0.6677)	<.0001	0.06 (0.02-0.22)	-94 (-98 to -78)
50-54	-0.2802 (0.3832)	0.4646	0.76 (0.36-1.60)	-24 (-64 to +60)
55-59	0.1710 (0.4202)	0.6840	1.19 (0.52-2.70)	19 (-48 to +170)
65-69	-1.8554 (1.3705)	0.1758	0.16 (0.01-2.29)	-84 (-99 to +129)
Ethnicity:				
Other			1.00	
Māori	0.1138 (0.4449)	0.7982	1.12 (0.47-2.68)	12 (-53 to +168)
Pacific	-0.5631 (0.8262)	0.4955	0.57 (0.11-2.88)	-43 (-89 to +188)
Intercept	-4.8778 (0.3429)	<.0001	-	-

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

‡ Total number of screening mammograms each woman has had

Māori women

In Māori women, a 41% reduction in breast cancer mortality was significantly associated with each additional screen (Table 3.31). The breast cancer mortality risk reduction associated with 2-3 screens was 64%, and 89% for ≥4 screens, compared to one screen only (Table 3.32). These results were not statistically significant for 2-3 screens, but were for ≥4 screens, and showed a dose-response relationship in the hypothesised direction of more screens being associated with lower breast cancer mortality.

Table 3.31: NZ Māori ever-screened women: breast cancer mortality by total mammograms, 1999-2011[10]

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Total number of mammograms	**-0.5332 (0.0835)**	**<.0001**	**0.59 (0.50-0.69)**	**-41 (-50 to -31)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-3.1908 (0.5067)	<.0001	0.04 (0.02-0.11)	-96 (-98 to -89)
50-54	-0.3084 (0.2547)	0.2259	0.73 (0.45-1.21)	-27 (-55 to +21)
55-59	-0.0266 (0.2855)	0.9258	0.97 (0.56-1.70)	-3 (-44 to +70)
65-69	-1.0630 (0.6863)	0.1214	0.35 (0.09-1.33)	-65 (-91 to +33)
Intercept	-4.0863 (0.2558)	<.0001	-	-

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

‡ Total number of screening mammograms each woman has had

[9] Relative risk† of breast cancer mortality by screening frequency category, ever-screened New Zealand women aged 45-69 years at first screening mammogram with non-screen detected breast cancer, 1999-2011

[10] Relative risk of breast cancer mortality by screening frequency, ever-screened New Zealand Māori women aged 45-69 years at first screening mammogram with non-screen detected breast cancer, 1999-2011

Table 3.32: NZ Māori ever-screened women: breast cancer mortality by category of screening frequency, 1999-2011[11]

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Screening frequency‡				
1 screen only			**1.00**	
2-3 screens	**-1.0257 (0.6192)**	**0.0976**	**0.36 (0.11-1.21)**	**-64 (-89 to +21)**
≥4 screens	**-2.1805 (0.9045)**	**0.0159**	**0.11 (0.02-0.67)**	**-89 (-98 to -33)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-2.7906 (1.3878)	0.0443	0.06 (0.00-0.93)	-94 (-100 to -7)
50-54	0.0342 (0.7837)	0.9652	1.03 (0.22-4.81)	3 (-78 to +381)
55-59	0.1707 (0.8764)	0.8455	1.19 (0.21-6.61)	19 (-79 to +561)
65-69	-0.7068 (1.8448)	0.7016	0.49 (0.01-18.3)	-51 (-99 to +1734)
Intercept	-4.9072 (0.7130)	<.0001	-	-

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

‡ Total number of screening mammograms each woman has had

Pacific women

In Pacific women the breast cancer mortality reduction associated with 61% lower breast cancer mortality for each additional screening mammogram (Table 3.33). Having had 2-3 screening mammograms was 80%, and with ≥4 screens 96% (Table 3.34). These estimates were not statistically significant but showed a dose-response relationship consistent with higher screening frequency and lower breast cancer mortality.

Table 3.33: New Zealand Pacific ever-screened women: breast cancer mortality by total mammograms, 1999-2011[12]

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Total number of mammograms	**-0.9407 (0.1810)**	**<.0001**	**0.39 (0.27-0.56)**	**-61 (-73 to -44)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-2.2072 (0.4816)	<.0001	0.11 (0.04-0.28)	-89 (-96 to -72)
50-54	-0.3200 (0.3490)	0.3591	0.73 (0.37-1.44)	-27 (-63 to +44)
55-59	-0.1837 (0.3931)	0.6403	0.83 (0.39-1.80)	-17 (-61 to +80)
Intercept	-4.1288 (0.3726)	<.0001	-	-

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

‡ Total number of screening mammograms each woman has had

[11] Relative risk of breast cancer mortality by screening frequency category, ever-screened New Zealand Māori women aged 45-69 years at first screening mammogram with non-screen detected breast cancer, 1999-2011

[12] Relative risk of breast cancer mortality by screening frequency, ever-screened New Zealand Pacific women aged 45-69 years at first screening mammogram with non-screen detected breast cancer, 1999-2011

Table 3.34: New Zealand Pacific ever-screened women breast cancer mortality by category of screening frequency, 1999-2011[13]

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Screening frequency‡				
1 screen only			**1.00**	
2-3 screens	**-1.6299 (1.0633)**	**0.1253**	**0.20 (0.02-1.57)**	**-80 (-98 to +57)**
≥4 screens	**-3.1512 (2.3750)**	**0.1846**	**0.04 (0.00-4.50)**	**-96 (-100 to +350)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-2.0672 (1.4516)	0.1544	0.13 (0.01-2.18)	-87 (-99 to +118)
50-54	-0.4289 (1.1221)	0.7023	0.65 (0.07-5.87)	-35 (-93 to +487)
55-59	-0.0725 (1.1994)	0.9518	0.93 (0.09-9.76)	-7 (-91 to +876)
65-69			Excluded due to small numbers	
Intercept	-5.1198 (0.8997)	<.0001	-	-

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

‡ Total number of screening mammograms each woman has had

Other women

In remaining (non-Māori, non-Pacific) or Other women, for each additional screening mammogram breast cancer mortality was 49% lower (significant) (Table 3.35). By screening frequency category, breast cancer mortality was 52% lower in women who had 2-3 screens, and 94% lower in women with ≥4 screens compared to women with one screen only (Table 3.36).

Table 3.35: New Zealand Other (non-Māori, non-Pacific) ever-screened women: breast cancer mortality by total mammograms, 1999-2011[14]

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Total number of mammograms	**-0.6694 (0.0466)**	**<.0001**	**0.51 (0.47-0.56)**	**-49 (-53 to -44)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-2.9244 (0.2704)	<.0001	0.05 (0.03-0.09)	-95 (-97 to -91)
50-54	-0.2962 0.1464)	0.0429	0.74 (0.56-0.99)	-26 (-44 to -1)
55-59	0.2592 (0.1571)	0.0991	1.30 (0.95-1.76)	30 (-5 to +76)
65-69	-1.5037 (0.4331)	0.0005	0.22 (0.10-0.52)	-78 (-90 to -48)
Intercept	-4.0341 (0.1411)	<.0001	-	-

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

‡ Total number of screening mammograms each woman has had

[13] Relative risk of breast cancer mortality by screening frequency category, ever-screened New Zealand Pacific women aged 45-69 years at first screening mammogram with non-screen detected breast cancer, 1999-2011

[14] Relative risk of breast cancer mortality by screening frequency, ever-screened New Zealand Other (non-Māori, non-Pacific) women aged 45-69 years at first screening mammogram with non-screen detected breast cancer, 1999-2011

Table 3.36: New Zealand Other (non-Māori, non-Pacific) ever-screened women breast cancer mortality by category of screening frequency, 1999-2011[15]

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Screening frequency‡				
1 screen only			**1.00**	
2-3 screens	**-0.7318 (0.5894)**	0.2144	**0.48 (0.15-1.53)**	**-52 (-85 to +53)**
≥4 screens	**-2.8670 (0.9430)**	0.0024	**0.06 (0.01-0.36)**	**-94 (-99 to -64)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-2.8439 (1.2293)	0.0207	0.06 (0.01-0.65)	-94 (-99 to -35)
50-54	-0.3154 (0.6971)	0.6509	0.73 (0.19-2.86)	-27 (-81 to +186)
55-59	0.1989 (0.7598)	0.7935	1.22 (0.28-5.41)	22 (-72 to +441)
65-69	-2.0236 (2.6846)	0.4510	0.13 (0.00-25.5)	-87 (-100 to +2449)
Intercept	-4.8868 (0.6137)	<.0001	-	-

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

‡ Total number of screening mammograms each woman has had

[15] New Zealand Other (non-Māori, non-Pacific) ever-screened women Relative risk† of breast cancer mortality by mammograms screening frequency category, ever-screened New Zealand Other (non-Māori, non-Pacific) women aged 45-69 years at first screening mammogram with non-screen detected breast cancer, 1999-2011

3.1.5.2. Ever-screened women diagnosed with breast cancer: screening frequency and mortality reduction

Narrowing the analysis to screened women diagnosed with breast cancer, the association between total mammograms and breast cancer mortality may be modified by whether the cancer was screen detected or non-screen detected. In all screened women diagnosed with cancer, the mortality reduction associated with screening frequency was 39% in women who had 2-3 screens prior to the cancer diagnosis compared to women with one screen only, and 81% in women with ≥4 screens (Table 3.37).

Table 3.37: New Zealand screened women breast cancer mortality by total mammograms, in women diagnosed with breast cancer[16]

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Screening frequency‡				
1 screen only			**1.00**	
2-3 screens	**-0.4973 (0.1216)**	**<.0001**	**0.61 (0.48-0.77)**	**-39 (-52 to -23)**
≥4 screens	**-1.6827 (0.1957)**	**<.0001**	**0.19 (0.13-0.27)**	**-81 (-87 to -73)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-1.3503 (0.2518)	<.0001	0.26 (0.16-0.42)	-74 (-84 to -58)
50-54	-0.0720 (0.1445)	0.6184	0.93 (0.70-1.24)	-7 (-30 to +24)
55-59	0.0581 (0.1586)	0.7142	1.06 (0.78-1.45)	6 (-22 to +45)
65-69	-1.1833 (0.5165)	0.0220	0.31 (0.11-0.84)	-69 (-89 to -16)
Ethnicity:				
Other			1.00	
Māori	0.0584 (0.1675)	0.7271	1.06 (0.76-1.47)	6 (-24 to +47)
Pacific	-0.0482 (0.3115)	0.8770	0.95 (0.52-1.75)	-5 (-48 to +75)
Intercept	-2.0218 (0.1263)	<.0001	-	-

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

‡ Total number of screening mammograms each woman has had

[16] Relative risk of breast cancer mortality by screening frequency, screened women with non-screen detected cancer, New Zealand women aged 45-69 years at first screening mammogram, 1999-2011

In screened women whose cancer was screen detected, the breast cancer mortality reduction associated with screening frequency was 43% in women screened 2-3 times before the cancer diagnosis and 84% in women with ≥4 screens (Table 3.38).

Table 3.38: New Zealand ever-screened women with screen-detected breast cancer, breast cancer mortality by total mammograms, 1999-2011[17]

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Screening frequency‡				
1 screen only			**1.00**	
2-3 screens	**-0.5671 (0.0979)**	**<.0001**	**0.57 (0.47-0.69)**	**-43 (-53 to -31)**
≥4 screens	**-1.8048 (0.1520)**	**<.0001**	**0.16 (0.12-0.22)**	**-84 (-88 to -78)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-1.4367 (0.2032)	<.0001	0.24 (0.16-0.35)	-76 (-84 to -65)
50-54	-0.1556 (0.1176)	0.1859	0.86 (0.68-1.08)	-14 (-32 to +8)
55-59	0.0141 (0.1263)	0.9114	1.01 (0.79-1.30)	1 (-21 to +30)
65-69	-1.1097 (0.3743)	0.0030	0.33 (0.16-0.69)	-67 (-84 to -31)
Ethnicity:				
Other			1.00	
Māori	-0.0869 (0.1365)	0.5243	0.92 (0.70-1.20)	-8 (-30 to +20)
Pacific	-0.0377 (0.2277)	0.8685	0.96 (0.62-1.50)	-4 (-38 to +50)
Intercept	-2.2826 (0.1029)	<.0001	-	-

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

‡ Total number of screening mammograms each woman has had

[17] Relative risk of breast cancer mortality by screening frequency, ever-screened New Zealand women aged 45-69 years at first screening mammogram with screen-detected breast cancer, 1999-2011

The breast cancer mortality differences in screened women by screening frequency were similar in women with non-screen detected cancer: women who had screened 2-3 times prior to diagnosis had 32% lower mortality than women who had screened once only; and women with 4 or more prior screens had 73% lower breast cancer mortality (Table 3.39).

Table 3.39: New Zealand ever-screened women with non-screen detected breast cancer Breast cancer mortality by total mammograms, 1999-2011[18]

Variable	Regression estimate (SE)	p-value	Relative Risk (95% CI)	% Mortality difference (95% CI)
Screening frequency‡				
1 screen only			**1.00**	
2-3 screens	**-0.3920 (0.1016)**	**<.0001**	**0.68 (0.55-0.82)**	**-32 (-45 to -18)**
≥4 screens	**-1.3070 (0.1684)**	**<.0001**	**0.27 (0.19-0.38)**	**-73 (-81 to -62)**
Variables adjusted				
Age at first screen (yr):				
60-64			1.00	
45-49	-1.1689 (0.2103)	<.0001	0.31 (0.21-0.47)	-69 (-79 to -53)
50-54	0.0698 (0.1198)	0.5601	1.07 (0.85-1.36)	7 (-15 to +36)
55-59	0.2341 (0.1338)	0.0803	1.26 (0.97-1.64)	26 (-3 to +64)
65-69	-1.1280 (0.4788)	0.0185	0.32 (0.13-0.83)	-68 (-87 to -17)
Ethnicity:				
Other			1.00	
Māori	0.2775 (0.1390)	0.0459	1.32 (1.01-1.73)	32 (1 to 73)
Pacific	0.1585 (0.2857)	0.5791	1.17 (0.67-2.05)	17 (-33 to +105)
Intercept	-1.7970 (0.1052)	<.0001	-	-

† From Poisson regression model adjusted for over-dispersion, screening inception cohort

‡ Total number of screening mammograms each woman has had

[18] Relative risk of breast cancer mortality by screening frequency, ever-screened New Zealand women aged 45-69 years at first screening mammogram with screen-detected breast cancer, 1999-2011

3.2. PROGNOSTIC INDICATORS IN DIAGNOSED BREAST CANCERS

Findings of apparent lower breast cancer mortality associated with mammography screening should be consistent with prognostic indicators indicative of better breast cancer outcomes in ever-screened versus never-screened women. Four key prognostic indicators expected to differ between ever- versus never-screened women with cancer are:

1. Grade of tumour (well differentiated, moderately differentiated, poorly differentiated), as proportions, which indicates the degree of histopathological malignancy;
2. Extent of disease (localised, regional, metastatic, unknown), as proportions;
3. Single versus multiple tumours, as proportions;
4. Mean or median maximum tumour size.

The corresponding hypotheses are that:

- Breast cancers diagnosed in ever-screened women should be significantly more likely to be of lower grade than in never-screened women;
- Breast cancers diagnosed in ever-screened women should be significantly more likely to be of lesser extent than in never-screened women;
- Breast cancers diagnosed in ever-screened women are significantly less likely to involve multiple tumours than in never-screened women;
- Breast cancers diagnosed in ever-screened women would have significantly smaller tumour sizes than in never-screened women.

For this particular analysis, women diagnosed with cancer in the screening age group only are analysed, in order to assess effects on intermediary variables relevant to breast cancer mortality in the screening target group, those aged 45-69 years.

3.2.1. Prognostic indicators in ever- compared to never-screened women

As indicated in Table 3.40 below, ever-screened women diagnosed with breast cancer have better prognostic indications than never-screened women, on all four of the indicators. A significantly higher proportion of ever-screened women diagnosed with breast cancer had well-differentiated tumours (30%) compared to 18% of never-screened diagnosed women; 63% of diagnosed ever-screened women had localised cancer compared to 46% in never-screened women, significantly higher; in ever-screened women with breast cancer, 1.8% had multiple tumours compared to 3.8% in never-screened women, converting to a relative risk of having multiple tumours in ever-screened women of 0.48 compared to never-screened women; and the median maximum tumour size in ever-screened women was 15 mm compared to 20 mm in never-screened women diagnosed with breast cancer (significantly smaller).

As is evident from Table 3.40, the main source of the breast cancer mortality benefit in ever-screened women is consistent with earlier detection of cancer with consequent better prognosis than in never-screened women.

All New Zealand women

Table 3.40: Prognostic indicators for breast cancers diagnosed in ever- versus never-BSA screened women, New Zealand women aged 45-69 years at year of diagnosis, 2000-2011

Prognostic Indicator	Ever screened	Never screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	3,725 (29.6)	1,624 (18.0)	
2: Moderately differentiated	5,196 (41.3)	3,679 (40.3)	
3: Poorly differentiated	3,013 (24.0)	2,877 (31.8)	$X^2_{(4)}$=558, p<.0001
4: Undifferentiated, anaplastic	1 (0.0)	1 (0.0)	
9: Not recorded/NA	638 (5.1)	860 (9.5)	
Extent of disease			
B: Localised	7,928 (63.1)	4,169 (46.1)	
C/D: Adjacent organ/regional lymph node	3,662 (29.1)	3,521 (38.9)	$X^2_{(3)}$=724, p<.0001
E: Distant	190 (1.5)	447 (4.9)	
F: Unknown	793 (6.3)	904 (10.0)	
Multiple tumours			
No	12,344 (98.2)	8,697 (96.2)	RR=0.48 (0.41-0.56)
Yes	229 (1.8)	344 (3.8)	$X^2_{(1)}$=80.2, p<.0001[†]
Maximum tumour size	**(mm)**	**(mm)**	
Mean	18.1	24.4	t=-25.8, p<.0001
Median	15.0	20.0	t=-27.8, p<.0001[‡]

[†] Mantel-Haenszel X^2 test

[‡] Two-sample median test

A breakdown of prognostic indicators by periods of diagnosis, 2000-04, 2005-09 and 2010-11 shows similar differences between ever- and never-screened women (Tables 3.41-3.43). Notable period trends included proportions of distant cancer in never-screened women (increasing from 4.8% to 9.1%), although these differences also partly reflect smaller numbers in the 2010-11 period. Corresponding proportions in ever-screened women also increased, from 1.0% to 1.4%. The proportion of localised cancer in ever-screened women increased from 61% to 64% over these periods.

Table 3.41: Prognostic indicators for breast cancers diagnosed in ever- versus never-BSA screened women, New Zealand women aged 45-69 years at year of diagnosis, 2000-2004

Prognostic Indicator	Ever screened	Never screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	1,121 (32.3)	672 (18.4)	
2: Moderately differentiated	1,347 (38.8)	1,453 (39.9)	
3: Poorly differentiated	700 (20.2)	1,050 (28.8)	$X^2_{(4)}$=219, p<.0001
4: Undifferentiated, anaplastic	1 (0.0)	0 (0.0)	
9: Not recorded/NA	305 (8.8)	470 (12.9)	
Extent of disease			
B: Localised	2,140 (61.6)	1,658 (45.5)	
C/D: Adjacent organ/regional lymph node	980 (28.2)	1,377 (37.8)	$X^2_{(3)}$=236, p<.0001
E: Distant	34 (1.0)	174 (4.8)	
F: Unknown	320 (9.2)	436 (6.1)	
Multiple tumours			
No	3,415 (98.3)	3,457 (94.8)	RR=0.33 (0.25-0.44)
Yes	59 (1.7)	188 (5.2)	$X^2_{(1)}$=63.5, p<.0001†
Maximum tumour size	**(mm)**	**(mm)**	
Mean	17.6	23.7	t=-15.4, p<.0001
Median	15.0	20.0	t=-15.0, p<.0001‡

† Mantel-Haenszel X^2 test

‡ Two-sample median test

Table 3.42: Prognostic indicators for breast cancers diagnosed in ever- versus never-BSA screened women, New Zealand women aged 45-69 years at year of diagnosis, 2005-2009

Prognostic Indicator	Ever screened	Never screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	1,661 (29.2)	476 (18.3)	
2: Moderately differentiated	2,409 (42.4)	1,050 (40.3)	
3: Poorly differentiated	1,395 (24.5)	863 (33.1)	$X^2_{(4)}$=203, p<.0001
4: Undifferentiated, anaplastic	0 (0.0)	1 (0.0)	
9: Not recorded/NA	221 (3.9)	218 (8.4)	
Extent of disease			
B: Localised	3,630 (63.8)	1,128 (43.3)	
C/D: Adjacent organ/regional lymph node	1,680 (29.6)	1,041 (39.9)	$X^2_{(3)}$=420, p<.0001
E: Distant	90 (1.6)	191 (7.3)	
F: Unknown	286 (5.0)	248 (9.5)	
Multiple tumours			
No	5,574 (98.0)	2,512 (96.3)	RR=0.54 (0.41-0.70)
Yes	112 (2.0)	96 (3.7)	$X^2_{(1)}$=21.4, p<.0001†
Maximum tumour size	**(mm)**	**(mm)**	
Mean	18.0	25.5	t=-16.8, p<.0001
Median	15.0	20.0	t=-17.7, p<.0001‡

† Mantel-Haenszel X^2 test

‡ Two-sample median test

Table 3.43: Prognostic indicators for breast cancers diagnosed in ever- versus never-BSA screened women, New Zealand women aged 45-69 years at year of diagnosis, 2010-2011

Prognostic Indicator	Ever screened	Never screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	815 (28.7)	153 (19.4)	
2: Moderately differentiated	1,206 (42.4)	335 (42.4)	
3: Poorly differentiated	737 (25.9)	240 (30.4)	$X^2_{(3)}$=60.7, p<.0001
4: Undifferentiated, anaplastic	0 (0.0)	0 (0.0)	
9: Not recorded/NA	85 (3.0)	62 (7.9)	
Extent of disease			
B: Localised	1,824 (64.2)	347 (43.9)	
C/D: Adjacent organ/regional lymph node	825 (29.0)	281 (35.6)	$X^2_{(3)}$=724, p<.0001
E: Distant	41 (1.4)	72 (9.1)	
F: Unknown	153 (5.4)	90 (11.4)	
Multiple tumours			
No	2,803 (98.6)	761 (96.3)	RR=0.38 (0.24-0.61)
Yes	40 (1.4)	29 (3.7)	$X^2_{(1)}$=17.0, p<.0001[†]
Maximum tumour size	**(mm)**	**(mm)**	
Mean	18.2	25.9	t=-8.68, p<.0001
Median	15.0	21.0	t=-11.5, p<.0001[‡]

[†] Mantel-Haenszel X^2 test

[‡] Two-sample median test

Māori women

Among Māori women, differences in prognostic indicators between ever- and never- screened women were similar to those overall (Table 3.44). The proportion of localised cancer in ever-screened Māori women with cancer was somewhat lower (59%) than in ever-screened women overall (63%), and in never-screened Māori women with cancer the proportion of localised cancer (39%) was substantially lower than in corresponding never-screened women overall (46%). While the median maximum tumour size in Māori ever-screened women diagnosed with cancer (16 mm) was 1 mm larger than that for equivalent ever-screened women overall, the median size in never-screened Māori women (25 mm) was 5 mm larger than for all never-screened women diagnosed with breast cancer (cf. Table 3.40), and 9 mm larger than ever-screened Māori women.

Table 3.44: Prognostic indicators for breast cancers diagnosed in ever- versus never-BSA screened women, New Zealand Māori women aged 45-69 years at year of diagnosis, 2000-2011

Prognostic Indicator	Ever screened	Never screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	398 (27.4)	177 (14.4)	
2: Moderately differentiated	646(44.5)	507 (42.1)	
3: Poorly differentiated	337 (23.2)	412 (34.3)	$X^2_{(4)}$=95.2, p<.0001
4: Undifferentiated, anaplastic	0 (0.0)	1 (0.1)	
9: Not recorded/NA	70 (4.8)	106 (8.8)	
Extent of disease			
B: Localised	857 (59.1)	463 (38.5)	
C/D: Adjacent organ/regional lymph node	459 (31.6)	536 (44.6)	$X^2_{(3)}$=122, p<.0001
E: Distant	25 (1.7)	63 (5.2)	
F: Unknown	110 (7.6)	141 (11.7)	
Multiple tumours			
No	1,427 (98.4)	1,167 (97.0)	RR=0.55 (0.33-0.92)
Yes	24 (1.7)	36 (3.0)	$X^2_{(1)}$=5.33, p=0.0209†
Maximum tumour size	**(mm)**	**(mm)**	
Mean	19.2	28.7	t=-13.7, p<.0001
Median	16.0	25.0	t=-15.2, p<.0001‡

† Mantel-Haenszel X^2 test

‡ Two-sample median test

The time trends for prognostic indicators in Māori women were similar as in all women for distant cancer in never-screened women (rising from 4% to 9% over the period, Tables 3.45-3.47). Proportions of localised cancer in ever-screened Māori women increased from 53% in 2000-04 to 64% by 2010-11.

Table 3.45: Prognostic indicators for breast cancers diagnosed in ever- versus never-BSA screened women, New Zealand Māori women aged 45-69 years at year of diagnosis, 2000-2004

Prognostic Indicator	Ever screened	Never screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	94 (29.4)	60 (14.5)	
2: Moderately differentiated	132 (41.3)	159 (38.3)	
3: Poorly differentiated	65 (20.3)	139 (33.5)	$X^2_{(3)}$=34.3, p<.0001
4: Undifferentiated, anaplastic	0 (0.0)	0 (0.0)	
9: Not recorded/NA	29 (9.1)	57 (13.7)	
Extent of disease			
B: Localised	169 (52.8)	150 (36.1)	
C/D: Adjacent organ/regional lymph node	107 (33.4)	187 (45.1)	$X^2_{(3)}$=236, p<.0001
E: Distant	5 (1.6)	18 (4.3)	
F: Unknown	39 (12.2)	60 (14.5)	
Multiple tumours			
No	319 (99.7)	398 (95.9)	RR=0.08 (0.01-0.57)
Yes	1 (0.3)	17 (4.1)	$X^2_{(1)}$=10.8, p=0.0010†
Maximum tumour size	**(mm)**	**(mm)**	
Mean	19.9	30.0	t=-7.53, p<.0001
Median	17.0	25.0	t=-7.87, p<.0001‡

† Mantel-Haenszel X^2 test

‡ Two-sample median test

Table 3.46: Prognostic indicators for breast cancers diagnosed in ever- versus never-BSA screened women, New Zealand Māori women aged 45-69 years at year of diagnosis, 2005-2009

Prognostic Indicator	Ever screened	Never screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	192 (27.7)	39 (10.5)	
2: Moderately differentiated	325 (46.9)	170 (45.7)	
3: Poorly differentiated	152 (21.9)	136 (36.6)	
4: Undifferentiated, anaplastic	0 (0.0)	1 (0.0)	$X^2_{(4)}$=60.6, p<.0001
9: Not recorded/NA	24 (3.5)	26 (7.0)	
Extent of disease			
B: Localised	415 (55.9)	131 (35.2)	
C/D: Adjacent organ/regional lymph node	225 (35.5)	169 (45.4)	$X^2_{(3)}$=76.5, p<.0001
E: Distant	12 (1.7)	34 (9.1)	
F: Unknown	41 (5.9)	38 (10.2)	
Multiple tumours			
No	682 (98.4)	362 (97.3)	RR=0.59 (0.25-1.38)
Yes	11 (1.6)	10 (2.7)	$X^2_{(1)}$=1.51, p= 0.2182 †
Maximum tumour size	**(mm)**	**(mm)**	
Mean	18.6	30.2	t=-9.47, p<.0001
Median	16.0	25.0	t=-10.0, p<.0001‡

† Mantel-Haenszel X^2 test

‡ Two-sample median test

Table 3.47: Prognostic indicators for breast cancers diagnosed in ever- versus never-BSA screened women, New Zealand Māori women aged 45-69 years at year of diagnosis, 2010-2011

Prognostic Indicator	Ever screened	Never screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	102 (26.0)	18 (16.4)	
2: Moderately differentiated	175 (44.5)	46 (41.8)	
3: Poorly differentiated	101 (25.7)	38 (34.6)	$X^2_{(3)}$=8.14, p=0.0433
4: Undifferentiated, anaplastic	0 (0.0)	0 (0.0)	
9: Not recorded/NA	15 (3.8)	8 (7.3)	
Extent of disease			
B: Localised	252 (64.1)	40 (36.4)	
C/D: Adjacent organ/regional lymph node	110 (28.0)	44 (40.0)	$X^2_{(3)}$=41.5, p<.0001
E: Distant	4 (1.0)	10 (9.1)	
F: Unknown	27 (6.9)	16 (14.6)	
Multiple tumours			
No	384 (97.7)	103 (93.6)	RR=0.36 (0.14-0.94)
Yes	9 (2.3)	7 (6.4)	$X^2_{(1)}$=4.62, p=0.0316[†]
Maximum tumour size	**(mm)**	**(mm)**	
Mean	19.6	28.3	t=-4.86, p<.0001
Median	15.0	26.0	t=-5.78, p<.0001[‡]

[†] Mantel-Haenszel X^2 test

[‡] Two-sample median test

Pacific women

Among Pacific women diagnosed with breast cancer, ever-screened women showed similar prognostic indicators with corresponding ever-screened Māori woman and all women diagnosed with breast cancer. However, among never-screened Pacific women, 11% of breast cancers were metastatic/distant compared to 5% in never-screened Māori and all women (Table 3.48). This was reflected in median tumour size: ever-screened Pacific women had a similar median size as Māori women (16.5mm versus 16mm) but in never-screened Pacific women the median tumour size was 30 mm, 5 mm larger than for never-screened Māori and 10 mm larger than in all never-screened women diagnosed with breast cancer. The median size maximum tumour size in never-screened Pacific women was 13.5 mm larger than in ever-screened Pacific women.

Table 3.48: Prognostic indicators for breast cancers diagnosed in ever- versus never-BSA screened women, New Zealand Pacific women aged 45-69 years at year of diagnosis, 2000-2011

Prognostic Indicator	Ever screened	Never screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	105 (27.1)	46 (9.7)	
2: Moderately differentiated	172 (44.3)	178 (37.6)	
3: Poorly differentiated	94 (24.2)	186 (39.2)	$X^2_{(3)}$=72.8, p<.0001
4: Undifferentiated, anaplastic	0 (0.0)	0 (0.0)	
9: Not recorded/NA	17 (4.4)	64 (13.5)	
Extent of disease			
B: Localised	216 (55.7)	168 (35.4)	
C/D: Adjacent organ/regional lymph node	121 (31.2)	188 (40.0)	$X^2_{(3)}$=52.4, p<.0001
E: Distant	7 (1.8)	54 (11.4)	
F: Unknown	44 (11.3)	64 (13.5)	
Multiple tumours			
No	383 (98.7)	461 (97.3)	RR=0.47 (0.17-1.31)
Yes	5 (1.3)	13 (2.7)	$X^2_{(1)}$=2.21, p=0.1375†
Maximum tumour size	**(mm)**	**(mm)**	
Mean	20.6	35.4	t=-9.1, p<.0001
Median	16.5	30.0	t=-8.35, p<.0001‡

† Mantel-Haenszel X^2 test

‡ Two-sample median test

The time trends in prognostic indicators for Pacific women show a sharp increase in proportions of distant cancers in never-screened women (Tables 3.49-3.51). Unlike in Māori women, the proportions of localised cancer in ever-screened Pacific women increased remained at 58% in 2000-04 and 2005-09, while the lower proportion of 50% in 2010-11 is based on low numbers.

Table 3.49: Prognostic indicators for breast cancers diagnosed in ever- versus never-BSA screened women, New Zealand Pacific women aged 45-69 years at year of diagnosis, 2000-2004

Prognostic Indicator	Ever screened	Never screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	15 (19.7)	14 (9.3)	
2: Moderately differentiated	40 (52.6)	57 (38.0)	
3: Poorly differentiated	18 (23.7)	52 (34.7)	$X^2_{(3)}$=16.2, p=0.0010
4: Undifferentiated, anaplastic	0 (0.0)	0 (0.0)	
9: Not recorded/NA	3 (4.0)	27 (18.0)	
Extent of disease			
B: Localised	44 (57.9)	58 (38.7)	
C/D: Adjacent organ/regional lymph node	23 (30.3)	61 (40.7)	$X^2_{(3)}$=8.0, p=0.0463
E: Distant	3 (4.0)	13 (8.7)	
F: Unknown	6 (7.9)	18 (12.0)	
Multiple tumours			
No	75 (98.7)	145 (96.7)	RR=0.39 (0.05-3.32)
Yes	1 (1.3)	5 (3.3)	$X^2_{(1)}$=0.79, p=0.3738†
Maximum tumour size	**(mm)**	**(mm)**	
Mean	21.8	33.4	t=-3.96, p=0.0001
Median	17.0	28.0	t=-4.26, p<.0001‡

† Mantel-Haenszel X^2 test

‡ Two-sample median test

Table 3.50: Prognostic indicators for breast cancers diagnosed in ever- versus never-BSA screened women, New Zealand Pacific women aged 45-69 years at year of diagnosis, 2005-2009

Prognostic Indicator	Ever screened	Never screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	59 (30.7)	18 (10.7)	
2: Moderately differentiated	79 (41.2)	62 (36.9)	
3: Poorly differentiated	43 (22.4)	66 (39.3)	$X^2_{(3)}$=30.9, p<.0001
4: Undifferentiated, anaplastic	0 (0.0)	0 (0.0)	
9: Not recorded/NA	11 (5.7)	22 (13.1)	
Extent of disease			
B: Localised	112 (58.3)	48 (28.6)	
C/D: Adjacent organ/regional lymph node	55 (28.7)	63 (37.5)	$X^2_{(3)}$=41.2, p<.0001
E: Distant	4 (2.1)	23 (13.7)	
F: Unknown	21 (10.9)	34 (20.2)	
Multiple tumours			
No	189 (98.4)	163 (97.0)	RR=0.53 (0.13-2.16)
Yes	3 (1.6)	5 (3.0)	$X^2_{(1)}$=0.82, p=0.3646†
Maximum tumour size	**(mm)**	**(mm)**	
Mean	19.3	38.2	t=-7.07, p<.0001
Median	16.0	30.0	t=-6.08, p<.0001‡

† Mantel-Haenszel X^2 test

‡ Two-sample median test

Table 3.51: Prognostic indicators for breast cancers diagnosed in ever- versus never-BSA screened women, New Zealand Pacific women aged 45-69 years at year of diagnosis, 2010-11

Prognostic Indicator	Ever screened	Never screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	29 (26.1)	4 (7.7)	
2: Moderately differentiated	51 (46.0)	19 (36.5)	
3: Poorly differentiated	28 (25.2)	19 (36.5)	$X^2_{(3)}$=20.4, p=0.0001
4: Undifferentiated, anaplastic	0 (0.0)	0 (0.0)	
9: Not recorded/NA	3 (2.7)	10 (19.2)	
Extent of disease			
B: Localised	55 (49.6)	16 (30.8)	
C/D: Adjacent organ/regional lymph node	39 (35.1)	17 (32.7)	$X^2_{(3)}$=39.7, p<.0001
E: Distant	0 (0.0)	16 (30.8)	
F: Unknown	17 (15.3)	3 (5.7)	
Multiple tumours			
No	111 (100)	52 (100)	-
Yes	0 (0.0)	0 (0.0)	-
Maximum tumour size	**(mm)**	**(mm)**	
Mean	21.9	39.6	t=-2.05, p=0.0472
Median	17.0	31.5	t=-3.54, p=0.0004‡

† Mantel-Haenszel X^2 test

‡ Two-sample median test

Other women

As would be expected from their preponderance in the population, Other women (non-Māori, non-Pacific) diagnosed with breast cancer had prognostic indicators by ever- and never-screened status similar to the population overall (Table 3.52).

Table 3.52: Prognostic indicators for breast cancers diagnosed in ever- versus never-BSA screened women, New Zealand Other women aged 45-69 years at year of diagnosis, 2000-2011

Prognostic Indicator	Ever screened	Never screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	3,222 (30.0)	1,401 (19.0)	
2: Moderately differentiated	4,378 (40.8)	2,994 (40.7)	
3: Poorly differentiated	2,582 (24.1)	2,279 (31.0)	$X^2_{(4)}$=399, p<.0001
4: Undifferentiated, anaplastic	1 (0.0)	0 (0.0)	
9: Not recorded/NA	551 (5.1)	690 (9.4)	
Extent of disease			
B: Localised	6,855 (63.9)	3,533 (48.0)	
C/D: Adjacent organ/regional lymph node	3,082 (28.7)	2,797 (38.0)	$X^2_{(3)}$=527, p<.0001
E: Distant	158 (1.5)	330 (4.5)	
F: Unknown	639 (6.0)	699 (9.5)	
Multiple tumours			
No	10,534 (98.1)	7,069 (96.0)	RR=0.47 (0.39-0.56)
Yes	200 (1.9)	295 (4.0)	$X^2_{(1)}$=75.4, p<.0001†
Maximum tumour size	**(mm)**	**(mm)**	
Mean	17.9	23.1	t=-20.4, p<.0001
Median	15.0	20.0	t=-21.5, p<.0001‡

† Mantel-Haenszel X^2 test

‡ Two-sample median test

The trends in prognostic indicators for Other women reflect those in the whole population (Tables 3.53-3.55).

Table 3.53: Prognostic indicators for breast cancers diagnosed in ever- versus never-BSA screened women, New Zealand Other women aged 45-69 years at year of diagnosis, 2000-2004

Prognostic Indicator	Ever screened	Never screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	1,012 (32.9)	598 (19.4)	
2: Moderately differentiated	1,175 (38.2)	1,237 (40.2)	
3: Poorly differentiated	617 (20.1)	859 (27.9)	$X^2_{(4)}$=168, p<.0001
4: Undifferentiated, anaplastic	1 (0.0)	0 (0.0)	
9: Not recorded/NA	273 (8.9)	386 (12.5)	
Extent of disease			
B: Localised	1,927 (62.6)	1,450 (47.1)	
C/D: Adjacent organ/regional lymph node	850 (27.6)	1,129 (36.7)	$X^2_{(3)}$=199, p<.0001
E: Distant	26 (0.8)	143 (4.6)	
F: Unknown	275 (8.9)	358 (11.6)	
Multiple tumours			
No	3,021 (98.2)	2,914 (94.6)	RR=0.34 (0.26-0.46)
Yes	57 (1.9)	166 (5.4)	$X^2_{(1)}$=55.2, p<.0001†
Maximum tumour size	**(mm)**	**(mm)**	
Mean	17.3	22.4	t=-12.7, p<.0001
Median	15.0	19.0	t=-12.4, p<.0001‡

† Mantel-Haenszel X^2 test

‡ Two-sample median test

Table 3.54: Prognostic indicators for breast cancers diagnosed in ever- versus never-BSA screened women, New Zealand Other women aged 45-69 years at year of diagnosis, 2005-2009

Prognostic Indicator	Ever screened	Never screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	1,410 (29.4)	419 (20.3)	
2: Moderately differentiated	2,005 (41.8)	818 (39.6)	
3: Poorly differentiated	1,200 (25.0)	661 (32.0)	$X^2_{(3)}$=125, p<.0001
4: Undifferentiated, anaplastic	0 (0.0)	0 (0.0)	
9: Not recorded/NA	186 (3.9)	170 (8.2)	
Extent of disease			
B: Localised	3,103 (64.6)	949 (45.9)	
C/D: Adjacent organ/regional lymph node	1,400 (29.2)	809 (39.1)	$X^2_{(3)}$=284, p<.0001
E: Distant	74 (1.5)	134 (6.5)	
F: Unknown	224 (4.7)	176 (8.5)	
Multiple tumours			
No	4,703 (98.0)	1,987 (96.1)	RR=0.34 (0.26-0.46)
Yes	98 (2.0)	81 (3.9)	$X^2_{(1)}$=55.2, p<.0001†
Maximum tumour size	**(mm)**	**(mm)**	
Mean	17.9	23.9	t=-12.7, p<.0001
Median	15.0	20.0	t=-14.1, p<.0001‡

† Mantel-Haenszel X^2 test

‡ Two-sample median test

Table 3.55: Prognostic indicators for breast cancers diagnosed in ever- versus never-BSA screened women, New Zealand Other women aged 45-69 years at year of diagnosis, 2010-2011

Prognostic Indicator	Ever screened	Never screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	684 (29.2)	131 (20.9)	
2: Moderately differentiated	980 (41.9)	270 (43.0)	
3: Poorly differentiated	608 (26.0)	183 (29.1)	$X^2_{(3)}$=37.3, p<.0001
4: Undifferentiated, anaplastic	0 (0.0)	0 (0.0)	
9: Not recorded/NA	67 (2.9)	44 (7.0)	
Extent of disease			
B: Localised	1,517 (64.9)	291 (46.3)	
C/D: Adjacent organ/regional lymph node	676 (28.9)	220 (35.0)	$X^2_{(3)}$=128, p<.0001
E: Distant	37 (1.6)	46 (7.3)	
F: Unknown	109 (4.7)	71 (11.3)	
Multiple tumours			
No	2,308 (98.7)	606 (96.5)	RR=0.38 (0.22-0.65)
Yes	31 (1.3)	22 (3.5)	$X^2_{(1)}$=13.4, p=0.0003†
Maximum tumour size	**(mm)**	**(mm)**	
Mean	17.8	24.6	t=-7.68, p<.0001
Median	15.0	20.0	t=-9.46, p<.0001‡

† Mantel-Haenszel X^2 test

‡ Two-sample median test

Non-screen detected breast cancers

From the corresponding prognostic indicators: there were no substantial differences in tumour grade proportions between ever- and never-screened women with non-screen detected cancer (despite significant heterogeneity); 50% of cancers in ever-screened women were localised compared to 44% in never-screened women with corresponding proportions of metastatic cancer of 3.2% and 6.4%; the other main contributor to better prognosis in ever-screened women was the relative risk of 0.64 of having multiple tumours compared to never-screened women (Table 3.56).

Table 3.56: Prognostic indicators for non-screen detected cancers in ever-BSA screened versus never-BSA screened New Zealand women aged 45-69 years at diagnosis, 1999-2011

Prognostic indicator	Ever screened	Never screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	861 (20.8)	1,374 (18.2)	
2: Moderately differentiated	1,520 (36.7)	3,025 (40.1)	
3: Poorly differentiated	1,449 (35.0)	2,258 (30.0)	$\chi^2_{(4)}$=86.2, p<.0001
4: Undifferentiated, anaplastic	1 (0.0)	1 (0.0)	
9: Not recorded/NA	308 (7.4)	881 (11.7)	
Extent of disease			
B: Localised	2,065 (49.9)	3,328 (44.1)	
C/D: Adjacent organ/ regional lymph nodes	1,609 (38.9)	2,872 (38.1)	$\chi^2_{(3)}$=100, p<.0001
E: Distant	133 (3.2)	480 (6.4)	
F: Unknown	332 (8.0)	859 (11.4)	
Multiple tumours			
No	4,024 (97.2)	7,210 (95.6)	RR=0.64 (0.52-0.78)
Yes	115 (2.8)	329 (4.4)	$\chi^2_{(1)}$=18.4, p=<.0001[†]
Maximum tumour size	**(mm)**	**(mm)**	
Mean	23.4	24.4	t=-2.82, p=0.0048
Median	20.0	20.0	Z=-3.0, p=0.0027[‡]

[†] Mantel-Haenszel χ^2 test

[‡] Two-sample median test

3.2.2. Prognostic indicators and Screening regularity

In this analysis a binary summary indicator of screening regularity (screened ≥3 time with mean screening interval ≤ 30 months versus not) is used as the comparison of interest with respect to tumour grade, extent of disease, multiple tumours and maximum tumour size.

All New Zealand Women

Screened women with 3 or more prior screening mammograms and a mean screening interval of ≤30 months prior to a cancer diagnosis had significantly higher proportions diagnosed with localised cancer (67% versus 60%), with correspondingly lower proportions in more distant degree-of-spread categories. They were also at significantly lower risk of having multiple tumours diagnosed (RR=0.57) and had a significantly lower median maximum tumour size of 14 mm compared to 15 mm in less frequently screened women. Proportions of well differentiated tumours (31% versus 30%), and proportions in less differentiated tumour grade categories were similar in regular and irregular screeners (Table 3.57).

Table 3.57: Prognostic indicators for breast cancers diagnosed in regularly screened women versus remainder[§], New Zealand women aged 45-69 years at diagnosis, 1999-2011

Prognostic indicator	Regularly screened	Irregularly screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	1,697 (30.6)	2,160 (29.7)	
2: Moderately differentiated	2,315 (41.8)	2,960 (40.6)	
3: Poorly differentiated	1,277 (23.0)	1,723 (23.7)	$\chi^2_{(4)}$=15.5, p=0.0038
4: Undifferentiated, anaplastic	0 (0.0)	1 (0.0)	
9: Not recorded/NA	255 (4.6)	441 (6.1)	
Extent of disease			
B: Localised	3,738 (67.4)	4,333 (59.5)	
C/D: Adjacent organ/ regional lymph nodes	1,433 (25.9)	2,310 (31.7)	$\chi^2_{(3)}$=93.0, p<.0001
E: Distant	53 (1.0)	115 (1.6)	
F: Unknown	320 (5.8)	527 (7.2)	
Multiple tumours			
No	5,475 (98.8)	7,127 (97.8)	RR=0.57 (0.43-0.76)
Yes	69 (1.2)	158 (2.2)	$\chi^2_{(1)}$=15.5, p<.0001[†]
Maximum tumour size	**(mm)**	**(mm)**	
Mean	16.3	19.3	t=-12.0, p<.0001
Median	14.0	15.0	Z=-10.5, p<.0001[‡]

[†] Mantel-Haenszel χ^2 test

[‡] Two-sample median test

[§] ≥3 times with average screening interval ≤30 months ('Regularly screened'); screened remainder ('Irregularly screened')

Māori women

In screened Māori women with breast cancer, the proportion of localised cancers (66%) in regularly screened women was substantially higher than in irregularly screened Māori women (55%) (Table 3.58). The median maximum tumour size was significantly (p<.0001) smaller in the regularly screened group (15 mm) than the screened remainder (17 mm). There was no significant difference in proportions of tumour grade or multiple tumours by screening group.

Table 3.58: Prognostic indicators for breast cancers diagnosed in regularly screened Māori women versus the screened remainder[§], Māori women aged 45-69 years at diagnosis, 1999-2011

Prognostic indicator	Regularly Screened	Irregularly screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	149 (27.0)	267 (28.3)	
2: Moderately differentiated	261 (47.4)	401 (42.5)	$\chi^2_{(3)}$=4.36, p=0.2250
3: Poorly differentiated	118 (21.4)	222 (23.5)	
9: Not recorded/NA	23 (4.2)	54 (5.7)	
Extent of disease			
B: Localised	365 (66.2)	516 (54.7)	
C/D: Adjacent organ/ regional lymph nodes	145 (26.3)	328 (34.8)	$\chi^2_{(3)}$=21.0, p=0.0001
E: Distant	4 (0.7)	19 (2.0)	
F: Unknown	37 (6.7)	81 (8.6)	
Multiple tumours			
No	544 (98.7)	930 (98.5)	RR=0.86 (0.35-2.11)
Yes	7 (1.3)	14 (1.5)	$\chi^2_{(1)}$=0.114, p=0.7361[†]
Maximum tumour size	**(mm)**	**(mm)**	
Mean	17.0	20.7	t=-4.96, p<.0001
Median	15.0	17.0	Z=-4.42, p<.0001[‡]

[†] Mantel-Haenszel χ^2 test

[‡] Two-sample median test

[§] $\geq$3 times with average screening interval $\leq$30 months ('Regularly Screened'); screened remainder ('Irregularly Screened')

Pacific women

In Pacific women with breast cancer (Table 3.59) the median maximum tumour size in the regularly screened group was 13 mm compared to 18 mm in irregularly screened Pacific women. This compares to 14 mm and 15 mm in Other women, and 15 mm and 17 mm in Māori women. The proportion of regularly screened women with a well-differentiated tumour (33%) was similar to Other (non-Māori, non-Pacific) women (31%) (Table 3.60), and higher than in Māori women (27%); the proportion of localised cancer in regularly screened women with cancer was 68% compared to 50% in irregularly screened women. These extent-of-disease proportions and differences were broadly similar to those in Māori and Other women.

Table 3.59: Prognostic indicators for breast cancers diagnosed in regularly screened Pacific women versus the screened remainder[§], Pacific women aged 45-69 years at diagnosis, 1999-2011

Prognostic indicator	Regularly Screened	Irregularly Screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	39 (32.5)	69 (24.3)	
2: Moderately differentiated	56 (46.7)	126 (44.4)	$\chi^2_{(3)}$=6.54, p=0.0882
3: Poorly differentiated	19 (15.8)	76 (26.8)	
9: Not recorded/NA	6 (5.0)	13 (4.6)	
Extent of disease			
B: Localised	81 (67.5)	143 (50.4)	
C/D: Adjacent organ/ regional lymph nodes	28 (23.3)	100 (35.2)	$\chi^2_{(3)}$=10.2, p=0.0167
E: Distant	1 (0.8)	6 (2.1)	
F: Unknown	10 (8.3)	35 (12.3)	
Multiple tumours			
No	118 (98.3)	282 (99.3)	RR=2.37 (0.34-16.6)
Yes	2 (1.7)	2 (0.7)	$\chi^2_{(1)}$=0.797, p=0.5855[†]
Maximum tumour size	**(mm)**	**(mm)**	
Mean	16.1	23.1	t=-4.27, p<.0001
Median	13.0	18.0	Z=-4.13, p<.0001[‡]

[†] Mantel-Haenszel χ^2 test

[‡] Two-sample median test

[§] ≥3 times with average screening interval <30 months ('Regularly Screened'); screened remainder ('Irregularly Screened')

Other women

Prognostic indicators by screening regularity in Other (non-Māori, non-Pacific) women are similar to those for all women (Table 3.60).

Table 3.60: Prognostic indicators for breast cancers diagnosed in regularly screened, Other (non-Māori, non-Pacific) women versus the screened remainder[§] of Other women aged 45-69 years at diagnosis, 1999-2011

Prognostic indicator	Regularly Screened	Irregularly Screened	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	1,649 (31.2)	1,684 (29.9)	
2: Moderately differentiated	2,173 (41.1)	2,258 (40.1)	
3: Poorly differentiated	1,229 (23.2)	1,336 (23.7)	$\chi^2_{(4)}$=19.1, p=0.0008
4: Undifferentiated, anaplastic	0 (0.0)	1 (0.0)	
9: Not recorded/NA	242 (4.6)	358 (6.4)	
Extent of disease			
B: Localised	3,586 (67.8)	3,380 (60.0)	
C/D: Adjacent organ/ regional lymph nodes	1,362 (25.7)	1,780 (31.6)	$\chi^2_{(3)}$=73.4, p<.0001
E: Distant	52 (1.0)	86 (1.5)	
F: Unknown	293 (5.5)	391 (6.9)	
Multiple tumours			
No	5,223 (98.7)	5,505 (97.7)	RR=0.56 (0.42-0.75)
Yes	70 (1.3)	132 (2.3)	$\chi^2_{(1)}$=15.6, p=<.0001[†]
Maximum tumour size	**(mm)**	**(mm)**	
Mean	16.3	19.1	t=-10.1, p<.0001
Median	14.0	15.0	Z=-9.16, p<.0001[‡]

[†] Mantel-Haenszel χ^2 test

[‡] Two-sample median test

[§] $\geq$3 times with average screening interval <30 months ('Regularly Screened'); screened remainder ('Irregularly Screened')

3.2.3. Prognostic indicators and initial or subsequent screen

The strongest correlation with prognostic indicators was in extent of disease, where localised cancer comprised 72% of the total in subsequent screeners and 64% in initial screeners; and in median maximum tumour size, which was 12 mm in subsequent screeners compared to 15 mm in initial screeners (Table 3.61).

Table 3.61: Prognostic indicators for **screen-detected breast cancers diagnosed in initial versus subsequent screeners,** New Zealand women aged 45-69 years at diagnosis, 1999-2011

Prognostic indicator	Subsequent screener	Initial screener	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	2,127 (34.9)	869 (33.6)	
2: Moderately differentiated	2,637 (43.2)	1,118 (43.2)	$\chi^2_{(3)}$=9.48, p=0.0235
3: Poorly differentiated	1,090 (17.9)	461 (17.8)	
9: Not recorded/NA	246 (4.0)	142 (5.5)	
Extent of disease			
B: Localised	4,361 (71.5)	1,645 (63.5)	
C/D: Adjacent organ/ regional lymph nodes	1,399 (22.9)	735 (28.4)	$\chi^2_{(3)}$=60.3, p<.0001
E: Distant	17 (0.3)	18 (0.7)	
F: Unknown	323 (5.3)	192 (7.4)	
Multiple tumours			
No	6,022 (98.7)	2,556 (98.7)	RR=0.97 (0.65-1.45)
Yes	78 (1.3)	34 (1.3)	$\chi^2_{(1)}$=0.02, p=0.8976[†]
Maximum tumour size	**(mm)**	**(mm)**	
Mean	14.9	17.4	t=-8.3, p<.0001
Median	12.0	15.0	Z=-9.15, p<.0001[‡]

[†] Mantel-Haenszel χ^2 test

[‡] Two-sample median test

With the exception of multiple tumours, the corresponding prognostic indicators were not significantly different for subsequent versus initial screeners with non-screen detected cancer (Table 3.62). Subsequent screeners with non-screen detected cancer had a relative risk of 0.66 of having multiple tumours compared to corresponding initial screeners. They also had smaller mean maximum tumour size but the median tumour sizes were not statistically significantly different.

Table 3.62: Prognostic indicators for **non-screen detected breast cancers diagnosed in initial versus subsequent screeners,** New Zealand women aged 45-69 years at diagnosis, 1999-2011

Prognostic indicator	Subsequent screener	Initial screener	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	564 (20.8)	297 (20.9)	
2: Moderately differentiated	1,000 (24.2)	520 (36.6)	
3: Poorly differentiated	965 (35.5)	484 (34.0)	$\chi^2_{(4)}$=5.41, p=0.2475
4: Undifferentiated, anaplastic	0 (0.0)	1 (0.0)	
9: Not recorded/NA	188 (6.9)	120 (8.4)	
Extent of disease			
B: Localised	1,376 (50.7)	689 (48.5)	
C/D: Adjacent organ/ regional lymph nodes	1,044 (38.4)	565 (39.7)	$\chi^2_{(3)}$=2.69, p=0.4427
E: Distant	81 (3.0)	52 (3.7)	
F: Unknown	216 (8.0)	116 (8.2)	
Multiple tumours			
No	2,653 (97.6)	1,371 (96.4)	RR=0.66 (0.46-0.94)
Yes	64 (2.4)	51 (3.6)	$\chi^2_{(1)}$=5.23, p=0.0221[†]
Maximum tumour size	**(mm)**	**(mm)**	
Mean	22.9	24.2	t=-2.1, p=0.0394
Median	20.0	20.0	Z=1.0, p=0.3180[‡]

[†] Mantel-Haenszel χ^2 test

[‡] Two-sample median test

3.2.4. Prognostic indicators for screen detected or non-screen-detected breast cancer

In screen-detected cancers, well differentiated tumours comprised 35% compared to 21% in non-screen detected cancers; 69% of screen-detected cancers were localised compared to 50% of non-screen detected cancers; the relative risk of multiple tumours was 0.46 in screen-detected cancers compared to non-screen detected cancers; and the median maximum tumour size was significantly smaller in screen-detected cancers (13mm) than non-screen detected cancers (20mm) (Table 3.63).

Table 3.63: Prognostic indicators for breast cancers diagnosed in **screen-detected versus non-screen detected cancers**, New Zealand women aged 45-69 years at diagnosis, 1999-2011

Prognostic indicator	Screen detected	Not screen detected	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	2,996 (34.5)	861 (20.8)	
2: Moderately differentiated	3,755 (43.2)	1,520 (36.7)	
3: Poorly differentiated	1,551 (17.9)	1,449 (35.0)	$\chi^2_{(4)}$=604, p<.0001
4: Undifferentiated, anaplastic	0 (0.0)	1 (0.0)	
9: Not recorded/NA	388 (4.5)	308 (7.4)	
Extent of disease			
B: Localised	6,006 (69.1)	2,065 (49.9)	
C/D: Adjacent organ/ regional lymph nodes	2,134 (24.6)	1,609 (38.9)	$\chi^2_{(3)}$=549, p<.0001
E: Distant	35 (0.4)	133 (1.0)	
F: Unknown	515 (5.9)	332 (8.0)	
Multiple tumours			
No	8,578 (98.7)	4,024 (97.2)	RR=0.46 (0.36-0.60)
Yes	112 (1.3)	115 (2.8)	$\chi^2_{(1)}$=35.8, p=<.0001[†]
Maximum tumour size	**(mm)**	**(mm)**	
Mean	15.6	23.4	t=-24.8, p<.0001
Median	13.0	20.0	Z=-27.5, p<.0001[‡]

[†] Mantel-Haenszel χ^2 test

[‡] Two-sample median test

All the prognostic indicators in initially screened women with screen-detected cancer versus non-screen detected cancer were significantly better: 34% of screen-detected cancers were well differentiated compared to 21% in non-screen detected cancers; 64% were localised compared to 49%; the relative risk of multiple tumours was 0.37; and the median maximum tumour size was 15 mm compared to 20 mm (Table 3.64).

Table 3.64: Prognostic indicators for breast cancers diagnosed in **screen-detected versus non-screen detected cancers, initially screened** New Zealand women aged 45-69 years at diagnosis, 1999-2011

Prognostic indicator	Screen detected	Not screen detected	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	869 (33.6)	297 (20.9)	
2: Moderately differentiated	1,118 (43.2)	520 (36.6)	
3: Poorly differentiated	461 (17.8)	484 (34.0)	$\chi^2_{(4)}$=177, p<.0001
4: Undifferentiated, anaplastic	0 (0.0)	1 (0.0)	
9: Not recorded/NA	142 (5.5)	120 (8.4)	
Extent of disease			
B: Localised	1,645 (63.5)	689 (48.5)	
C/D: Adjacent organ/ regional lymph nodes	735 (28.4)	565 (39.7)	$\chi^2_{(3)}$=119, p<.0001
E: Distant	18 (0.7)	52 (3.7)	
F: Unknown	192 (7.4)	116 (8.2)	
Multiple tumours			
No	2,556 (98.7)	1,371 (96.4)	RR=0.37 (0.24-0.56)
Yes	34 (1.3)	51 (3.6)	$\chi^2_{(1)}$=22.9, p=<.0001[†]
Maximum tumour size	**(mm)**	**(mm)**	
Mean	17.4	24.2	t=-11.1, p<.0001
Median	15.0	20.0	Z=-11.7, p<.0001[‡]

[†] Mantel-Haenszel χ^2 test

[‡] Two-sample median test

All prognostic indicators were significantly worse in non-screen detected cancers than screen-detected cancers diagnosed in subsequently screened women (Table 3.65). Well differentiated cancer comprised 35% of screen-detected cancers compared to 21% in non-screen detected cancers; localised cancer comprised 72% of screen detected cancers and 51% of non-screen detected cancers; the relative risk of multiple tumours was 0.54 in women with screen-detected cancer compared to non-screen detected cancer; and the corresponding median maximum tumour sizes were 12 mm versus 20 mm.

Table 3.65: Prognostic indicators for breast cancers diagnosed in **screen-detected versus non-screen detected cancers, subsequently screened** New Zealand women aged 45-69 years at diagnosis, 1999-2011

Prognostic indicator	Screen detected	Not screen detected	Significance of difference
Grade of tumour	**n (%)**	**n (%)**	
1: Well differentiated	2,127 (34.9)	564 (20.8)	
2: Moderately differentiated	2,637 (42.2)	1,000 (36.8)	$\chi^2_{(3)}$=424, p<.0001
3: Poorly differentiated	1,090 (17.9)	965 (35.5)	
9: Not recorded/NA	246 (4.0)	188 (6.9)	
Extent of disease			
B: Localised	4,361 (71.5)	1,376 (50.6)	
C/D: Adjacent organ/ regional lymph nodes	1,399 (22.9)	1,044 (38.4)	$\chi^2_{(3)}$=433, p<.0001
E: Distant	17 (0.3)	81 (3.0)	
F: Unknown	323 (5.3)	116 (8.0)	
Multiple tumours			
No	6,022 (98.7)	2,653 (97.6)	RR=0.54 (0.39-0.75)
Yes	78 (1.3)	64 (2.4)	$\chi^2_{(1)}$=13.8, p=<.0001[†]
Maximum tumour size	**(mm)**	**(mm)**	
Mean	14.9	22.9	t=-22.8, p<.0001
Median	12.0	20.0	Z=-24.1, p<.0001[‡]

[†] Mantel-Haenszel χ^2 test

[‡] Two-sample median test

APPENDIX for 3.2.2: Prognostic factors

Prognostic indicators in Grade 3 cancer

It is useful to examine mortality outcomes and prognostic indicators in women with Grade 3 (poorly differentiated) cancer as these cancers are aggressive and outcomes would be less affected by length time bias. That is, if observed breast cancer mortality benefits from screening were substantially due to length bias then the mortality benefit should reduce and become non-significant in comparing ever- and never-screened women with Grade 3 cancer.

Ever-screened women had significantly higher proportions of localised cancer, a significantly lower risk of multiple tumours (RR=0.43) and significantly smaller median maximum tumour size (Table A3.1).

Table A3.1: Prognostic indicators from Grade 3 (poorly differentiated) cancer in ever- versus never-screened New Zealand women aged 45-69 years at diagnosis, 1999-2011

Prognostic indicator	Ever screener	Never screener	Significance of difference
Extent of disease	**n (%)**	**n (%)**	
B: Localised	1,580 (52.7)	893 (39.6)	
C/D: Adjacent organ/ regional lymph nodes	1,239 (41.3)	1,123 (49.7)	$\chi^2_{(3)}$=115, p<.0001
E: Distant	44 (1.5)	99 (4.4)	
F: Unknown	137 (4.6)	143 (6.3)	
Multiple tumours			
No	2,959 (98.6)	2,187 (96.9)	RR=0.43 (0.30-0.64)
Yes	41 (1.4)	71 (3.1)	$\chi^2_{(1)}$=19.5, p<.0001[†]
Maximum tumour size	**(mm)**	**(mm)**	
Mean	23.2	29.2	t=-11.5, p<.0001
Median	20.0	25.0	Z=-13.5, p<.0001[‡]

[†] Mantel-Haenszel χ^2 test

[‡] Two-sample median test

3.3. CASE CONTROL STUDY

3.3.1. Ever-and never-screened women

From the case-control analysis by conditional logistic regression, ever-screened NZ women were significantly less likely to die from breast cancer than never-screened women (OR=0.46) (Table 3.1). After adjustment for screening selection bias based on mean screening participation for 2001-2011 of 64%, the estimated OR was 0.77, with breast cancer mortality correspondingly estimated to be 23% lower for women with screening available compared to women with screening not offered to the population. At 2012-13 screening participation of 71%, breast cancer mortality was estimated to be 27% lower in women offered screening compared to women not offered screening, the same as the target screening rate of 70%.

In Māori women, the estimate of breast cancer mortality in those ever-screened was also significantly lower (OR=0.61) than in never-screened Māori women, but somewhat higher than for the corresponding all NZ women comparison (OR=0.46). After adjustment for screening selection bias, breast cancer mortality in Māori women with screening available was estimated to be 4% lower than in Māori women not offered screening (non-significant) at 48% screening coverage for 2001-11. When screening selection bias was adjusted according to the 65% Māori screening participation for 2012-13, breast cancer mortality was estimated to be 12% lower than in Māori women not offered screening.

In Pacific women, breast cancer mortality was significantly lower in ever-screened compared to never-screened women (OR=0.32). After adjustment for screening selection bias based on mean screening participation over 2001-2011 of 49%, breast cancer mortality was estimated as 22% lower in Pacific women when screening is available compared to Pacific women where screening is not offered or available. Based on 72% screening participation in 2012-13, the breast cancer mortality reduction in Pacific women with screening available was estimated to be 40% compared to Pacific women if screening were not available.

In other (non-Māori, non-Pacific) women, likelihood of breast cancer mortality was significantly lower in ever- versus never-screened women (OR=0.45). After adjustment for screening selection bias at 68% coverage for 2001-2011, mortality from breast cancer was estimated to be 27% less likely in other women with screening available compared to other women not offered screening. At 2012-13 screening participation (72%) breast cancer mortality was estimated to be similarly lower (28%) than in corresponding women not offered screening.

Hypothesis H1, that ever-screening is associated with significantly lower breast cancer mortality compared to that in never-screened women, is confirmed. Based on intention to treat, hypothesis H1 is also confirmed. Also, hypothesis H4, that ever-screening is associated with lower breast cancer mortality than never-screening in women in Māori and Pacific women, is also confirmed. When the comparison is between women offered screening and women not offered screening, hypothesis H1 is also confirmed for all women, while hypothesis H4 is confirmed for Pacific women but not Māori women from the case control analysis.

Table 3.66: Odds ratio and breast cancer mortality difference estimates† in ever- and never- screened New Zealand women, 1999-2011

Variable	Regression Estimate (SE)	p-value	Odds ratio (95% CI)	% Mortality difference (95% CI)
All				
Never screened			1.00	
Ever screened	-0.7729 (0.1113)	<.0001	0.46 (0.37-0.57)	-54 (-63 to -43)
Intercept	-7.5774 (0.1167)	<.0001		
Ever screened (adjusted)[a]			0.77 (0.68-0.87)	-23 (-32 to -13)
Ever screened (adjusted)[b]			0.72 (0.63-0.83)	-28 (-37 to -17)
Ever screened (adjusted)[c]			0.73 (0.64-0.83)	-27 (-36 to -17)
Māori				
Never screened			1.00	
Ever screened	-0.4969 (0.0513)	<.0001	0.61 (0.55-0.67)	-39 (-45 to -33)
Intercept	-7.3467 (0.1250)	<.0001		-
Ever screened (adjusted)[a]			0.96 (0.89-1.05)	-4 (-11 to +5)
Ever screened (adjusted)[b]			0.87 (0.80-0.96)	-13 (-20 to -4)
Ever screened (adjusted)[c]			0.85 (0.77-0.93)	-15 (-23 to -7)
Pacific				
Never screened			1.00	
Ever screened	-1.1403 (0.0863)	<.0001	0.32 (0.27-0.38)	-68 (-73 to -62)
Intercept	-7.1815 (0.1524)	<.0001		
Ever screened (adjusted)[a]			0.78 (0.72-0.85)	-22 (-28 to -15)
Ever screened (adjusted)[b]			0.60 (0.54-0.66)	-40 (-46 to -34)
Ever screened (adjusted)[c]			0.61 (0.55-0.68)	-39 (-45 to -32)
Other				
Never screened			1.00	
Ever screened	-0.7935 (0.1416)	<.0001	0.45 (0.34-0.60)	-55 (-66 to -40)
Intercept	-7.6199 (0.1323)	<.0001		
Ever screened (adjusted)[a]			0.73 (0.63-0.86)	-27 (-37 to -14)
Ever screened (adjusted)[b]			0.71 (0.60-0.84)	-29 (-40 to -16)
Ever screened (adjusted)[c]			0.72 (0.61-0.85)	-28 (-39 to -15)

† From conditional logistic regression model with strata matching of cases and controls by age group and ethnicity for all, and by age group for ethnic-specific models

a. Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and screening participation rates of 64% (All), 45% (Māori), 49% (Pacific), 68% (Other)

b. Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and screening participation rates for 2012-13 of 71% (All), 65% (Māori), 72% (Pacific), 72% (Other)

c. Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and the target screening participation rate of 70%

3.3.2. Screening regularity

3.3.2.1. Regular, non-regular and never-screening

NZ women who screened regularly, defined as having at least 3 screening mammograms with an average screening interval of ≤30 months, had 73% lower breast cancer mortality than never-screened women (statistically significant)(Table 3.67). After adjusting for screening selection bias, a population offered screening with 64% participation and assumed to be screened regularly would have 35% lower breast cancer mortality than women not offered screening; this estimate would be 44% lower breast cancer mortality at the 2012-13 screening participation rate of 71%. Less regularly screened women were estimated to be 48% less likely to die from breast cancer than never-screened women (statistically significant). After adjusting for screening selection bias, based on 2012-13 screening participation (71%) and assuming women offered screening screened less regularly, breast cancer mortality would be 23% lower than in women not offered screening.

In Māori women, those regularly screened were estimated to be 75% less likely to die from breast cancer than never-screened Māori women (statistically significant). After adjusting for screening selection bias based on 2012-13 screening participation (65%), and assuming Māori women offered screening screened regularly breast cancer was estimated to be 38% lower than in Māori women not offered screening (also statistically significant). Less regularly screened Māori women were estimated to be 32% less likely to die from breast cancer than corresponding never-screened women (statistically significant). After adjusting for screening selection bias, based on 2012-13 screening participation and assuming Māori women with available screening screened irregularly, breast cancer mortality would be 6% lower compared to Māori women with screening unavailable or not offered (not statistically significant).

Among Pacific women, those regularly screened were estimated to be 85% less likely to die from breast cancer than never-screened Pacific women. After adjusting for screening selection bias, based on 2012-13 screening participation (72%) and assuming Pacific women offered screening screened regularly, breast cancer mortality was estimated to be 53% lower than in Pacific women not offered screening (statistically significant). Less regularly screened Pacific women were estimated to be 65% less likely to die from breast cancer than never-screened Pacific women, and after adjusting for screening selection bias as above, assuming 2012-13 screening participation and Pacific women offered screening screened less regularly, breast cancer mortality was estimated to be 36% lower than in Pacific women not offered screening (statistically significant). Note that these estimates are not likely to be affected by differential bias due to higher out-migration of screened Pacific women diagnosed with breast cancer whose death from breast cancer would then be less likely recorded in New Zealand, compared to never-screened Pacific women diagnosed with breast cancer. This is because all controls for this case-control study comprise only those known to be alive at the end of the study period.

In Other (non-Māori, non-Pacific) women, regular screening was estimated to be associated with 73% lower breast cancer mortality than in never-screened women. After adjusting for screening selection bias based on 2012-13 screening participation (72%) and assuming that women with screening available screened regularly, breast cancer mortality was estimated to be 24% lower than in corresponding women not offered screening. Less regular screening in other women was significantly associated with 50% lower breast cancer mortality compared to never-screening. After adjusting for screening selection bias, assuming 2012-13 participation and that women with screening available screened less regularly, breast cancer mortality was estimated to be 24% lower (significant) than in similar women not offered screening.

Table 3.67: Odds ratio and breast cancer mortality difference estimates† in regularly‡ screened, less regularly screened and never-screened NZ women 1999-2011

Variable	Regression Estimate (SE)	p-value	Odds ratio (95% CI)	% Mortality difference (95% CI)
All				
Never screened			1.00	
Less regularly screened	-0.6618 (0.1262)	<.0001	0.52 (0.40-0.66)	-48 (-60 to -34)
Regularly screened	-1.3269 (0.1445)	<.0001	0.27 (0.20-0.35)	-73 (-80 to -65)
Intercept	-7.5774 (0.1167)	<.0001		
Less regularly screened (adjusted)[a]			0.81 (0.70-0.96)	-19 (-30 to -4)
Less regularly screened (adjusted)[b]			0.77 (0.66-0.90)	-23 (-34 to -10)
Less regularly screened (adjusted)[c]			0.77 (0.66-0.90)	-23 (-34 to -10)
Regularly screened (adjusted)[a]			0.62 (0.55-0.70)	-35 (-45 to -30)
Regularly screened (adjusted)[b]			0.56 (0.49-0.64)	-44 (-51 to -36)
Regularly screened (adjusted)[c]			0.57 (0.50-0.65)	-43 (-50 to -35)
Māori				
Never screened			1.00	
Less regularly screened	-0.3834 (0.0913)	<.0001	0.68 (0.57-0.82)	-32 (-43 to -18)
Regularly screened	-1.3925 (0.4020)	0.0005	0.25 (0.11-0.55)	-75 (-89 to -45)
Intercept	-7.3467 (0.1250)	<.0001		
Less regularly screened (adjusted)[a]			1.00 (0.91-1.11)	0 (-9 to +11)
Less regularly screened (adjusted)[b]			0.93 (0.82-1.05)	-7 (-18 to +5)
Less regularly screened (adjusted)[c]			0.91 (0.80-1.04)	-9 (-20 to +4)
Regularly screened (adjusted)[a]			0.77 (0.66-0.90)	-23 (-34 to -10)
Regularly screened (adjusted)[b]			0.60 (0.46-0.78)	-40 (-54 to -22)
Regularly screened (adjusted)[c]			0.55 (0.41-0.75)	-45 (-59 to -25)
Pacific				
Never screened			1.00	
Less regularly screened	-1.0522 (0.0833)	<.0001	0.35 (0.30-0.41)	-65 (-70 to -59)
Regularly screened	-1.9198 (0.3404)	<.0001	0.15 (0.08-0.29)	-85 (-92 to -71)
Intercept	-7.1815 (0.1524)	<.0001		
Less regularly screened (adjusted)[a]			0.80 (0.73-0.87)	-20 (-27 to -13)
Less regularly screened (adjusted)[b]			0.62 (0.56-0.69)	-38 (-44 to -31)
Less regularly screened (adjusted)[c]			0.64 (0.57-0.71)	-36 (-43 to -29)
Regularly screened (adjusted)[a]			0.68 (0.61-0.76)	-32 (-39 to -24)
Regularly screened (adjusted)[b]			0.45 (0.37-0.55)	-55 (-63 to -45)
Regularly screened (adjusted)[c]			0.47 (0.39-0.57)	-53 (-61 to -43)
Other				
Never screened			1.00	
Less regularly screened	-0.6863 (0.1587)	<.0001	0.50 (0.37-0.69)	-50 (-63 to -31)
Regularly screened	-1.2923 (0.1611)	<.0001	0.27 (0.20-0.38)	-73 (-80 to -62)
Intercept	-7.6199 (0.1323)	<.0001		
Less regularly screened (adjusted)[a]			0.77 (0.65-0.93)	-23 (-35 to -7)
Less regularly screened (adjusted)[b]			0.76 (0.63-0.91)	-24 (-37 to -9)
Less regularly screened (adjusted)[c]			0.76 (0.64-0.92)	-24 (-36 to -8)
Regularly screened (adjusted)[a]			0.59 (0.52-0.68)	-41 (-48 to -32)
Regularly screened (adjusted)[b]			0.56 (0.49-0.65)	-44 (-51 to -35)
Regularly screened (adjusted)[c]			0.58 (0.50-0.67)	-42 (-50 to -33)

† From conditional logistic regression model with strata matching of cases and controls by age group and ethnicity for all, and by age group for ethnic-specific models

a. Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and screening participation rates of 64% (All), 45% (Māori), 49% (Pacific), 68% (Other)

b. Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and screening participation rates for 2012-13 of 71% (All), 65% (Māori), 72% (Pacific), 72% (Other)

c. Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and the target screening participation rate of 70%

In summary, there is a consistent dose-response relationship between amount and regularity of screening mammography and likelihood of mortality from breast cancer, which is in the hypothesised direction of more regular screening being associated with lower likelihood of dying from breast cancer than less regular screening. While these findings are largely consistent across ethnic groups, this case-control analysis shows irregular screening in Māori women not to be associated with significantly lower breast cancer mortality than in Māori women not offered screening, although regular screening is associated with mortality reduction similar to other ethnic groups.

Hypothesis H2 is confirmed with respect to women not screening, despite availability of screening and, with the exception of Māori in this case control analysis, H2 is confirmed with respect to populations offered compared to not offered screening.

3.3.2.2. Regular versus non-regular screening in screened women

Among screened women, breast cancer mortality reduction in those regularly screened compared to those irregularly screened was 49% lower overall, 64% lower in Māori women and 58% lower in Pacific women (all statistically significant, Table 3.68). Breast cancer mortality in Other (non-Māori, non-Pacific) women was 45% lower. These estimates were all statistically significant. Hypothesis H2 is confirmed.

Table 3.68: Odds ratio and breast cancer mortality difference estimates† in regular versus non-regularly screened New Zealand women, 1999-2011

Variable	Regression Estimate (SE)	p-value	Odds ratio (95% CI)	% Mortality difference (95% CI)
All				
Irregularly screened			1.00	
Regularly screened	-0.6651 (0.1021)	<.0001	0.51 (0.42-0.63)	-49 (-58 to -37)
Intercept	-8.2392 (0.1423)	<.0001		
Māori				
Irregularly screened			1.00	
Regularly screened	-1.0091 (0.4562)	0.0270	0.36 (0.15-0.89)	-64 (-85 to -11)
Intercept	-7.7301 (0.2001)	<.0001		
Pacific				
Irregularly screened			1.00	
Regularly screened	-0.8677 (0.3690)	0.0187	0.42 (0.20-0.87)	-58 (-80 to -13)
Intercept	-8.2337 (0.1069)	<.0001		
Other				
Irregularly screened			1.00	
Regularly screened	-0.6060 (0.1074)	<.0001	0.55 (0.44-0.67)	-45 (-56 to -33)
Intercept	-8.3062 (0.1627)	<.0001		

† From conditional logistic regression model with strata matching of cases and controls by age group and ethnicity (all) and age group for ethnic-specific models

3.3.3. Screen-detected versus non-screen detected cancer, screened women

Screen-detected versus non-screen detected cancer, all screened women

Among screened women diagnosed with breast cancer, breast cancer mortality in those with cancer detected at screening was estimated to be 65% lower compared to screened women whose cancer was detected outside of screening (statistically significant, Table 3.69). In Māori and Pacific women, the difference was greater, 78% and 75% lower, respectively, and also statistically significant. Hypothesis H3a is confirmed.

Table 3.69: Odds ratio and breast cancer mortality difference estimates† in screen-detected versus non-screen detected cancer, screened New Zealand women with breast cancer, 1999-2011

Variable	Regression Estimate (SE)	p-value	Odds ratio (95% CI)	% Mortality difference (95% CI)
All				
Not screen detected			1.00	
Screen detected	-1.0607 (0.1074)	<.0001	0.35 (0.28-0.43)	-65 (-72 to -57)
Intercept	-1.8048 (0.0964)	<.0001		
Māori				
Not screen detected			1.00	
Screen detected	-1.4921 (0.1035)	<.0001	0.22 (0.18-0.28)	-78 (-82 to -72)
Intercept	-1.3483 (0.1252)	<.0001		
Pacific				
Not screen detected			1.00	
Screen detected	-1.3941 (0.2256)	<.0001	0.25 (0.16-0.39)	-75 (-84 to -61)
Intercept	-1.3863 (0.1768)	<.0001		
Other				
Not screen detected			1.00	
Screen detected	-0.9983 (0.1215)	<.0001	0.37 (0.29-0.47)	-63 (-71 to -53)
Intercept	-1.8750 (0.1114)	<.0001		

† From conditional logistic regression model with strata matching of cases and controls by age group and ethnicity (all) and age group for ethnic-specific models

Screen-detected versus non-screen detected cancer, subsequent screened women

Among subsequently screened **NZ women** diagnosed with breast cancer, breast cancer mortality in those with cancer detected at screening was estimated to be 67% lower compared to subsequently screened women with cancer detected outside of screening (statistically significant, Table 3.70). In **Māori** and **Pacific** women, the difference was greater, at 78% and 71%, respectively, but for Pacific women this difference was statistically non-significant. For subsequent screened women (those who have screened twice more); hypothesis H3a is confirmed.

Table 3.70: Odds ratio and breast cancer mortality difference estimates† in screen-detected versus non-screen detected cancer, subsequent screened New Zealand women with breast cancer, 1999-2011

Variable	Regression Estimate (SE)	p-value	Odds ratio (95% CI)	% Mortality difference (95% CI)
All				
Not screen detected			1.00	
Screen detected	-1.0952 (0.1450)	<.0001	0.33 (0.25-0.44)	-67 (-75 to -56)
Intercept	-2.0199 (0.0907)	<.0001	-	-
Māori				
Not screen detected			1.00	
Screen detected	-1.4985 (0.0936)	<.0001	0.22 (0.19-0.27)	-78 (-81 to -73)
Intercept	-1.6619 (0.1643)	<.0001	-	-
Pacific				
Not screen detected			1.00	
Screen detected	-1.2465 (0.9810)	0.2039	0.29 (0.04-1.97)	-71 (-96 to +97)
Intercept	-2.4423 (0.6543)	0.0002	-	-
Other				
Not screen detected			1.00	
Screen detected	-1.0448 (0.1628)	<.0001	0.35 (0.26-0.48)	-65 (-74 to -52)
Intercept	-2.0513 (0.1013)	<.0001	-	-

† From conditional logistic regression model with strata matching of cases and controls by age group and ethnicity (all) and by age group for ethnic-specific models

3.3.4. Subsequent screened versus initially screened women

Among screened women, breast cancer mortality in subsequent screened women, defined as women who have screened 2 or more times, was estimated to be 51% lower compared to screened women who had no subsequent screening (i.e. had screened once only)(Table 3.71). This difference was statistically significant. In Māori and Pacific women, the difference was greater, at 57% and 84%, respectively.

Table 3.71: Odds ratio and breast cancer mortality difference estimates† in subsequently‡ screened versus initially screened New Zealand women, 1999-2011

Variable	Regression Estimate (SE)	p-value	Odds ratio (95% CI)	% Mortality difference (95% CI)
All				
Non-subsequent screeners			1.00	
Subsequent screeners	-0.7233 (0.1761)	<.0001	0.49 (0.34-0.69)	-51 (-66 to -31)
Intercept	-7.9263 (0.2379)	<.0001	-	-
Māori				
Non-subsequent screeners			1.00	
Subsequent screeners	-0.8440 (0.3701)	0.0226	0.43 (0.21-0.89)	-57 (-79 to -11)
Intercept	-7.4287 (0.3170)	<.0001	-	-
Pacific				
Non-subsequent screeners			1.00	
Subsequent screeners	-1.8260 (0.3073)	<.0001	0.16 (0.09-0.29)	-84 (-91 to -71)
Intercept	-7.6968 (0.1933)	<.0001	-	-
Other				
Non-subsequent screeners			1.00	
Subsequent screeners	-0.6494 (0.2043)	0.0015	0.52 (0.35-0.78)	-48 (-65 to -22)
Intercept	-8.0188 (0.2768)	<.0001	-	-

† From conditional logistic regression model with strata matching of cases and controls by age group and ethnicity (all) and by age group for ethnic-specific models

‡ Subsequent screeners are women who have had 2 or more screening mammograms in a given year of breast cancer diagnosis; initial screeners are women who have had one screening mammogram only

3.3.3.5. Non-screen detected cancer: Screened versus non-screened women

This comparison is to test whether screening is associated with lower breast cancer mortality despite the cancer being non-screen detected (Hypothesis (**H3b**). In all **NZ women**, ever-screening was associated with 65% lower breast cancer mortality in those with non-screen detected cancer than in corresponding never-screened women (statistically significant) (Table 3.72). After adjusting for screening selection bias, based on 2012-13 screening participation, women offered screening with non-screen detected cancer were estimated to have 36% lower breast cancer mortality compared to corresponding women not offered screening (statistically significant). In **Māori** and **Pacific** women these estimates were 22% and 34% respectively, also statistically significant. Hypothesis H3b is confirmed and indicates that exposure to screening mammography will produce a better prognosis for a breast cancer even if detected outside of screening.

Table 3.72: Odds ratio and breast cancer mortality difference estimates† in ever- and never- screened New Zealand women with non-screen detected cancer, 1999-2011

Variable	Regression Estimate (SE)	p-value	Odds ratio (95% CI)	% Mortality difference (95% CI)
All				
Never screened			1.00	
Ever screened	-1.0411 (0.1359)	<.0001	0.35 (0.27-0.46)	-65 (-73 to -54)
Intercept	-0.7636 (0.1496)	<.0001		
Ever screened (adjusted)[a]			0.69 (0.60-0.78)	-31 (-40 to -22)
Ever screened (adjusted)[b]			0.63 (0.55-0.73)	-37 (-45 to -27)
Ever screened (adjusted)[c]			0.64 (0.56-0.74)	-36 (-44 to -26)
Māori				
Never screened			1.00	
Ever screened	-0.7457 (0.1012)	<.0001	0.47 (0.39-0.58)	-53 (-61 to -42)
Intercept	-0.6026 (0.1606)	0.0002		
Ever screened (adjusted)[a]			0.89 (0.81-0.98)	-11 (-19 to -2)
Ever screened (adjusted)[b]			0.77 (0.68-0.87)	-23 (-32 to -13)
Ever screened (adjusted)[c]			0.74 (0.65-0.84)	-26 (-35 to -16)
Pacific				
Never screened			1.00	
Ever screened	-1.0116 (0.1831)	<.0001	0.36 (0.25-0.52)	-64 (-75 to -48)
Intercept	-0.3747 (0.1470)	0.0108		
Ever screened (adjusted)[a]			0.80 (0.71-0.91)	-20 (-29 to -9)
Ever screened (adjusted)[b]			0.63 (0.52-0.76)	-37 (-48 to -24)
Ever screened (adjusted)[c]			0.65 (0.54-0.78)	-35 (-46 to -22)
Other				
Never screened			1.00	
Ever screened	-1.0759 (0.1693)	<.0001	0.34 (0.24-0.48)	-66 (-76 to -52)
Intercept	-0.7991 (0.1704)	<.0001		
Ever screened (adjusted)[a]			0.65 (0.55-0.76)	-35 (-45 to -24)
Ever screened (adjusted)[b]			0.62 (0.52-0.73)	-38 (-48 to -27)
Ever screened (adjusted)[c]			0.63 (0.53-0.74)	-37 (-47 to -26)

† From conditional logistic regression model with strata matching of cases and controls by age group and ethnicity for all, and by age group for ethnic-specific models

[a.] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and screening participation rates of 64% (All), 45% (Māori), 49% (Pacific), 68% (Other)

[b.] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and screening participation rates for 2012-13 of 71% (All), 65% (Māori), 72% (Pacific), 72% (Other)

[c.] Adjusted for screening selection bias, assuming relative risk in non-screeners to women not offered screening=1.17 and the target screening participation rate of 70%

Chapter 4: DISCUSSION AND CONCLUSIONS

4.1 SUMMARY OF MAIN FINDINGS

4.1.1. Breast cancer mortality in ever screened and never screened women

The purpose of analysis of breast cancer mortality in ever screened and never screened women is to assess the results of population mammographic screening for all NZ women, non-Māori and non-Pacific women, Māori women , and Pacific women, in relation to findings from randomised controlled trials.

All NZ women

In the NZ population 1999-2011 women who constituted the **inception cohort** who were ever screened manifested a 62% (95% CI: 51-70) lower breast cancer mortality than those never screened, adjusted for age and ethnic group. When also adjusted for screening selection bias, the mortality reduction was 29% (95% CI: 20-38) at average coverage of 64% for the 2001-11 period. For current coverage of 71% (2012-13) the estimated mortality reduction is 34% (95% CI: 25-43).

From the **case-control study**, lower breast cancer mortality was demonstrated in relation to service mammographic screening for ever- compared to never-screened NZ women. Ever-screening was significantly associated with lower breast cancer mortality, compared to never screening (54% lower), and when adjusted for screening selection bias for the study period (64%) the estimate was 23% (13-32) lower mortality, and a 28% (17-37) lower mortality using recent screening coverage (71%).

There is no statistically significant difference between the similar results for the most comparable estimates of mortality reduction across 1999-2011. The adjusted results of the inception cohort analysis are considered to be the least biased for all NZ women.

Other women (non-Māori, non-Pacific)

For the Other group (non-Māori, non-Pacific) in the **inception cohort**, a 60% (95% CI: 42-72) lower breast cancer mortality (age adjusted) in ever- compared to never-screened women was estimated, and when also adjusted for screening selection bias the estimate was 29% (95% CI: 16-41) at average coverage of 66% for the period 2001-11. For current coverage of 72% (2012-13) this estimated mortality reduction is 33% (95% CI: 19-45).

From the **case-control** study, the Other group (non-Māori, non-Pacific) manifested a 55% (95% CI: -66 to -40) lower breast cancer mortality (age adjusted) in ever- compared to never-screened women. When also adjusted for screening selection bias the estimate was 27% (95% CI: 14-37) at average coverage of 66% for the period 2001-11. For current coverage of 72% (2012-13) the estimated mortality reduction is 29% (95% CI: 16-40).

There is no statistically significant difference between the similar results for the most comparable estimates of mortality reduction across 1999-2011. The adjusted results of the inception cohort analysis are considered to be the least biased for non-Māori, non-Pacific women.

Māori women

From the **inception cohort** study in Māori the ever screened had a 60% (95% CI: 47-69) lower breast cancer mortality compared to never screened (age adjusted), and when also adjusted for screening selection bias this was 17% (95% CI: 7-25) at average coverage of 48% for the period 2001-11. For current coverage of 65% (2012-13) the estimated mortality reduction is 28% (95% CI: 18-38).

In the **case-control** study Māori women showed a reduction for ever- compared to never-screened women (39%), and a small non-significant reduction in mortality when adjusted for screening selection bias, either using coverage for the entire period (45%) producing 4% (95% CI: -5%-11%, not significant) lower mortality, or for recent coverage (65%) yielding 13% (95% CI: 4-20) lower mortality.

The adjusted results of the inception cohort analysis are considered to be the least biased for Māori women.

Pacific women

From the **inception cohort**, for Pacific ethnicity, the mortality differential for ever and never screened was larger than other groups at 74% mortality reduction; with adjustment for screening selection bias, the mortality reduction was (25%) for a screening coverage of 49% (2001-11), and the highest and implausible adjusted mortality reduction of 45% using recent screening coverage (72% for 2012-13).

The implausible results for Pacific women from cohort analyses are most likely due to differential mortality ascertainment bias from out-migration of some women with breast cancer and thus unrecorded deaths (in NZ). For this reason a **case control study** was undertaken which is not affected by attrition bias. The case-control study produced breast cancer mortality reduction estimates for ever-screened Pacific women of 68% compared to those never screened, and of 23% (16-29) when adjusted for a screening coverage of 49% (2001-11); of 40% (34-46) when adjusted for a screening coverage of 72% (2012-13). Under the circumstances, it is considered that the adjusted estimates from the case control study are least biased for Pacific women.

This adjusted estimate of 40% (95%CI: 34-46) mortality reduction for ever compared to never screened from the case-control study is of a similar magnitude and not statistically different from the mortality reduction for all NZ women (also adjusted for recent screening coverage) from the inception cohort study of 34% (95% CI: 25-43).

Table 4.1. Summary of breast cancer mortality, ever-screened compared with never-screened women

Indicator	Inception cohort	Case-control study
NZ women Adjusted for	*Table 3.3* -29 (-38 to -20) Screening selection bias (64% coverage 2001-11)	*Table 3.66* -23 (-32 to -13) Screening selection bias (64% coverage 2001-11)
NZ women Adjusted for	*Table 3.3* **-34 (-43 to -25)** Screening selection bias (71% coverage 2012-13)	*Table 3.66* -28 (-37 to -17) Screening selection bias (71% coverage 2012-13)
Other NZ Adjusted for	*Table 3.6* -29 (-16 to -41) Screening selection bias (66% coverage 2001-11)	*Table 3.66* -27 (-14 to- 37) Screening selection bias (66% coverage 2001-11)
Other NZ Adjusted for	*Table 3.6* **-33(-19 to -45**) Screening selection bias (72% coverage 2012-13)	*Table 3.66* -28 (-16 to- 39) Screening selection bias (72% coverage 2012-13)
Māori Adjusted for	*Table 3.4* -17 (-25 to -7) Screening selection bias (45% coverage 2001-11)	*Table 3.66* *-4 (-11 to +5)* *Screening selection bias* *(45% coverage 2001-11)*
Māori Adjusted for	*Table 3.4* **-28 (-38 to -18)** Screening selection bias (65% coverage 2012-13)	*Table 3.66* *-13 (-20 to -4)* *Screening selection bias* *(65% coverage 2012-13)*
Māori Adjusted for	*Table 3.4* **-32 (-41 to -21)** Screening selection bias (Target coverage: 70%)+	*Table 3.66* *-15 (-23 to -7)* *Screening selection bias* *(Target coverage: 70%)+*
Pacific Adjusted for	*Table 3.5* *-24 (-32 to -14)* *Screening selection* *(49% coverage 2001-11)*	*Table 3.66* *-22 (-28 to -15)* *Screening selection* *(49% coverage 2001-11*
Pacific Adjusted for	*Table 3.5* *-45 (-52 to -37)* *Screening selection* *(72% coverage 2012-13)*	*Table 3.66* **-40 (-46 to -34)** Screening selection (72% coverage 2012-13)

+ Projection of mortality reduction if target coverage of 70% is reached

Implausible and/or non-statistically significant results are in *italics*

Other: non-Māori and non-Pacific NZ women

The most reasonable and consistent results, employing the appropriate preferred methodology, that reflect coverage for the most recent period are in **bold**

Conclusions of comparisons between never screened and ever screened women

The magnitude of the breast cancer mortality reduction from ever screening compared to never screening from the inception cohort analysis, when adjusted to be comparable, provides estimates which are consistent with the effects of mammography screening from randomised controlled trials which produced mortality reductions of 30-35% (at around 70% participation) for populations offered screening compared to those not offered screening.

Results for all NZ women, non-Māori, non-Pacific (Other), and Māori women, at recent and/or target screening coverage of around 70% are all consistent with trial results. In particular, reduction of breast cancer mortality with screening in Māori would be no different to all NZ or non-Māori and non-Pacific NZ (Other) women if target screening coverage of 70% were reached.

In Pacific women, breast cancer mortality reduction in relation to screening coverage appears inflated compared with other ethnic groups and trial evidence, which is likely to be affected by differential attrition bias (deaths) from out-migration. The case control study, which is not affected by attrition bias, produces more plausible estimates of breast cancer mortality reduction from screening which are not statistically significantly different to all NZ women, non-Māori, non-Pacific (Other), or Māori women.

These findings constitute the best evidence that the Breast Screen Aotearoa is achieving anticipated results at target screening coverage.

4.1.2. Breast cancer mortality and regularity of screening

The purpose of the analysis of breast cancer mortality in relating to screening is to examine the expectation that a 'dose-response' should be evident, such that more engagement in mammographic screening is associated with greater mortality reduction compared with lesser or no screening. This analysis provides further evidence for the effectiveness of screening beyond a dichotomous ever/never analysis, and provides evidence for benefits of greater regularity of screening in ever screeners, if such effects are evident.

4.1.2.1. Composite measure of screening regularity

Breast cancer mortality is investigated in relation to a composite measure of screening regularity incorporating frequency and length of interval between screens. Regular screeners are defined as those screened ≥3 times with ≤30 months mean screening interval. Irregular screeners are those who have ever screened, but do not qualify as regular screeners.

All NZ women

In the **inception cohort** for the entire NZ population, compared to never-screened women, irregular screeners manifested a 58% (95% CI: 48-66) lower breast cancer mortality, and regular screeners manifested a 67% (95% CI: 46-81) lower breast cancer mortality, adjusted for age and ethnic group. When also adjusted for screening selection bias, the mortality reduction in irregular screeners was 26% (95% CI: 17-35) at prevalent screening coverage 2001-11 (64%); this was **31%** (95%CI: 21-40) mortality reduction at current screening coverage (71%). In regular screeners the breast cancer mortality reduction was estimated as 33% (95% CI: 19-46) at the average coverage for 2001-11 of 64%, and **39%** (95%CI: 22-52) at current screening coverage (71%).

In the **case-control study**, for the entire NZ population, compared to never-screened women, irregular screeners manifested a 48% (95% CI: 34-60) lower breast cancer mortality, and regular screeners manifested a 73% (95% CI: 65-80) lower breast cancer mortality, adjusted for age and ethnic group. When also adjusted for screening selection bias, the mortality reduction in irregular screeners was 19% (95% CI: 4-30) at prevalent

screening coverage 2001-11 (64%); this was **23%** (95%CI: 10-34) mortality reduction at current screening coverage (71%). In regular screeners the breast cancer mortality reduction was estimated as 35% (95% CI: 30-45) at the average coverage for 2001-11 of 64%, and **44%** (95%CI: 36-51) at current screening coverage (71%).

Compared to never screeners, mortality reductions for irregular screeners and larger reductions in regular screener were similar in trend and magnitude in both the inception and case control analyses for all NZ women and not statistically significantly different across the different study types. The adjusted results of the inception cohort analysis are considered to be the least biased for all NZ women.

Other women (non-Māori, non-Pacific)

From the **inception cohort** for non-Māori non-Pacific (Other) women, compared to never-screened women, irregular screeners manifested a 56% (95% CI: 40-67) lower breast cancer mortality, and regular screeners manifested a 66% (95% CI: 34-83) lower breast cancer mortality, adjusted for age. When also adjusted for screening selection bias, the mortality reduction in Other women irregular screeners was 26% (95% CI: 13-37) at prevalent screening coverage 2001-11 (66%), and **29%** (95%CI: 16-41) at current screening coverage (72%). In Other women regular screeners the breast cancer mortality reduction was estimated to be 34% (95% CI: 13-50) at prevalent screening coverage 2001-11 (66%), and **38%** (95%CI: 16-55) at current screening coverage (72%).

From the **case control study** for non-Māori non-Pacific (Other) women, compared to never-screened women, irregular screeners manifested a 50% (95% CI: 31-63) lower breast cancer mortality, and regular screeners manifested a 73% (95% CI: 62-80) lower breast cancer mortality, adjusted for age. When also adjusted for screening selection bias, the mortality reduction in Other women irregular screeners was 23% (95% CI: 7-35) at prevalent screening coverage 2001-11 (68%), and **24%** (95%CI: 9-37) at current screening coverage (71%). In Other women regular screeners the breast cancer mortality reduction was estimated to be 41% (95% CI: 32-48) at prevalent screening coverage 2001-11 (66%), and **43%** (95%CI: 34-51) at current screening coverage (72%).

Compared to never screeners, mortality reductions for irregular screeners, and larger reductions in regular screeners (demonstrating trend), were similar in trend and magnitude in both the inception and case control analyses for Other NZ women and not statistically significantly different across the different study types. The adjusted results of the inception cohort analysis are considered to be the least biased for all NZ women.

Māori women

In Māori in the **inception cohort**, compared to the never screened, the irregularly screened had a 57% (95% CI: 40-69) lower breast cancer mortality, and the regular screeners 58% (95% CI: 7-81) lower mortality (age adjusted). When also adjusted for screening selection bias the estimate for irregular screeners was 15% (95% CI: 4-25) reduction at 64% screening coverage for 2001-11; and **26%** (95%CI: 13-37) at current screening coverage (65%). For Māori regular screeners breast cancer mortality was estimated to be 16% lower (95% CI: -7-33, not significant) at prevalent screening coverage 2001-11 (48%), and **27%** (95% CI: -4-54, not significant) at current screening coverage (65%).

In Māori in the **case control study**, compared to the never screened, the irregularly screened had a 32% (95% CI: 18-43) lower breast cancer mortality, and the regular screeners 75% (95% CI: 45-89) lower mortality (age adjusted). When also adjusted for screening selection bias the estimate for irregular screeners was 0% (95% CI: -11-9) reduction at 45% screening coverage for 2001-11; and **6%** (95%CI: -6 to +17) at current screening coverage (65%). For Māori regularly screened women breast cancer mortality was estimated to be **23%** lower

(95% CI: 10-34) at prevalent screening coverage for 2001-11 (45%), and **38%** lower (95% CI: 21-52) at current screening coverage (65%).

For Māori, findings of the inception cohort study and case control studies are inconsistent for reduction of mortality in irregular and regular screeners, compared with never screeners, and some estimates are not significantly different to zero. These estimates are unreliable and will not be reported.

Pacific women

From the **inception cohort study** of Pacific women, the breast cancer mortality differentials compared to never screened were larger than for other ethnicities and not plausible, at 43% lower mortality for irregularly screened women and 64% lower for regularly screened women after adjusting for screening selection bias using recent screening coverage. Such estimates may be affected by differential under-enumeration of deaths from out-migration.

From the **case-control study**, compared to the never screened, the irregularly screened Pacific women had 65% (95% CI: 59-70) lower breast cancer mortality, and those regularly screened 85% (95% CI: 71-92) lower mortality (age adjusted). When also adjusted for screening selection bias, the estimate for irregularly screened women was 20% (95% CI: 13-27) reduction at 49% screening coverage for 2001-11; and **36%** (95%CI: 29-42) at current screening coverage (72%). For regularly screened Pacific women, breast cancer mortality was estimated to be 32% lower (95% CI: 24-39) at screening coverage prevalent for 2001-11 (50%), and **53%** lower (95% CI: 43-61) at recent screening coverage (72%).

Mortality reduction in the case-control analyses for Pacific women, compared with never screeners, for irregular screeners and regular screeners (adjusted for screening selection bias) showed a trend with increased screening, and although point estimates were higher, these were not statistically significantly greater than those for all NZ women, taking into account 95% CIs. The adjusted results of the case-control study are considered to be the least biased for Pacific women.

Table 4.2. Summary of breast cancer mortality in irregular screened, regularly screened compared with never-screened women (as reference)

Indicator	Inception cohort	Case-control study
NZ women (Ref: never screened)	*Table 3.15*	*Table 3.67*
Irregular	-26 (-35 to -17)	-19 (-30 to -4)
Regular	-33 (-45 to -18)	-35 (-45 to -30)
Adjusted for	Screening selection bias (64% coverage 2001-11)	Screening selection bias (64% coverage 2001-11
NZ women (Ref: never screened)	*Table 3.15*	*Table 3.67*
Irregular	**-31 (-40 to -21)**	-23 (-34 to -10)
Regular	**-39 (-52 to -22)**	-44 (-51 to -36)
Adjusted for	Screening selection bias (71% coverage 2012-13)	Screening selection bias (71% coverage 2012-13)
Other (Ref: never screened)	*Table 3.15*	*Table 3.67*
Irregular	-26 (-37 to -13)	-23 (-35 to -7)
Regular	-34 (-50 to -13**)**	-41 (-48 to -32)
Adjusted for	Screening selection bias (66% coverage 2001-11)	Screening selection bias (66% coverage 2001-11)
Other (Ref: never screened)	*Table 3.15*	*Table 3.67*
Irregular	**-29 (-41 to -16)**	-24 (-37 to -9)
Regular	**-38 (-55 to -16)**	-44 (-51 to -35)
Adjusted for	Screening selection bias (72% coverage 2012-13)	Screening selection bias (72% coverage 2012-13)
Māori (Ref: never screened)	*Table 3.16*	*Table 3.67*
Irregular	*-15 (-25 to -4)*	*0 (-9 to +11)*
Regular	*-16 (-33 to +7)*	*-23 (-34 to -10)*
Adjusted for	*Screening selection bias (45% coverage 2001-11)*	*Screening selection bias (45% coverage 2001-11)*
Māori (Ref: never screened)	*Table 3.16*	*Table 3.67*
Irregular	**-26 (-37 to -13)**	*-7 (-18 to +5)*
Regular	*-27 (-49 to +4)*	**-40 (-54 to -22)**
Adjusted for	Screening selection bias (65% coverage 2012-13)	Screening selection bias (65% coverage 2012-13)
Pacific (Ref: never screened)	*Table 3.17*	*Table 3.67*
Irregular	*-24 (-32 to -15)*	*-20 (-27 to -13)*
Regular	*-38 (-44 to -32)*	*-32 (-39 to -24)*
Adjusted for	*Screening selection bias (49% coverage 2001-11)*	*Screening selection bias (49% coverage 2001-11)*
Pacific (Ref: never screened)	*Table 3.17*	*Table 3.67*
Irregular	*-43 (-52 to -32)*	**-36 (-43 to -29)**
Regular	*-64 (-70 to -57)*	**-53 (-61 to -43)**
Adjusted for	*Screening selection (72% coverage 2012-13)*	Screening selection bias (72% coverage 2012-13)

Implausible and/or non-statistically significant results are in *italics*

The most reasonable and consistent results, employing the appropriate preferred methodology, that reflect coverage for the most recent period are in **bold**

Greater mortality reduction in Pacific women may also be affected by higher baseline mortality in unscreened Pacific women, compared to other groups.

Conclusions of comparison of regular and irregular screeners with never screened women

Results for all NZ women and non-Māori non-Pacific women are consistent, indicating a trend across screening categories for breast cancer mortality reduction of plausible magnitude in both inception cohort and case-control studies. Analyses for Pacific women are consistent and plausible, with results of the case control study likely to be more reliable than the inception cohort study because of likely differential attrition bias (deaths) from out-migration. However, greater mortality reduction in Pacific women may also be affected by higher baseline mortality in unscreened Pacific women, compared to other groups. Results of analyses of this screening indicator for Māori are inconsistent and some results are not statistically significant for both inception cohort and case-control studies.

4.1.2.1.2. Regular compared to irregular screened women

All NZ women

In the **Inception cohort,** for ever screened NZ women mortality in those with any breast cancer was 81% (95% CI: 78-84) lower in those regularly screened compared to irregularly screened, adjusted for age and ethnic groups.

In the **case control study**, for ever screened NZ women, breast cancer mortality was 49% (95% CI: 37-58) lower in those regularly screened compared to irregularly screened, adjusted for age and ethnic groups.

Other women (non-Māori, non-Pacific)

In the **inception cohort**, for ever screened non-Māori, non-Pacific (Other) women, breast cancer mortality was 25% (95% CI: -40-60, not significant) lower in those regularly screened compared to irregularly screened, adjusted for age.

In the **case control study**, for ever screened non-Māori, non-Pacific (Other) women, breast cancer mortality was 49% (95% CI: 33-56) lower in those regularly screened compared to irregularly screened, adjusted for age.

Māori women

In the **inception cohort**, for ever-screened Māori women, breast cancer mortality was +4% higher (95% CI: -68 to +233, not significant) in those regularly screened compared to irregularly screened, adjusted for age.

In the **case control study**, for ever screened Māori women, breast cancer mortality was 64% (95% CI: 11-85) lower in those regularly screened compared to irregularly screened, adjusted for age.

Pacific women

In the **inception cohort**, for ever screened Pacific women, breast cancer mortality was 86% (95% CI: 25-97) lower in those regularly screened compared to irregularly screened, adjusted for age.

In the **case control study**, for ever screened Pacific women, breast cancer mortality was 58% (95% CI: 13-80) lower in those regularly screened compared to irregularly screened, adjusted for age.

Table 4.3. Breast cancer mortality in regularly screened compared with irregularly screened (reference) women (ever screened), percentage differences

Indicator	Inception cohort	Case-control study
NZ women Regular screeners	*Table 3.11* -81 (-84 to -78)	*Table 3.68* -49 (-58 to -37)
Other NZ women Regular screeners	*Table 3.14* *-25 (-60 to +40)*	*Table 3.68* -45 (-56 to -33)
Māori Regular screeners	*Table 3.12* *4 (-68 to +233)*	*Table 3.68* -64 (-85 to -11)
Pacific Regular screeners	*Table 3.13* -86 (-97 to -25)	*Table 3.68* -58 (-80 to -13)

Implausible and/or non-statistically significant results are in *italics*

The most reasonable and consistent results, employing the appropriate preferred methodology, that reflect coverage for the most recent period are in **bold**

Conclusions from analyses of regular compared to irregular screening

For the inception cohort study estimates are not significant for Other NZ women and Māori women. The results from the case-control study are more conservative and possibly more plausible. The case-control study indicates a significant breast cancer mortality reduction in regular screeners compared to irregular screeners for all ethnic groups and all NZ women.

Conclusions from analyses of regular and irregular screening

Despite some inconsistencies in results from some analyses, especially for sub-groups, the weight of evidence suggests that regular screening is associated with lower breast cancer mortality compared with irregular screening, and with no screening. Further, in most analyses irregular screening was associated with significantly lower breast cancer mortality than no screening.

4.1.2.2. Screening frequency (number)

All NZ women

In the **inception cohort**, for all NZ women there is significantly lower breast cancer mortality with greater number of mammograms: compared to 1 screen only, women who had 2-3 screens were had 55% (95% CI: 15-76) lower breast cancer mortality adjusted for age and ethnic group. In women with 4 or more screens, the reduction was 94% (83-98).

Other women (non-Māori, non-Pacific)

In the **inception cohort**, for non-Māori, non-Pacific women there is significantly lower breast cancer mortality with greater number of mammograms: compared to 1 screen only, women who had 2-3 screens were had 52% (95% CI: -53-85, not significant) lower breast cancer mortality adjusted for age. In women with 4 or more screens, the reduction was 94% (64-99). The test for linear trend for total mammograms and mortality reduction was statistically significant (p<.0001).

Māori women

In the **inception cohort**, for Māori women there is significantly lower breast cancer mortality with greater number of mammograms: compared to 1 screen only, women who had 2-3 screens were had 64% (95% CI: -21-89, not significant) lower breast cancer mortality adjusted for age. In women with 4 or more screens, the reduction was 89% (33-98). The test for linear trend for total mammograms and mortality reduction was statistically significant (p<.0001)

Pacific women

In the **inception cohort**, for Pacific women there is significantly lower breast cancer mortality with greater number of mammograms: compared to 1 screen only, women who had 2-3 screens had 80% (95% CI: -57-98, not significant) lower breast cancer mortality adjusted for age. In women with 4 or more screens, the reduction was 96% (-100 to +350, not significant). Test for linear trend for total mammograms and mortality reduction was statistically significant (p<.0001).

Table 4.4. Breast cancer mortality by category of screening frequency prior to cancer diagnosis, New Zealand women aged 45-69 years at diagnosis, 1999-2011

Indicator	Inception cohort	Case-control study
NZ women 1 screen (reference) compared to: 2-3 screens ≥4 screens Linear trend+	Table 3.30 **-55 (-76 to -15)** **-94 (-98 to -83)** p <0.0001 (Table 3.29) -48 (-51 to -45)	-
Other women 1 screen (reference) compared to: 2-3 screens ≥4 screens Linear trend+	Table 3.36 *-52 (-85 to+ 53)* **-94 (-99 to -64)** p <0.0001 (Table 3.35) -49 (-53 to -44)	-
Māori 1 screen (reference) compared to: 2-3 screens ≥4 screens Linear trend+	Table 3.32 *-64 (-89 to +2)* **-89 (-98 to -33)** p <0.0001 (Table 3.31) -41 (-50 to -31)	-
Pacific 1 screen (reference) compared to: 2-3 screens ≥4 screens Linear trend+	*Table 3.34* *-80 (-98 to +57)* *-96 (-100 to +350)* p <0.0001 (Table 3.33) -61 (-73 to -44)	-

+ Number of screens as a continuous (integer) variable ≥1.

Results for all NZ women adjusted for age and ethnicity and ethnic specific analyses adjusted for age.

Implausible and/or non-statistically significant results are in *italics*

The most reasonable and consistent results, employing the appropriate preferred methodology, that reflect coverage for the most recent period are in **bold**

Conclusions from analyses of frequency (number) of screens

A trend for greater mortality reduction with increasing number of screens (age adjusted) is demonstrable and consistent for all ethnic groups and all NZ women, in the inception cohort analysis. Although the level of mortality reduction is of similar magnitude, some of the mortality reductions in the inception cohort analyses are not statistically significant, although the linear trend for mortality reduction with increased number of screens (age adjusted) is statistically significant in the inception study for all ethnic groups and all NZ women. These findings accord with expectations.

4.1.3. Screen-detected compared to non-screen detected breast cancer

All NZ women

In the **inception cohort**, for ever screened NZ women, breast cancer mortality in those with a screen-detected cancer was 45% (95% CI: 31-57) lower than in similar ever-screened women whose cancer was detected outside screening, adjusted for age and ethnic groups.

In the **case control study**, for ever screened NZ women, breast cancer mortality in those with a screen-detected cancer is 65% (57-72) lower than in similar ever-screened women whose cancer was detected outside screening, adjusted for age and ethnic group.

Other women (non-Māori, non-Pacific)

In the **inception cohort**, for ever screened non-Māori, non-Pacific (Other), breast cancer mortality in those with a screen-detected cancer was 43% (95% CI: 7-65) lower than in similar ever-screened women whose cancer was detected outside screening, adjusted for age.

In the **case control study**, for ever screened non-Māori, non-Pacific (Other), breast cancer mortality in those with a screen-detected cancer is 65% (52-74) lower than in similar ever-screened women whose cancer was detected outside screening, adjusted for age.

Māori

In the **inception cohort**, for ever-screened Māori women, breast cancer mortality in those with a screen-detected cancer was 56% (95% CI: 23-75) lower than in ever-screened Māori women whose cancer was non-screen detected (age adjusted).

In the **case control study**, for ever-screened Māori women, breast cancer mortality in those with a screen-detected cancer was -78 (73-81) lower than in similar ever-screened women whose cancer was detected outside screening (age adjusted).

Pacific women

In the **inception cohort**, for ever-screened Pacific women, breast cancer mortality in those with a screen-detected cancer was 42% (-46-77) lower (not significant) than in ever-screened Pacific women whose cancer was non-screen detected (age adjusted).

In the **case control study**, for ever screened Pacific women, breast cancer mortality in those with a screen-detected cancer is 71% (-96 to +61) lower than in similar ever-screened women whose cancer was detected outside screening, adjusted for age.

Table 4.5. Breast cancer mortality from screen-detected compared with non-screen detected breast cancer in cancer in ever-BSA screened women aged 45-69 years at year of diagnosis, 1999-2011, percentage differences

Indicator	% Mortality difference (95% CI)	
	Inception cohort	Case-control study
Breast cancer mortality in women with screen detected compared with non-screen detected (referent) breast cancer		
All NZ women	*Table 3.19*	*Table 3.69*
Screen detected	**-45 (-57 to -31)**	-65 (-72 to -57)
Other NZ women	*Table 3.22*	*Table 3.69*
Screen detected	**-43 (-65 to -7)**	-63 (-71 to -53)
Māori women	*Table 3.20*	*Table 3.69*
Screen detected	**-56 (-75 to -23)**	-78 (-82 to -72)
Pacific women	*Table 3.21*	*Table 3.69*
Screen detected	*-42 (-77 to +46)*	-75 (-84 to -61)

Implausible and/or non-statistically significant results are in *italics*

The most reasonable and consistent results, employing the appropriate preferred methodology, that reflect coverage for the most recent period are in **bold**

Conclusions from analyses of screen-detected and non-screen detected breast cancer in cancer

Both study types indicate a substantial lower mortality for screen detected compared with non-screen detected cancer which accords with expectations.

4.1.4. Prognostic indicators

Analysis of prognostic indicators of diagnosed breast cancers in relation to mammographic screening provide the explanation for the observed differentials in breast cancer mortality.

4.1.4.1. Ever and never screened women

From data on diagnosed breast cancers, women who were ever screened had more favourable prognostic indicators than women never screened with respect to: grade of tumour (30% well differentiated in ever-screened, 18% in never-screened); extent of spread (63% localised in ever-screened, 46% in never-screened); and maximum tumour size (average 18 mm in ever-screened and 24 mm in never-screened). Differences between prognostic indicators were all statistically significant for all NZ women, and for Māori, Pacific and Other women.

4.1.4.2. Regular and irregularly screened

In all NZ women, non-Māori and non-Pacific (Other) women, and Māori women, there were only slight differences by grade of tumour as assessed by proportion of well differentiated in diagnosed breast cancers for those regularly screened compared to those who were irregularly screened. However, from data on diagnosed breast cancers, all NZ women who were regularly screened had more favourable prognostic indicators than those who were irregularly screened with respect to: extent of spread (67% localised in regularly screened, 60% in irregularly screened); and maximum tumour size (average 16 mm in regularly screened and 19 mm in irregularly screened).

In non-Māori and non-Pacific (Other) women, those who were regularly screened had more favourable prognostic indicators than those who were irregularly screened, with respect to: extent of spread (68%

localised in regularly screened, 60% in irregularly screened); and maximum tumour size (average 16 mm in regularly screened women and 19 mm in irregularly screened women).

In Māori women, those who were regularly screened had more favourable prognostic indicators than those who were irregularly screened, with respect to: extent of spread (66% localised in regularly screened, 55% in irregularly screened); and maximum tumour size (average 17 mm in regularly screened and 21 mm in irregularly screened).

In Pacific women, those who were regularly screened had more favourable prognostic indicators than those who were irregularly screened, with respect to: grade of tumour (33% well differentiated in regularly screened, 24% in irregularly screened); extent of spread (68% localised in regularly screened, 50% in irregularly screened); and maximum tumour size (average 16 mm in regularly screened women and 23 mm in irregularly screened women).

Although in non-Māori and non-Pacific (Other) women, and thus in all NZ women, and in Māori, there was no difference in grade of tumour between regularly screened and irregularly screened women, there were less favourable prognostics as assessed by extent of spread and mean tumour size for irregularly screened women compared to the regularly screened.

In Pacific women, there were less favourable prognostics as assessed by grade of tumour, extent of spread, and maximum tumour size for those who were irregularly screened compared to the regularly screened.

4.1.4.3. Screen detected and non-screen detected cancers

From data on diagnosed breast cancers, women whose cancers were screen detected had more favourable prognostic indicators than those whose cancers were detected outside of screening with respect to: grade of tumour (differentiation on histology, 35% for screen detected versus 21% for non-screen detected); extent of spread (localised, 69% for screen detected, 50% for non-screen detected); and maximum tumour size (average 16 mm for screen detected and 23 mm for non-screen detected).

4.2. METHODOLOGICAL ASPECTS

A number of issues arise in comparing breast cancer mortality in screened versus unscreened populations, chief of which are the potential for lead-time and screening selection bias.

4.2.1. Study types

For the **screening inception cohort analysis**, in which breast cancer mortality in ever-screened women is compared with never-screened women in relation to exposure to screening, without regard to time of diagnosis of breast cancer, lead-time bias is not a major issue. This is because relative risk and mortality difference estimates are based on person-time denominators defined by time exposed to screening or never screening, not on time since diagnosis of the cancer. However, a screening inception cohort approach is limited by the changes from never- to ever-screened status with time, particularly in denominator populations which remain free of breast cancer. Additionally, the changing screening status of women in screening inception cohorts cannot completely capture person-times of exposure to never-screening. This is because population denominators for never-screened populations are available only in annual aggregations of 5-year age groups (by ethnicity) from deduction of screened populations from the census. Information on women who screened, or who were diagnosed with, or died from, breast cancer, is known individually from the screening register and/or cancer registry and mortality data. Estimation of person-times for never-screened women not diagnosed with breast cancer was based on subtracting known screened women at a

given time from the aggregate population (from the census), and person-time of never-screening calculated from the median age for each 5-year age group (by ethnicity) in the remainder 45-69 year populations.

To minimise effects due to changing screening status over time in the screening inception cohort analysis, the follow-up time for breast cancer mortality was limited to the 12-month period following establishment of ever- and never-screened population denominators for a given year. This procedure was repeated for each year and analysed using repeated measures negative binomial or Poisson regression. The population denominators were converted to person-years of exposure to screening or non-screening. This analysis minimises the inherent bias in an incidence-based analysis where breast cancer mortality in screened and unscreened populations is compared only from breast cancers diagnosed since the commencement of the mammography screening programme. The bias stems from a shrinking population denominator of never-screened women, and a corresponding increase in the ever-screened population denominator, with time since the commencement of the screening programme. This bias can produce an artefactually higher breast cancer mortality benefit in ever-screened women compared to never-screened women.

A **case-control study** design is a cost-effective means for assessing associations between risk factors and rare outcomes, such as death from breast cancer, since it does not require follow-up of populations exposed and unexposed to risk factors, or exposed to varying degrees to risk factors. Additionally, a case-control study can largely overcome attrition bias (loss to follow-up from out migration, for example) that may affect cohort studies. The case-control design used here is population-based, regarded as the highest quality case-control design, and nested within the 1999-2011 NZ inception population cohort study as the sampling frame. While a well-designed case-control study may be expected to provide similar results to an historic cohort study, there often are questions about appropriateness of cases and chosen controls. Although there is potential in case control studies for differential recall bias for (retrospective) exposure in cases and controls, such is not be an issue in this study as information on the cases (deaths from breast cancer) with respect to exposure to screening is not collected any differently to (live) non-cases (controls). The two main purposes of the case-control study are to cross-validate the previous BSA cohort study results, and to counter bias stemming from possible loss to follow-up that can affect cohort studies, especially possible out-migration in Pacific women. Not all breast cancer deaths or live controls (non-cases) are required in a case-control study, and thus the effects of the tendency for attrition from the cohort from out-migration that may artefactually lower mortality are minimised.

4.2.2. Strengths and weaknesses of studies

4.2.2.1 Inception Cohort

Strengths

The screening inception cohort study design has enabled detailed analysis of the association between screening and breast cancer mortality mitigating the effects of lead time bias. This is because the screening inception cohorts are defined with regard to time from first screen, or eligibility to screen, without regard to when breast cancers contributing to breast cancer mortality are diagnosed. The inception cohort approach has allowed analysis of mortality differences between never- and ever-screened women with respect to screen-detected and non-screen detected cancers, minimally affected by lead time effects. And it has allowed the assessment of possible length time effects as well, and this has been shown to be minimal.

Weaknesses

As in any cohort study, sample attrition is the major issue and is difficult to address. For the present study this is particularly the case with Pacific women diagnosed with breast cancer whose mortality may be under-recorded because they have returned to their country of origin following diagnosis, and this may be an underestimate of their true breast cancer mortality. Further, under-enumeration of deaths in Pacific women may be of a different magnitude in Pacific women stratified by differing screening or diagnosis characteristics. Most of these issues can be addressed in the case-control component of this evaluation. It is likely that breast cancer mortality in Pacific women is under-recorded in New Zealand as Pacific people may repatriate to their country of origin to die causing attrition bias (of deaths). Cohort studies suggest inflated estimates for effects of screening in Pacific women, which indicate that the Pacific women diagnosed with breast cancer who out-migrate are not representative of all Pacific women with breast cancer. That is, the attrition bias is likely differential with respect to categories of screening (or no screening) exposure, and suggests that more deaths are lost to the cohort from those women who screen or with greater screening regularity, than never screeners or irregular screeners.

4.2.2.2. Case-control study

Strengths

The main strength of a case control study is that it avoids the issue of attrition bias from deaths from breast cancer in a cohort because they are not followed-up, or registered (in the same jurisdiction); as in the case of out-migration of Pacific women.

Since the control population was selected to include only women known to be alive by the end of the study period, the findings are not affected by attrition bias. The case control study produces lower effects of screening than for the cohort analyses of Pacific women, but still a higher yet likely plausible screening effect than all NZ women. The larger screening effect in screened versus unscreened Pacific women compared with Other (non-Māori, non-Pacific) women, may reflect a higher baseline breast cancer mortality in unscreened Pacific women, compared to baseline breast cancer mortality in Other (non-Māori, non-Pacific) unscreened women.

Weaknesses

Overall, the central weakness of a case-control study design is that it can establish association between an outcome (e.g., death from breast cancer) and a postulated exposure factor (e.g., screening mammography), as cases are compared with controls cross-sectionally. As such they provide only weak, indicative evidence for causation. To varying degrees, case-control studies are also subject to selection bias (particularly controls), and differential misclassification of exposure, for example from recall bias.

Breast cancer deaths (cases) in the case control study are, like in the cohort analyses, deaths which occurred in New Zealand only. In Pacific women this is likely to not be representative of characteristics of all breast cancer deaths in Pacific women, as evidenced by the likely differential attrition bias evident in cohort studies. Thus, although the issue of attrition bias is mitigated by the case control design, the breast cancer deaths in Pacific women available for analysis are likely not representative of all deaths from breast cancer incident in Pacific women in New Zealand.

Appropriateness of controls for cases is always an important issue in case control studies. For this study controls (non-cases) consisted of those: (a) screened or diagnosed with breast cancer alive up to the end of the study (end December 2011) as determined by the 'last up-dated' flag on the individual record, plus (b) never screened or diagnosed (with breast cancer) obtained by deduction of the known screened or diagnosed (breast cancer) populations from the aggregate census population data by 5 year age group, by ethnicity for

each year. A strata-matched analysis was performed based on matching on year of diagnosis, age group diagnosis and ethnicity.

The controls may not be completely appropriate for the cases since, *inter alia*: they were all alive at the end on the study period; alive status was determined for those screened or diagnosed (with breast cancer) by use of the 'last updated flag' on their individual record which is a consequence of health service use; and that never screened or diagnosed (with breast cancer) controls were obtained by deduction of known populations from census derived populations.

4.2.2.3. Adjustment for screening selection bias

The main advantage of adjusting for screening selection bias is that it allows for estimation of the effects of screening mammography on breast cancer mortality in a population offered screening compared to a population not offered screening. This produces an assessment of the effects of a screening programme on a whole population, rather than in a sub-population that takes up screening compared to another sub-population that is unable or chooses not to participate in screening mammography.

A potential weakness in the present analysis is the use of mortality differentials from Swedish service screening studies for adjusting for screening selection bias. The relative risk (RR) of breast cancer mortality in women not screening, in spite of it being offered, compared to women not offered screening, from the Swedish trials is RR=1.17.[46] While this may well be similar to the New Zealand population overall, it may not be so similar in magnitude for Māori and Pacific women, although the direction of effect is likely to be the same. Adjustment for screening selection bias relies partly on screening participation, and provides an estimate of screening based on an intention-to-treat basis with a comparison of a population offered screening versus a population not offered screening. This concept can be difficult to grasp when comparing screening regularity, for example in regular versus irregular screening. Accordingly, these latter estimates, after adjustment for screening selection bias, are somewhat artificial, as each is based on the intention-to-treat assumption of the screening population offered screening, at a given overall participation rate, being all irregular or all regular screeners, as the case may be.

As in most screening service studies, which by nature are observational, the factors contributing to differences in breast cancer mortality between those participating in screening, compared to those not participating, cannot all be known or measured. It is possible that women who screen when it is offered also have other (unmeasured, unknown) characteristics that may contribute to lower breast cancer mortality (in addition to screening), or that screening services are more accessible or responsive to them, than they are to women who do not screen. Such factors may contribute to higher breast cancer mortality in women who do not screen when offered through higher incidence and/or higher case fatality, compared to those who screen when offered. Additionally, in New Zealand not all women are directly offered breast screening, but screening is promoted through media campaigns and other health promotion activities.

4.2.2.4. Control of confounding by age and ethnicity

The main potential confounders in this study are age and ethnicity, and these were adjusted for in cohort analyses by stratification using appropriate regression techniques. For ethnic-specific cohort analyses observations were adjusted for 5-year age group only. For the case control study, cases and controls were matched on 5-year age group and ethnicity.

4.3 COMPARISON WITH OTHER STUDIES

Few observational cohort studies of established screening mammography programmes have been conducted using individual-based data linking screening history with cancer prognostic data with breast cancer mortality data. Such data linkage for BreastScreen Aotearoa has allowed an unprecedented examination of the efficacy of screening mammography in a real-world population setting. Most existing service studies have related aggregate population screening data to aggregate breast cancer mortality data, as area-based, or as secular, time-based comparisons. Some of the better aggregate studies have managed to separate breast cancer mortality stemming from cases diagnosed prior to screening versus those diagnosed post screening (so-called incidence-based mortality studies), and the results from these are congruent with those found for New Zealand.

Evaluations of mammography service screening employing individual data include case control and cohort studies. Cohort studies can be used as the basis for evidence for the effectiveness of screening in a quasi-experimental design whereby cohorts with different exposures to the offer of screening (in time or place) are compared with respect to breast cancer mortality. Most of the cohort studies of service mammography screening use this method which involves potential bias and confounding from differences between comparison cohorts. These studies have shown a breast cancer mortality RR of 0.72 (mortality reduction 28%) for invitation for screening (7 studies), and RR=0.57 (mortality reduction 43%) for actual screening (5 studies).[54] Non-randomised comparative studies of breast cancer screening demonstrated a 24% breast cancer mortality reduction from invitation to screening (3 studies) and a 33% mortality reduction for screening attendance (1 study).[54]

The above studies differ from the current cohort NZ study which is conducted within an entire population and limited to the screening epoch (from 1999) where all age-eligible may participate in screening mammography without direct charge. Although conducted in the screening epoch, the mortality evaluation of breast screen Australia[29,31] for 1990-2004 used an aggregate cohort approach with small area incidence-linked mortality correlated with the mammography screening rate. This study found mortality reduction from screening projected to 70% (target) participation of 25%-34% (from Poisson or Cox proportional hazard regression).[29,31]

4.4 CONCLUSIONS

This report concerns breast cancer mortality in relation to service mammography screening within the screening epoch using inception and case-control studies in NZ women, and ethnic subgroups.

Individual information from the breast screening services supply data for the study factor, exposure to screening, and data from the cancer registry and death register are used for the outcome factor, breast cancer mortality. Denominator populations constructed from these data are deducted from census-derived NZ female populations (by age, ethnic group, and period) to provide aggregate population estimates of never screened (alive) women without breast cancer.

Lower breast cancer mortality was demonstrated in relation to service mammographic screening for ever compared to never-screened for all NZ women, and non-Māori, non-Pacific (Other) women showed similar trends to the general population. A dose-response effect was apparent with lower breast cancer mortality with greater screening regularity (frequency and interval combined) using cohort and case control analyses.

Māori women demonstrate lower breast cancer mortality in the ever screened compared to the never screened in the inception cohort, although somewhat less than non-Māori, non-Pacific (Other) women,

because of lower screening coverage. The projected reduction in breast cancer mortality in the ever screened compared to the never screened Māori women would be no different to non-Māori, non-Pacific (Other) women at target screening coverage of 70%.

Analyses of Pacific women produced likely inflated estimates of mortality reduction associated with screening in cohort analyses, which may be partly due to differential under-recording of deaths from out-migration. This is addressed by case-control analyses, but may also reflect higher baseline breast cancer mortality in unscreened Pacific women, than in other groups.

The inception cohort and case control methods involving comparisons with the never screened are affected by screening selection bias since women who do not screen when offered have been shown to manifest higher breast cancer mortality than (unscreened) women not offered screening, and inflated estimates of mortality reduction compared to never-screened can be produced. Adjustments have been made based on an estimate of higher breast cancer mortality from Swedish service studies of RR=1.17 in women who are offered but do not participate in screening, compared to unscreened women not offered screening. Projected screening effectiveness compared to those not offered screening is estimated using this RR and average screening coverage for the study period, and for the most recent coverage, and for target biennial coverage of 70%. Observational cohort studies can be affected by under-enumeration of deaths which may occur from differential (by screening exposure) out-migration after diagnosis.

Analysis of women with breast cancer who were ever screened, compared to never screened, with respect to prognostic factors at diagnosis (tumour grade, extent of spread, multiple tumours, and maximum size), revealed statistically significant more favourable indicators for all NZ women, non-Māori, non-Pacific (Other) women, Māori women, and Pacific women. There were similar findings for screen detected compared to non-screen detected breast cancer.

This report has shown that screening mammography in New Zealand has been associated with clear and significant reductions in breast cancer mortality in New Zealand women participating in mammography screening.

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