



# **Summary of the BreastScreen Aotearoa Mortality Evaluation**

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1999–2011

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# Introduction

## Population-based breast screening programmes

This paper provides an overview of the recently published BreastScreen Aotearoa (BSA) mortality evaluation, which assessed the impact of New Zealand's breast screening programme from 1999 to 2011 on breast cancer mortality.

The aim of population-based breast screening programmes is to reduce mortality from breast cancer. Breast cancer is the commonest cancer in women in developed countries and is the leading cause of non-tobacco-related cancer deaths for New Zealand women. In 2012, 3025 women were diagnosed with breast cancer (almost 30% of all new female cancer cases) and 617 women died of the disease.<sup>1</sup> Māori women have a higher incidence of breast cancer, and Māori and Pacific women have significantly higher mortality from breast cancer. For this reason, BSA prioritises screening these women, as well as those who are unscreened and under-screened.<sup>2</sup>

Breast screening does not prevent the development of cancer, but rather detects the disease at an earlier stage. Early detection can reduce both illness and death from breast cancer.

Evidence to support organised breast screening comes from international randomised controlled trials from the 1970s and 1980s. Breast screening programmes achieving coverage (or participation) of 70% of eligible women, can reduce mortality from breast cancer by 30–35% for women who are screened, compared with women who are not screened.<sup>3</sup> A similar result was expected from New Zealand's established breast screening programme.

This mortality study evaluated breast cancer deaths occurring among women screened in the BSA programme, compared to those who were not. It is standard in breast screening programmes internationally to undertake this type of research more than 10 years after implementation of the programme. This is because the natural history of breast cancer means a long period of time needs to elapse before the impact of screening on breast cancer mortality can be assessed.<sup>4</sup>

BSA started screening eligible New Zealand women aged 50–64 years in December 1998 after two successful pilots. In 2004, the eligible age range was extended to 45–69 years.

For the duration of this study, most of the screening was done using film mammography. BSA became fully digital in 2013.

<sup>1</sup> Ministry of Health. 2015. Cancer: New registrations and deaths 2012. Wellington: Ministry of Health.

<sup>2</sup> Under screened women were those had been screened in BSA but did not meet the definition of regularly screened.

<sup>3</sup> World Health Organization. 2002. International Agency for Research on Cancer Handbook of Cancer Prevention. Volume 7. Breast Cancer Screening. IARC Press, Lyon.

<sup>4</sup> In the intervening time, BSA monitored for improvements in the proportion of detected cancer that were small, that had not spread outside the breast, and that were detected between screens (interval cancers). All of these markers would indicate that mortality is likely to be improving.

# Research questions

These are the questions tested in this evaluation.

- Is mortality from breast cancer in New Zealand women who have ever had a BSA mammogram lower than in women who have never had a mammogram in BSA?
- Is breast cancer mortality lower in women who have regular and more frequent BSA mammograms than those who do not?
- Is mortality from breast cancer lower among women whose breast cancers were detected by BSA than among those who were not detected by BSA?
- Do the breast cancers found in women ever screened in BSA have features that would suggest a better chance of recovery or reduced likelihood of recurrence (eg, smaller tumour and earlier stage) than those found in women never screened in BSA?
- Despite the higher death rates from breast cancer in Māori and Pacific women, will any reduction in breast cancer death rates seen in the total population also be found for Māori and Pacific women ever screened in BSA?

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# Study design

This study examined all women screened from 1999-2011, and then examined women by ethnicity according to BSA priority groups. The study was not designed to confirm reductions in mortality in specific age groups, including the 2004 age extension groups, ie, 45–49 years and 64–69 years.

The overall study is made up of two separate studies.

1. A retrospective inception cohort study.
2. A case-control study.

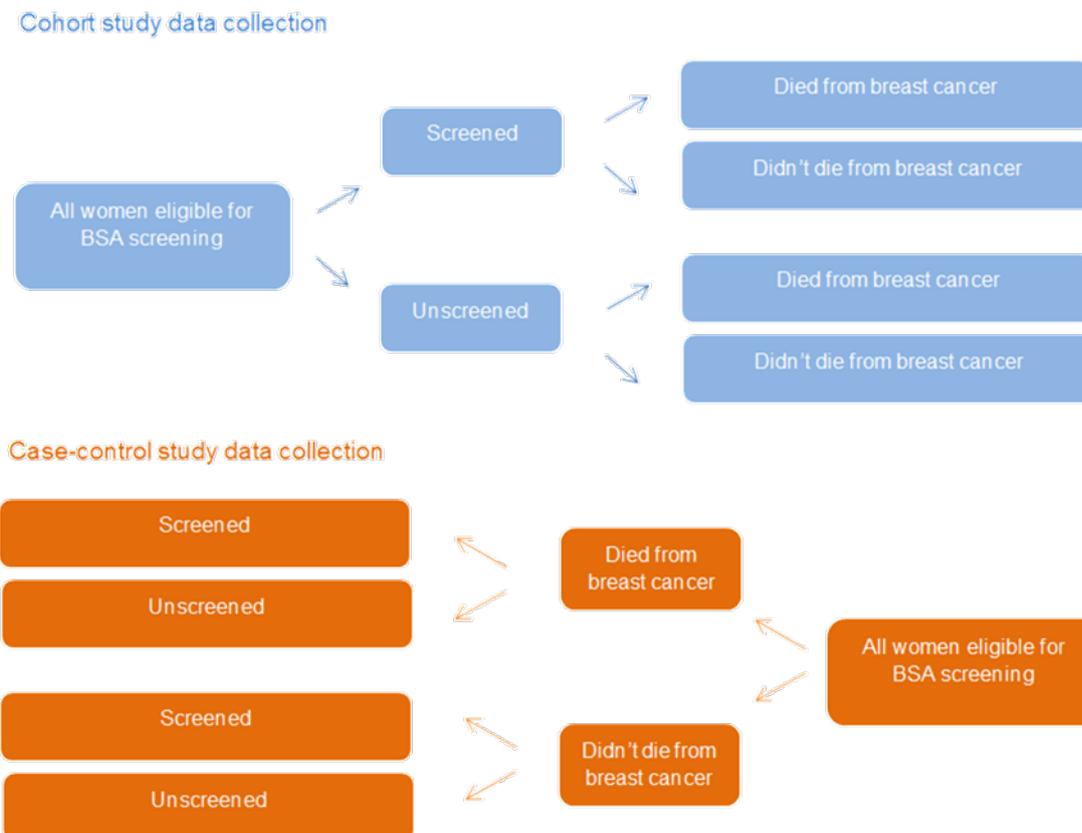
The difference between the cohort and case-control studies is shown in Figure 1. Each study was deliberately included to make sure that all of the evaluation questions could be answered. A separate benefit was that findings could often be checked between the different study designs. All studies have strengths and weaknesses and finding similar results through different methods can provide reassurance and confidence in the results.

Unless otherwise indicated, results presented are adjusted for age, ethnicity<sup>5</sup> and screening selection bias (described on page 4). In New Zealand, we were fortunate to be able to use National Health Index (NHI) numbers to link screening, mortality and cancer data.

The inception cohort study analysed data relating to all women and Māori women. Findings relating to Pacific Island women, however, were taken from the case-control study. This is because it was indicated by the implausible finding from the cohort analysis, that results for Pacific women might be affected by under-reporting of deaths due to women returning to their home country after a diagnosis was made.

<sup>5</sup> Except where data is relating to a specific ethnic group.

**Figure 1: The difference between the cohort and case-control studies**



## 1 Retrospective inception cohort study

This study followed all women who were eligible for breast screening during the period 1999 to 2011. Due to changes in the age at which women were eligible for screening during the period of evaluation, women aged 50–64 years were included in the study for 1999–2003, widening to women aged 45–69 years from 2004.

The Ministry of Health’s Mortality Collection data was used to identify which of the eligible women died during the study period, and the New Zealand Cancer Registry was used to confirm if they had died of breast cancer. The BSA database was used to track if, and when, women received screening mammograms.

Each eligible woman was followed through until 2011 if they did not die, or until the year they died. Women were re-classified each year as either never screened, or ever screened. The number of women never screened was found by subtracting the number of women known to have screened from estimates of the eligible population from Statistics New Zealand. For women who were screened, dates of screening visits were checked to see whether the women were screened regularly or not as often as recommended.

Breast cancer deaths from cancers diagnosed after the advent of screening were compared between women ever and never screened in BSA, and between women who were screened on a regular basis and those who were screened but not regularly.

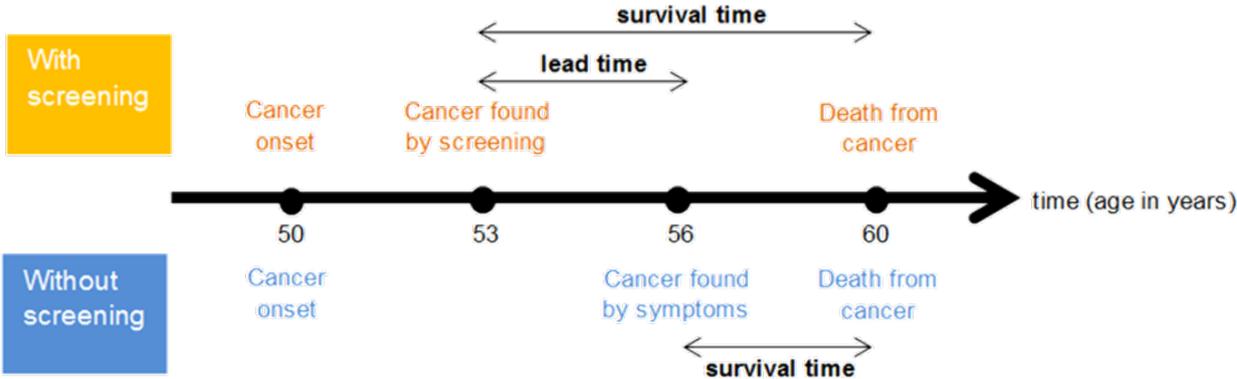
An analysis was also undertaken using only those women in the cohort known to have been diagnosed with breast cancer. This analysis was used to compare prognostic indicators at time of breast cancer diagnosis between screened and non-screened women, and women with screen-detected and non-screen detected cancers. Prognostic indicators are factors such as tumour size and grade that are known to be associated with likelihood of breast cancer survival or recurrence/death.

The authors used an adjustment factor to reduce the impact of screening selection bias on the findings. Screening selection bias refers to the fact that women who do not screen (compared to those who do screen with BSA) may possess characteristics that make them more susceptible to dying from breast cancer. For example, women who don't screen and then develop breast cancer may have more medical problems, and may have more difficulty accessing cancer treatment.

The adjustment factor used in the inception cohort study of 1.17 was developed by Professor Stephen Duffy (UK) and adjusts for the known worse outcomes for women who are invited to screen but who do not attend.<sup>6</sup> This was developed from published Swedish Mammography Service Screening Assessments and is considered by the authors to be the best currently available to adjust for screening selection bias. There is ongoing discussion about whether this is the best adjustment factor for New Zealand women, especially for Māori and Pacific women. Future work in this area may be needed. This adjustment allows results of mammography screening service studies to be compared to those of the previous randomised controlled trials, which compared breast cancer mortality in populations with screening available, to that in populations not offered screening.

The strength of this study design is that it is not affected by lead time bias. Lead time is the time between detecting a disease through screening and detection due to appearance of symptoms. Lead time bias means there is no change in the length of time between cancer onset and death, but the person appears to have survived the disease for longer. This is because the cancer was diagnosed earlier through screening than if the person had not been screened (see Figure 2).

**Figure 2: The effect of lead time bias on perceived survival time among screened and unscreened women**



## 2 Case-control study

There were concerns that accuracy of data on deaths would be affected by women diagnosed with breast cancer subsequently leaving New Zealand. In particular, it has been reported that

<sup>6</sup> Swedish Organised Service Screening Evaluation Group. 2006. Reduction in breast cancer mortality from organised service screening with mammography: 1. Further confirmation with extended date. *Cancer Epidemiol Biomarkers Prev.* 15 (1): 45–51.

breast cancer death reporting for Pacific women may be low, due to women returning to their home country after cancer diagnosis. If a woman dies from breast cancer in the Pacific Islands, the New Zealand Cancer Registry is not notified, and our data would consider them to still be alive. For this reason a case-control study was included in the mortality evaluation to provide better estimates of the extent of benefit for Pacific women from screening.

In the case-control study, participation in breast screening by BSA was compared between Pacific women who were diagnosed with breast cancer during the evaluation period, those who died in New Zealand (cases), and Pacific women for whom there was evidence they were alive (controls). The controls included women with breast cancer and women without breast cancer.

### **3 Time periods used in analyses**

There are varied time periods used in the main report. Screening and mortality data were available for the period 1999–2011. However, data from this entire time period was not used for all analyses for a number of reasons, including:

- coverage in the earlier years was considered too low to include in the averages (when adjusting for screening selection bias)
- sufficient time had to pass for women to meet the definition of regularly screened.

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# Key findings

## Results for New Zealand women overall

Values below are adjusted for screening selection bias, age and ethnicity, and show that New Zealand women who had ever screened in BSA prior to 2011 were estimated to have:

- 29% lower breast cancer mortality than women never screened, at the average participation rate of 64%
- 34% lower breast cancer mortality than women never screened, using the current participation rate of 71%.

Women who were regular screeners (those who screened three or more times at regular intervals of less than 30 months) compared with never screened women, were estimated to have:

- 33% lower breast cancer mortality at the average participation rate of 64%
- 39% lower breast cancer mortality using the current participation rate of 71%.

Irregular screeners (who had ever screened but did not qualify as regular) were estimated to have:

- 26% lower breast cancer mortality than never screened women at the average participation rate of 64%
- 31% lower breast cancer mortality than never screened women using the current participation rate of 71%.

## Māori women

In the inception cohort, adjusted for screening selection bias and age:

- Māori women who had ever screened in BSA prior to 2011 were estimated to have:
  - 17% lower breast cancer mortality than women never screened at the average participation rate of 48%
  - 28% lower breast cancer mortality than women never screened using the current Māori coverage of 65%
- for Māori women, if a target participation rate of 70% were achieved, it has been estimated that there would be:
  - 32% lower breast cancer mortality for women ever screened in BSA compared to women never screened.

## **Pacific women**

These results are from the case-control study, which is not biased by under-reporting of women's deaths if women return to their home country after diagnosis and treatment.

Pacific women who had ever screened in BSA prior to 2011 were estimated to have:

- 22% lower breast cancer mortality than Pacific women never screened, at the average participation rate of 49%
- 40% lower breast cancer mortality when calculated using more the more recent participation rate of 72%.

## **Screen-detected vs non-screen-detected breast cancer**

For all New Zealand women, Māori women and Pacific women, whose cancer was detected by screening, there was a substantially lower mortality from breast cancer compared to those women whose breast cancers were not screen-detected. This was seen in both the cohort and case-control study types.

This is the result of detection of early stage breast cancer in BSA compared to when a woman presents with symptoms and is diagnosed with breast cancer from a clinical examination by a health professional.

## **Screening frequency**

For all New Zealand women, Māori women and Pacific women, significantly lower breast cancer mortality was found among women who had had two or more mammograms, compared to those having their first mammogram.

The difference is more marked with increasing rounds of screening. There was significantly lower breast cancer mortality among women who had four or more mammograms, compared to women who had two or three mammograms.

This is explained by the fact that women having their first mammogram may have larger, undetected cancers, whereas at later mammograms, there has been a shorter period of time for the cancer to grow (or become detectable on a mammogram).

## **Indicators of improved survival**

As well as experiencing lower rates of breast cancer mortality, women who had ever been screened in BSA had an improved prognosis, when compared to women who have never been

screened. There are four key indicators of prognostic outcomes from breast cancer that would be expected to differ between these two groups of women.

1. Grade of tumour (low – grade 1, intermediate – grade 2, high – grade 3).
2. Stage of disease (localised to the breast, regional spread to the armpit, metastatic spread to distant parts of the body, unknown).
3. Single versus multiple tumours.
4. Mean and median tumour size.

These four measures are well established from the medical literature as prognostic indicators of outcome from breast cancer. Among screened women, disease is expected to be less advanced at diagnosis (see Table 1).

## Ever screened versus never screened

From data on women with diagnosed breast cancers, women who were ever screened in BSA had more favourable indicators than those never screened. Differences between prognostic indicators were all statistically significant for all New Zealand women, and for Māori, Pacific and Other women<sup>7</sup> (see Table 1).

- Women who have ever been screened are more likely to have low grade (slower growing) tumours and less likely to have high grade (faster growing) tumours.
- Women who have been screened are also more likely to have disease localised only in the breast at diagnosis, and less likely to have regional spread.
- Median maximum tumour size is smaller for women ever screened in BSA compared to tumour size in never-screened women.

**Table 1: Comparison of prognostic indicators in ever screened women, compared with never screened women (2000-2011)**

Prognostic indicators		Ever screened	Never screened
Grade of tumour	Well differentiated (low grade)	30%	18%
	Moderately differentiated (medium grade)	41%	40%
	Poorly differentiated (high grade)	24%	32%
Extent of disease	Localised	63%	46%
	Regional	29%	39%
	Distant	2%	5%
More than 1 tumour		2%	4%
Median maximum tumour size <sup>8</sup>		15 mm	20 mm

Analysis by ethnic group shows, the differences in these indicators for Māori and Pacific women ever screened in BSA compared to those never screened are similar to the overall differences (Table 2). However, some dissimilarities were reported. In particular:

<sup>7</sup> According to the Ministry of Health ethnicity protocols, 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.

<sup>8</sup> Figures have been rounded for simplicity, more detailed and specific information can be found in the full report.

- the proportion of localised breast cancer in both Māori women ever screened and never screened was lower (59% and 39% respectively) compared with New Zealand women overall (63% and 46% respectively)
- the average tumour size for Māori women who had never been screened was 5mm larger than for all never screened women diagnosed with breast cancer, and 9mm larger than for Māori women who had ever been screened
- in Pacific women never screened in BSA, 11% of women had metastatic (distant spread of) breast cancer at diagnosis, compared to 5% of Māori women and 5% of all women who have never been screened
- the average tumour size for Pacific women who have ever been screened was 13 mm smaller than for Pacific women who have never been screened
- in Pacific women who had never been screened, the average tumour size was 30 mm, 5 mm larger than for Māori women never screened in BSA, and 10 mm larger than for all New Zealand women who have never been screened.

These figures suggest that over the time period of this study, Māori and Pacific women outside BSA were being diagnosed with more advanced disease than Other New Zealand women who had never been screened, and had significantly more advanced disease than Māori and Pacific women who had been screened. This will contribute to differences in survival from breast cancer. This translates into continued poorer outcomes for Māori and Pacific women if they are not able to access the screening programme. Increased work is needed across the entire health sector to improve equitable access to services for Māori and Pacific women, both screening and symptomatic.

**Table 2: Prognostic indicators by ethnic group (2000–2011)**

Prognostic indicators		Māori		Pacific		Other	
		Ever screened	Never screened	Ever screened	Never screened	Ever screened	Never screened
Grade of tumour	Well differentiated (low grade)	27%	14%	27%	10%	30%	19%
	Moderately differentiated (medium grade)	45%	42%	44%	38%	41%	41%
	Poorly differentiated (high grade)	23%	34%	24%	39%	24%	31%
Extent of disease	Localised	59%	39%	56%	35%	64%	48%
	Regional	32%	45%	31%	40%	29%	38%
	Distant	2%	5%	2%	11%	2%	5%
More than 1 tumour		2%	3%	1%	3%	2%	4%
Median maximum tumour size <sup>9</sup>		16 mm	25 mm	17 mm	30 mm	15 mm	20 mm

Analysis was also done to look at whether there were changes over time in prognostic indicators. The time periods used were 2000–2004, 2005–2009, and 2010–2011.

- The proportion of Māori women ever been screened in BSA with localised disease had increased from 53% (in 2000–2004) to 64% (in 2010–2011).
- The proportion of Māori women ever screened with regional lymph nodes involved had come down from 33% (in 2000–2004) to 28% (in 2010–2011).
- Both of these proportions are now the same as ever screened women overall.

<sup>9</sup> Figures have been rounded for simplicity, more detailed and specific information can be found in the full report.

- The average size of breast cancer in Māori women who had ever been screened in BSA is also the same as for all New Zealand women ever screened.
- The data for Pacific and Other women showed little variation over time.

These changes in the proportions of breast cancer size and lymph node involvement suggest significantly improving outcomes with reducing mortality from breast cancer for Māori women taking part in BSA. It is a very positive finding that as coverage improves, more Māori women are being diagnosed with earlier stage breast cancer, which has a better prognosis.

## Screen-detected versus non-screen-detected

From data on diagnosed breast cancers, women who have ever been screened in BSA whose cancers were screen-detected in the programme had more favourable indicators of breast cancer outcomes than those whose cancers were detected outside of screening (see Table 3).

**Table 3: Prognostic indicators for screen-detected and not screen-detected breast cancer (1999–2011)**

Prognostic indicators		Screen-detected	Not screen-detected
Grade of tumour	Well differentiated (low grade)	35%	21%
	Moderately differentiated (medium grade)	43%	37%
	Poorly differentiated (high grade)	18%	35%
Extent of disease	Localised	69%	50%
	Regional	25%	39%
	Distant	0.4%	1%
More than 1 tumour		1%	3%
Median maximum tumour size <sup>10</sup>		13 mm	20 mm

In women with screen-detected cancers:

- 69% had localised disease compared to 50% of women with non-screen-detected cancers
- the breast cancers were more likely to be moderately or well differentiated (78%), compared to non-screen-detected (58%)
- the average size was significantly smaller (13 mm v 20 mm).

Localised disease, lower grade and smaller breast cancers are all markers of more positive outcomes from breast cancer. It also means they are more likely to be able to be treated by breast conserving surgery and more limited axillary lymph node surgery. These women are also less likely to require chemotherapy.<sup>11</sup>

All of these markers in first screen or subsequently screened women were also significantly better compared to non-screen detected cancers in either group. Screen-detected cancers were well differentiated compared to non-screen detected cancers, were more localised, had a significantly lower risk of multiple tumours and average tumour size was significantly lower.

<sup>10</sup> Figures have been rounded for simplicity, more detailed and specific information can be found in the full report.

<sup>11</sup> BREASTSurgANZ audit, 2013.

## Prognostic indicators in grade 3 cancer

It is useful to examine the same indicators and therefore prognosis for women with grade 3 (the fastest growing) cancers, as outcomes would be less affected by length time bias<sup>12</sup> due to the aggressive nature of these cancers. If observed reductions in mortality from breast cancer from screening were substantially due to length time bias, then the mortality benefits should reduce and become non-significant when comparing ever- and never-screened women with grade 3 breast cancers (see Table 4).

Ever screened women:

- had significantly higher proportions of breast cancer localised to the breast (53% v 40%)
- were significantly less likely to have regional lymph nodes involved (41% v 50%)
- had an average breast cancer size that was significantly smaller at 20mm than the never screened women at 25 mm.

This confirms that in women diagnosed with aggressive breast cancers who had ever been screened in BSA, there are significant positive differences in these indicators of more favourable outcome compared to never-screened women.

**Table 4: Prognostic indicators in grade 3 cancer for ever and never screened women (2000–2011)**

Prognostic indicators		Ever screened	Never screened
Extent of disease	Localised	53%	40%
	Regional	41%	50%
	Distant	2%	4%
More than 1 tumour		1%	3%
Median maximum tumour size <sup>13</sup>		20 mm	25 mm

<sup>12</sup> Length time bias can occur because screen-detected cancers are slower-growing cancers than non-screen-detected and faster growing tumours. If slow growing tumours have better clinical outcomes than fast growing tumours in terms of recovery, people with screen-detected cancer will have better outcomes irrespective of the screening programme.

<sup>13</sup> Figures have been rounded for simplicity, more detailed and specific information can be found in the full report.

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# Conclusion

Findings from these studies suggest that the New Zealand BSA programme has been effective in reducing mortality from breast cancer, with this being demonstrated across priority ethnic groups and all New Zealand women. The reductions in rates of mortality from breast cancer seen in the programme are consistent with findings demonstrated in the randomised controlled trials (see the bibliography in the main report).

Increased coverage of screening results in better outcomes for all women screened. Achieving a breast screening coverage of 70% or more equates to a relative reduction in breast cancer mortality of 30% or more, compared to women who are not offered screened.

Improved outcomes are seen for New Zealand women if they regularly attend screening compared to those women who are irregular screeners or who do not participate in the screening programme. There is, therefore, greater benefit realised if New Zealand women are regular attenders to screening.

A dose-response effect was apparent with generally lower breast cancer mortality with more frequent, regular screening.

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

It is clear that Māori and Pacific women had low average participation in screening through the study time period. This has been significantly improved in recent years, and when calculations are performed using more recent coverage, clearly both groups would benefit from the same reductions in mortality from breast cancer as other New Zealand women, with similarly favourable prognostic indicators of lower breast cancer mortality being achieved.

Māori and Pacific women who are not being screened in BSA continue to present with larger breast cancers than other New Zealand women not screened, and have larger cancers than Māori and Pacific women screened in BSA.

For these reasons, it is a continued and major priority for BSA to achieve equity in access and treatment of breast cancer, as priority women, particularly Māori, have a higher incidence of breast cancer, and higher rates of mortality from breast cancer.

This report has shown that organised screening mammography in New Zealand has been associated with clear and significant reductions in mortality from breast cancer for all New Zealand women participating in BSA, particularly if they do so in a regular, ongoing way. These results are evidence that BSA is achieving predicted results in an established screening programme, outside of the very controlled settings of a randomised controlled trial. It also confirms that greater reductions in breast cancer mortality are possible if coverage targets are achieved.

The National Screening Unit encourages New Zealand women to continue screening, and acknowledges that easy access to clear concise information about the potential benefits and harms of enrolling in BSA must be available.