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Effect of Mammography Screening on Incidence and Mortality of Breast Cancer in Alberta

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Effect of Mammography Screening on Incidence and Mortality of Breast Cancer in Alberta

by

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Abstract

Background

Breast cancer is the second leading cause of cancer death among Canadian women, and to decrease this burden mammography screening is widespread. If effective, mammography screening should reduce the incidence of late stage cancer by early detection, allow time for prompt treatment and result in lower mortality.

Given Alberta's universal health system, with organised screening reaching around 63% of the target population annually, we set out to determine how much screening mammography has decreased presentation of late stage cancer, and potentially reduced mortality from breast cancer, among Alberta women.

Methods

We conducted a historical birth-cohort study and trend analysis using data from the Alberta Cancer registry from 1982 to 2017. We compared stage specific incidence and mortality over the years and by birth cohorts, taking into consideration the introduction and evolution of screening mammography to measure how much effect screening has on observed trends. We used Joinpoint regression analysis to test statistically significance of observed trends.

Results

From 2006 to 2017, incidence of early stage breast cancers among women aged 50 to 79 years increased by 33 per 100,000 women at an average rate of 1.2% annually ($p<0.001$), while incidence of late-stage cancer decreased by 3 per 100,000 women at a rate of 0.8 annually ($p=0.3$). From 2001 to 2018, deaths from breast cancer reduced by 29 per 100,000 women at 2.3% annually ($p<0.001$), while all-cause mortality reduced by 9 per 100,000 at 0.5% annually ($p=0.1$) in women previously diagnosed with breast cancer. Each subsequent recent birth

cohort had higher rates of early breast cancer at specific ages while the incidence of late stage cancers reduced with recent cohorts at specific ages.

Conclusion

There has been some reduction in the incidence of late stage breast cancer and breast cancer deaths between 2006 and 2018. This has been associated with an excess increase in early stage cancers, which may be explained by overdiagnosis. These may be related to changes in screening mammography in that period. Women need to be educated on the effectiveness of screening mammography in order to make informed decisions about their screening practices

Preface

This thesis is an original, unpublished, independent work by the author, Yvonne Efegoma. Ethical approval for this work was received from the Health Research Ethics Board of Alberta Cancer Committee (HREBA-CC). HREBA.CC-19-0239 on July 20, 2019.

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Dedication

To God Almighty who is my pillar, in Him I live and move and have my being. He made it possible for this work to be completed.

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List of Acronyms

AAPC	Average Annual Percent Change
ABCSP	The Alberta Breast Cancer Screening Program
ACR	Alberta Cancer Registry
AHS	Alberta Health Services
AJCC	American Joint Committee on Cancer
APC	Annual Percent Change
ASR	Alberta Society of Radiologists
CTFPHC	Canadian Task Force on Preventive Health Care
HRT	Hormone Replacement Therapy
RCT	Randomised controlled trial
SEER	Surveillance Epidemiology and End Results
TNM	Tumour-Node-Metastasis system
WHO	World Health Organization

Chapter One: Introduction

1.1 Background

Breast cancer is the second leading cause of cancer deaths among Canadian women.[1] In Alberta, under the existing screening circumstances approximately 1 in 8 women are predicted to be diagnosed with breast cancer in their lifetime and women have a 1 in 35 risk of dying from breast cancer.[2] Cancer Control Alberta, a part of Alberta Health Services (AHS), projected that there would be 3,011 new cases and 419 deaths from breast cancer in 2020.[2]

Mammography is the most widely used screening technique for breast cancer and has evolved over the years to include more sensitive techniques. Its aim is to decrease the burden of breast cancer by detecting early breast cancer in asymptomatic women, resulting in earlier stage at diagnosis and early treatment that should produce better outcomes. Earlier treatment should also confer some advantage over treatment provided at clinical presentation. An effective screening program should therefore decrease the incidence of late stage breast cancer, since cancers that are likely to progress to advanced disease should be detected earlier by screening.

However, mammography screening has led to an increase in the number of cancers being detected. One would assume that this would be advantageous, because these women should be diagnosed earlier, leading to better outcomes. Yet, some researchers assert that the incidence of late stage cancer has not decreased concomitantly, as screening does not tend to prevent such late stage cancers from occurring[3]. The excess incidence is attributed to women being diagnosed with tumours that would never be clinically relevant (overdiagnosis). It is thought that many of these small tumours detected during screening do not grow fast enough

to cause any problem in a woman's lifetime. [3] This overdiagnosis leads to overuse of the healthcare system and harms women, as it typically requires further testing and otherwise unnecessary procedures and treatments, for no benefit.

Mammography screening can also be associated with test errors, the common ones being a false positive error or a false negative error. [4] [5] A false positive error occurs when a woman without the disease is classified as having the disease. This misleading impression leads to a lot of anxiety and the woman usually undergoes further unnecessary testing and procedures. On the other hand, a false negative error occurs when screening fails to detect cancer in a woman who has the disease. This results in delayed diagnosis and treatment, leading to more adverse morbidity and mortality outcomes.

There could also be interval cancers, which are cancers that occur between scheduled screening and so were absent or initially too small to be detected by previous screening exercises.[6] The degree of breast density (which is the extent of radio-dense fibroglandular tissue in a woman's breast) can affect screening accuracy and may be the reason behind many interval cancers. All these errors can contribute to harms from screening and can reduce its effectiveness. [7] [8]

1.2 Rationale

Mammography may be effective in achieving some reduction in breast cancer mortality (ranging from 15% to 25%).[9] [10] [11] However, its overall effectiveness is questionable and a delicate balance exists between beneficial and harmful effects. Moreover, much of the improvement in breast cancer mortality in recent years may arise from more effective treatments for women. Screening proponents argue that incidence of late stage cancers has

reduced with screening mammography, but this issue is confounded by increases in apparent incidence that may be due to overdiagnosis.

Given this controversy, it is worthwhile measuring the effectiveness of the mammography program in Alberta to test if the breast cancer program has been effective in reducing the incidence of late stage cancers as well as mortality from breast cancer.

1.3 Study objectives

1. To describe changes in incidence and mortality from breast cancer in Alberta that could be related to screening mammography
2. To describe changes in stage at presentation of breast cancer, that could be associated with mammography screening
3. To compare incidence rates and mortality from breast cancer by age and stage at diagnosis among five-year birth cohorts in Alberta from 1982 to 2017
4. To explain the possible effect of mammography screening on the incidence and mortality trends among birth cohorts in Alberta from 1982 to 2017

1.4 Research questions

1. Has incidence risen and mortality reduced in Alberta, in the same way as in other settings?
2. Has presentation of late stage breast cancer reduced in association with increased mammography screening?
3. Is there a difference in the incidence of late stage breast cancer and mortality from breast cancer among five-year birth cohorts in Alberta women?
4. Can mammography screening explain any of the observed trends in the incidence and mortality from breast cancer among five-year birth cohorts in Alberta women?

Chapter Two: Literature Review

2.1 Breast cancer overview

Breast cancer is characterised by irregular growth and multiplication of cells arising in the breast tissue.[12] Increasing age has been identified as one of the risk factors for developing breast cancer. With increasing age comes the likelihood of exposure to carcinogens which can lead to a slow accumulation of DNA damage. There is also a gradual deterioration in host defence mechanisms as one gets older.[13] Other identified risk factors associated with breast cancer include positive family history (genetic factors), reproductive factors (early menarche, late menopause),estrogen factors (hormone replacement therapy, some contraceptives) and lifestyle factors (smoking, alcohol consumption and obesity).[14–16]

Breast cancer in younger women is known to be more aggressive, driven by genetic factors, diagnosed at an advanced stage and has worse prognosis relative to cancers that occur in older women.[17–20] On the other hand, breast cancer in elderly women (those 75 years and older) have been found to be underdiagnosed and undertreated. Elderly patients may not be offered aggressive treatments since they likely have other comorbidities which can influence the outcome of cancer treatments.[13,21] Consequently, these extreme age groups would not likely benefit from screening while women in the middle might be better positioned to have any benefits screening could provide and most screening programs recommend screening in these women.

2.2 Staging of breast cancer

The stage at which breast cancer is diagnosed is an important indicator for treatment options as well as determining the effectiveness of screening mammography. Breast cancer is usually staged using the Tumour-Node-Metastasis (TNM) system.[22] This system groups patients into four categories based on the tumor size (T), the status of the regional lymph nodes (N) and the presence of distant metastasis (M). In-situ cancers are present when the tumour is confined (usually to the milk duct) and has not invaded tissues. Ductal carcinoma in-situ is the commonest type of non-invasive cancers.

Table 2.1: TNM staging of breast cancer

Stage	Primary Tumour	Nodes	Metastasis
Stage 0	Tis	None	None
Stage IA	≤20 mm	None	None
Stage IB	≤20 mm	Nodal micrometastasis (>0.2mm <2.0mm)	None
Stage IIA	<20 mm	N1	None
	>20 mm ≤50mm	None	
Stage IIB	>20 mm≤50mm	N1	None
	>50mm	None	
Stage IIIA	≤50mm	N2	None
	>50mm	N1 or N2	
Stage IIIB	Extension to chest wall	N0 -N2	None
Stage IIIC	Any size	N3	None
Stage IV	Any size	Any involvement	Detectable

N0 = No regional lymph node metastasis
N1 = 1-3 axillary lymph nodes involved and/or internal mammary nodes in the absence of axillary nodal involvement
N2 = 4-9 axillary lymph nodes involved or clinically detected internal mammary nodes in the absence of axillary nodal involvement
N3 = ≤ 10 axillary lymph nodes involved or infraclavicular lymph nodes, or clinically detected internal mammary nodes with axillary involvement, or >3 axillary nodes with internal mammary nodes detected by biopsy, or in ipsilateral supraclavicular lymph nodes

**Source: American Joint Committee on Cancer 7th edition breast cancer staging*

Most cases of breast cancers in Canada are detected early. Part of the reason is women having mammograms, but also women are more aware of the disease, as breast cancer has received a lot of public attention in Canada from awareness creation campaigns carried out by advocacy groups.[23] Breast cancer incidence estimates between 2015 and 2016 in Alberta showed that 46% were diagnosed at stage I, 37% at stage II, 11% at stage III and 6 % at stage IV. Sceptics assert that most of the cancers detected by screening at stage I are overdiagnosed as screening is known to increase the incidence of early stage breast cancer.[24] Screening proponents, on the other hand, believe these cancers are important to identify.[25]

Screening also causes the time of cancer diagnosis to be advanced and can result in a 'stage shift' which is a situation where the stage at diagnosis is shifted to a lower stage, or diagnosis is made earlier in the same stage, than would have been found if there were no screening.[26] For screening to be effective, treatment at this earlier stage should prevent death or prolong true survival compared to a situation without screening.

2.3 Breast cancer incidence

Incidence of female breast cancer in Canada, as measured by the Canadian Cancer Registry rose by 2.1% per year between 1984 and 1991 and was on a decline (-0.2% per year) till 2015[1]The age standardized incidence of breast cancer in Alberta was 138.9 per 100,000 women in 1997 and increased to 140.2 per 100,000 women in 2016.[2]

Incidence of breast cancer increases with age. Data in Alberta between 2012 to 2016 (figure 2.1 below) shows that the age specific incidence of female breast cancer begins to rise at age 25 (52.7 per 100,000), reaches a peak at age 70 years (491.6 per 100,000) and then declines afterwards.[2]

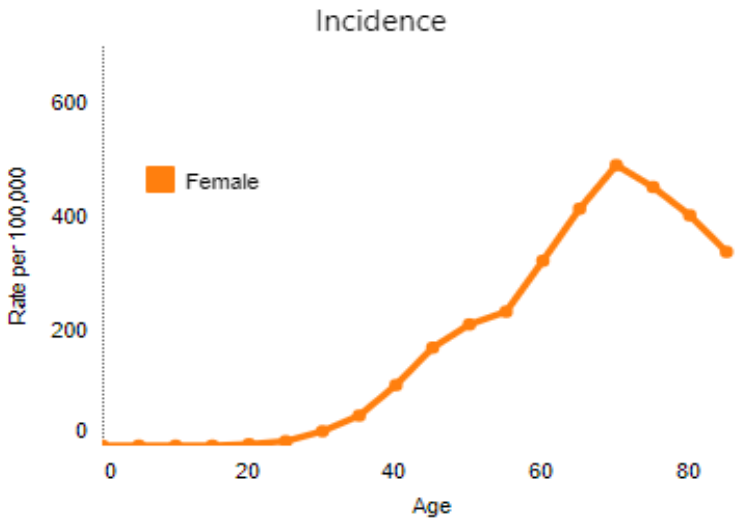


Figure 2.1: Age-specific incidence rate for breast cancer, Alberta. 2012 to 2016. Source: Surveillance & Reporting Cancer Research & Analytics Alberta Health Services.

Other factors may influence the incidence of breast cancer over time. Hormone Replacement Therapy (HRT) is a known risk factor for breast cancer and its use increased the incidence of breast cancer.[27,28] Bleyer et al [29] analysed data from the Surveillance, Epidemiology, and End Results (SEER) and defined 1990 to 2005 as the period of intense HRT usage. De and colleagues obtained data from different Canadian registries and demonstrated the end of the effect of hormone replacement therapy on breast cancer incidence at 2006 after the publication of the Women's Health Initiative trial in 2002.[30] They observed reduced prevalence in the use of HRT from 12.7% to 4.9% from 2002 to 2004 alongside a 9.6% reduction in the incidence of breast cancer from 296.3 per 100,000 women in 2002 to 273.5 per 100,000 women in 2004. They noted that mammography screening rates remained stable during this period in Canada.

Another factor which may have influenced the incidence of breast cancer over the years, is the advancement in breast cancer screening methods which are now more sensitive in detecting early disease. Film screen which was less sensitive has been replaced by two dimensional digital mammography which allows manipulation of the degree of contrast in the mammography image and is especially useful for women with dense breasts.[31] Breast tomosynthesis also became available and has been shown to have a higher sensitivity compared to digital mammography. It involves the use of computed tomography in creating three-dimensional images and avoids overlapping images of breast structures.[32] The practice of double reading where the interpretation of results is done by two readers has also been shown to increase detection of breast cancers.[33]

Increasing incidence of breast cancers can be an indicator of either effective screening or overdiagnosis, which is the detection of cancers that would never have become clinically relevant. It is a major concern with screening mammography and is difficult to assess, as it is impossible to tell which of the identified cancers will be harmful and which will be harmless.[3, 24, 34] In the absence of overdiagnosis, a decrease in the incidence of late cancers should follow the increased incidence of early stage cancers. Women who are overdiagnosed undergo subsequent testing and treatments that are probably unnecessary. Often, this causes harm from side effects of treatment and also from anxiety. The twenty-five year follow up of the Canadian National Breast Cancer Screening Study trial estimated that 22% (106/484) of invasive breast cancers detected by screening had been overdiagnosed, resulting in one over-diagnosed breast cancer for every 424 women screened with mammography.[35]

Here, they compared the excess incidence of breast cancer in women in the screening and non-screening arms. Revised estimates of overdiagnosis by age group were released for the

same trial in 2016, and when they included carcinoma in situ, they concluded overdiagnosis was responsible for 40% of invasive screen-detected tumors in women aged 40 to 49 and 30% in women aged 50-59 years [36]

2.4 Breast Cancer mortality

Death from breast cancer increases with age as shown in data from Alberta from 2012 to 2016. Mortality begins to rise at about age 45 (15.7 per 100,000 women) and continues rising, reaching 180.8 per 100,000 women at 85 years. (figure 2.2 below). Death rates from female breast cancer in Canada have decreased by about 48% since they peaked in 1986 and are projected to reduce further[1].

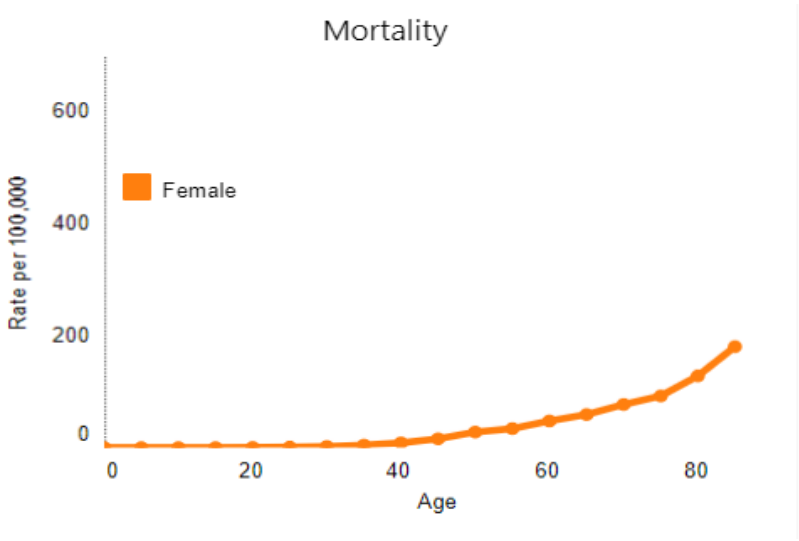


Figure 2.2: Age-specific mortality rate for breast cancer, Alberta. 2012 -2016. Source: Surveillance & Reporting Cancer Research & Analytics Alberta Health Services

Pham et al. assessed premature mortality from breast cancer among Canadian women over a 30-year period from 1980 to 2010 by analysing Canadian data from the World Health Organization (WHO) mortality database. Their findings showed a reduction in age standardized mortality from 23.2 to 14.2 per 100 000 women and the average years of life lost decreased from 20.8years to 18.3 years from 1980 to 2010 leading to a 4.1% prolongation in average life span of women diagnosed with breast cancer over the study period.[10] This could be an apparent increase in survival as a result of earlier diagnosis (lead time-bias). Similarly in Alberta, age standardized mortality from breast cancer has reduced from 36.5 per 100,000 women in 1997 to 21.6 per 100,000 women in 2016 and it is projected to reduce further to 19.1 per 100,000 women in 2021.[2]

Reduction in mortality has occurred despite increasing incidence and may be as a result of increased survival of women with breast cancer.[23] This was also postulated by Narod and colleagues after analysing data from the Surveillance Epidemiology and End Result (SEER) database. They concluded that the decline in breast cancer mortality is most likely as a result of a decline in case fatality as women diagnosed with breast cancer were surviving longer from better treatment options.[37] Breast cancer awareness has also increased, leading to earlier clinical presentation and subsequent treatment including surgery, chemotherapy and radiotherapy. In addition, hormonal therapy is currently being recommended for estrogen receptor positive disease.[38] All these options in addition to screening may have contributed to reducing mortality from breast cancer over the years.

2.5 Overview of mammography in Alberta

Mammography is the primary method for breast cancer screening and involves the use of x-rays to detect the presence of breast cancer before a lump becomes apparent. The screening program in Alberta has evolved over the years with advances in mammography techniques, from the use of plain films to digital films and more recently, the use of tomosynthesis.

Mammography began in Alberta in the 1980s, with community radiologists initially using non-dedicated machines, and then population-based breast cancer screening originated with Screen Test in 1990. They offered mammography services from two bases in Edmonton and Calgary, developed mobile services for rural women, and subsequently sent invitation letters to women across the province. The participation of women was already occurring in private practices before Screen Test but accelerated thereafter. The Alberta Breast Cancer Screening Program (ABCSP) was established in 2004 as a cooperation between Screen Test and the Alberta Society of Radiologists (ASR) to encourage and ensure quality in mammography. The ABCSP has a goal to ensure 70% of its target population get screened every 2 years and all abnormalities found during the screening program are assessed through follow up tests. The participation rate for the year 2017-2018 was 63.9% with over 350,000 women screened. As of 2018, there were 67 mammography clinics in Alberta.[39, 40]

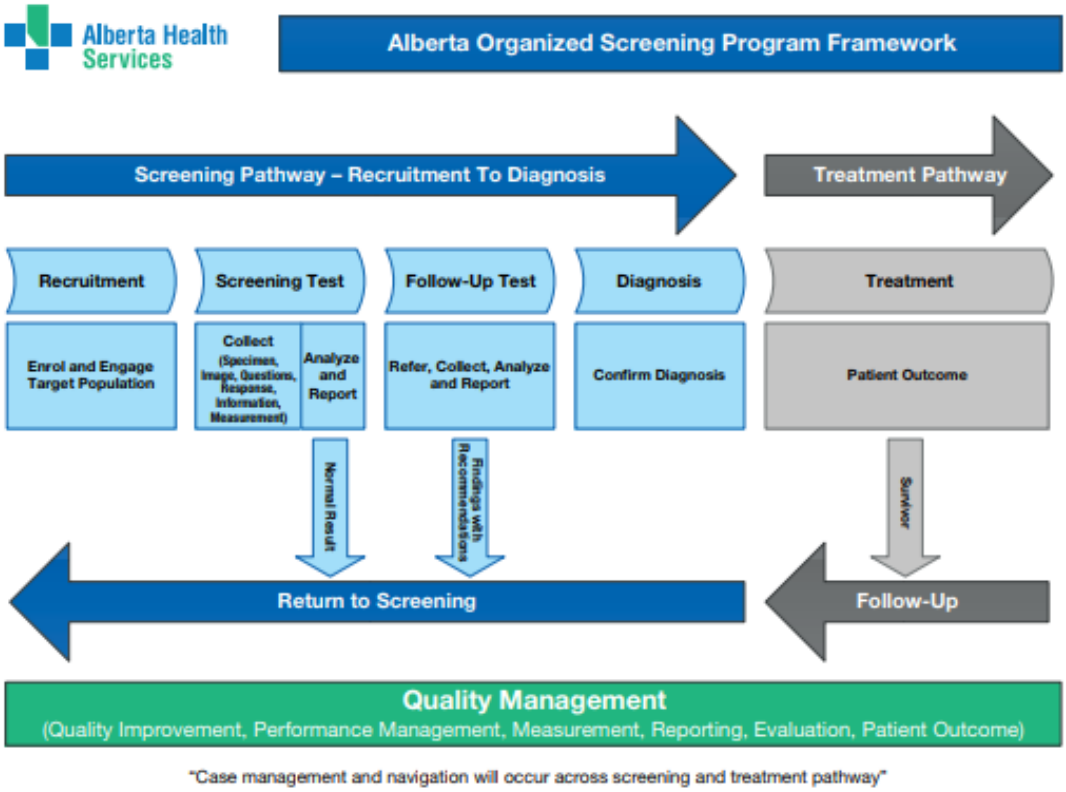


Figure 2.3: Framework for organized screening programs in Alberta. Source: Alberta Health Services. Organized Cancer Screening in Alberta 2015.

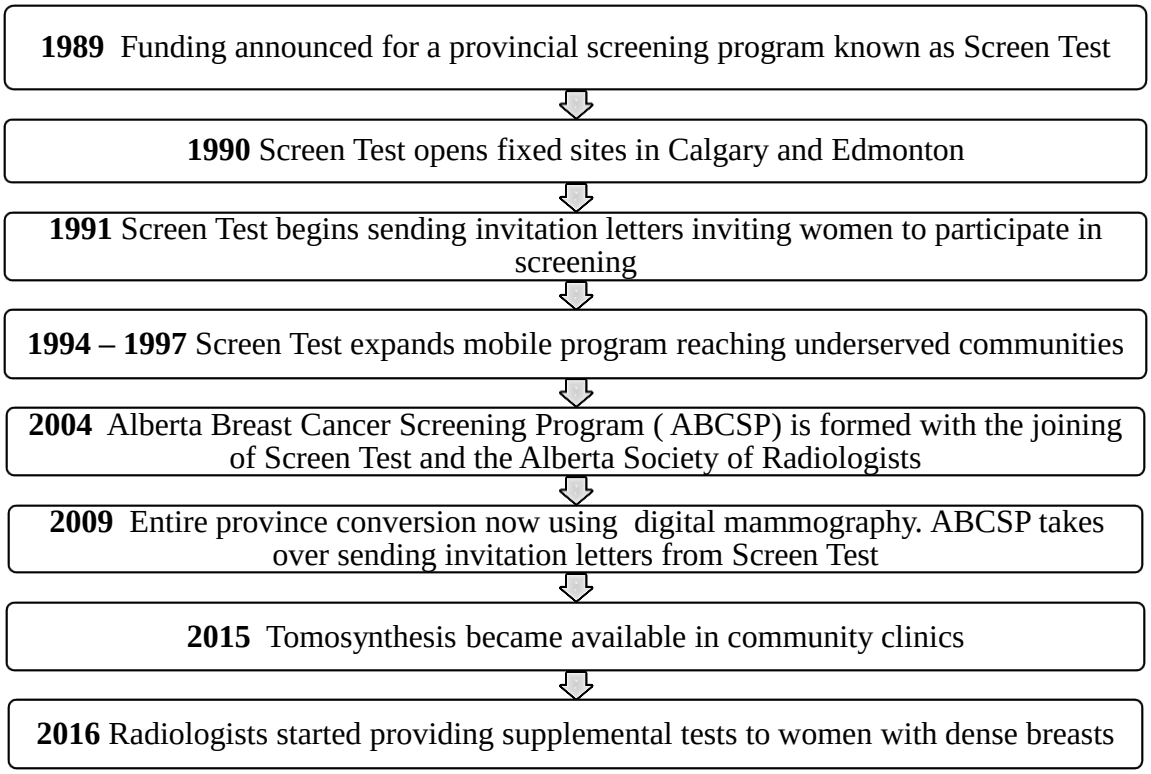


Figure 2.4: Evolution of breast cancer screening program in Alberta. Source: Alberta Health Services. Organized Cancer Screening in Alberta 2015.

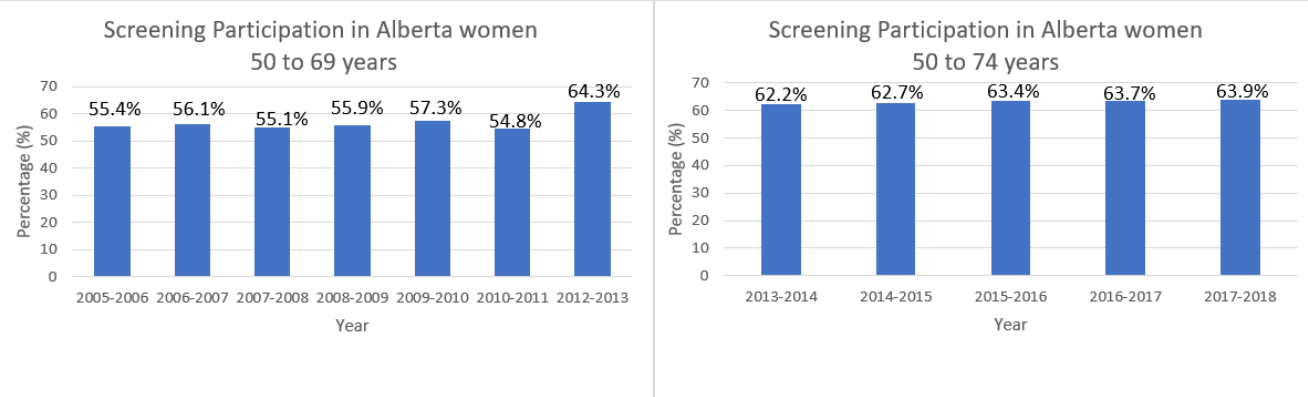


Figure 2.5: Screening Mammography Participation Rates in Alberta. Source: Alberta Breast Cancer Screening Program (ABCSP)

Data from the ABCSP shows that participation rates for screening mammography have ranged from about 55% to 64% between 2005 and 2013. Screening rates from 2013 onward included women aged 70 to 74 years, after they were included in the screening eligible age. Since then there has been no change to 2018. Participation rates prior to 2005 only included

clients utilizing Screen Test, as the community radiologist data was not available and would be considered opportunistic screening.

2.6 Breast cancer screening recommendations in Canada

The optimal screening recommendation for breast cancer has remained a controversial topic.[41] in 2018 The Canadian Task Force on Preventive Health Care (CTFPHC) released an updated guideline on screening for breast cancer in women aged 40 to 74 years who are not at increased risk for breast cancer.[42] They recommend that women aged 40 to 49 years should not be screened for breast cancer with mammography while women aged 50 to 74 years may choose to screen every 2 to 3 years with mammography.[42] They graded these recommendations as made with low or very low certainty evidence and conditional on the relative value the woman places on the risk and benefits of screening. For women to make informed decisions about mammography screening that are consistent with their values and preferences, balanced information on the benefits and harms of screening need to be provided. In a study published in 2019 exploring informed decision-making by the general population about mammography screening in Canada, the educational materials provided by organized screening programs in eight provinces in Canada, including Alberta, were considered insufficient to support informed decision-making.[43]

The recommendations produced by the task force were based on a review that used three systematic reviews (after considering eighteen systematic reviews) and three new primary studies.[11] The systematic reviews selected were done by the U.S. Preventive Services Task Force (USPSTF 2016), American Cancer Society (ACS 2014) and the Canadian Task Force on Preventive Health Care (CTFPHC 2011). The three primary studies reported updated randomised controlled trial (RCT) data. The quality of the evidence from this review was

rated as low due to inconsistencies across studies and incomplete reporting. The reviewers found no difference in all-cause mortality between women who had screening. mammography and those who had usual care (relative risk of 0.99 {95% CI :0.98 to 1.00}) after a median follow-up of 16 years. [11] They assessed that mammography reduced mortality from breast cancer by 15% (RR 0.85, 95% CI: 0.78-0.93) during the study's screening period and by 18% (RR 0.82, 95% CI: 0.71-0.94) after adding all cases identified during the follow up period, compared with usual treatment.

Radiologists in Canada raised objections to these recommendations and say the task force ignored evidence from newer observational studies which used more modern mammography techniques in favour of old randomized trials from the 1960s to 1990s.[44] In an online survey among Canadian radiologists published in 2017 with a response rate of seventeen per cent, 98% of those responding recommended that screening should be done every 1 to 2 years beginning at age 40 years.[45]

2.7 Effectiveness of screening mammography

The effectiveness of screening mammography has remained a subject of debate for some time with varying estimates of the benefits and harms. Effective mammography screening should detect early stage cancer, prevent the occurrence of late stage disease and ultimately lead to a reduction in mortality from breast cancer. Systematic reviews have estimated a 15 to 20% reduction in mortality from breast cancer in women aged 40 to 74 years with follow up periods greater than 10 years. However, all-cause mortality does not seem to have reduced.[42],[46] After searching the literature for systematic reviews and studies which used registry data, we found that some studies asserted that mammography screening is effective

in reducing the incidence of advanced cancers and mortality from breast cancer while others conclude that it may not be effective.

The Swedish two-county trial[47] published in 1985, was a momentous trial that sparked the introduction of mass screening in many countries around the world in the early 1990s. It was a randomised control trial which started in 1977. They randomised women in two Swedish counties into active screening population (ASP) and passive screening population (PSP). Women aged 40 to 49 years and 50 to 59 years in the ASP were invited to screen every 24 months and 33 months respectively while women in the PSP received usual care. After 7 years of follow up, they found a significant reduction (25%, $p<0.001$) in the incidence of stage II or more advanced cancer. The authors went on to say that this reduction far outweighed any excesses of stage I or in-situ cancers observed in the study arm. They also found that mammography reduced breast cancer-specific mortality by 31% compared to usual care.[9] (the absolute rates were not reported). This study however used a cluster randomization technique rather than individual randomization that may have given rise to some bias. There was also a lack of baseline characteristics of women other than age, so it was difficult to say whether the groups were comparable.

The Swedish two county trial was followed by some trials which estimated the effectiveness of screening mammography. These included trials in the United States of America,[48] United Kingdom,[49] Canada,[50] as well as a meta analysis of four Swedish trials,[51] and screening was generally considered beneficial. However, the result of a metanalysis[52] published in the year 2000 raised concerns that screening may not be as effective as previously thought. The authors identified eight trials after searching the Cochrane library for trials assessing effectiveness of mammography screening. Six of the eight trials were assessed to be biased

with imbalances observed at baseline as well as inconsistent randomization in four of them. Screening did not impact mortality from breast cancer (pooled relative risk 1·04 [95% CI 0·84–1·27]) or total mortality (0·99 [0·94–1·05]) in the remaining two trials with adequate randomisation. This publication raised a huge storm and led to huge debates with several studies published afterwards attempting to quantify the benefits and harms of screening mammography.

An update to the Swedish two county trial was published in 2011 where Tabar and colleagues estimated the 29-year effect of screening on breast cancer mortality. The screening stage of the trial lasted seven years and 351 of the 77080 women in the ASP and 367 of 55985 women in the PSP were diagnosed with breast cancer. The study found a reduction in breast cancer mortality in the population invited to screen RR =0.69 (95%CI-0.56 – 0.84).[9] This study's analysis was done by invitation to screen, and populations, rather than individual women, were randomised, which could have biased their estimates, as the populations may not be comparable.

A review evaluating the effects of mammography screening on mortality and morbidity of breast cancer was published by Goetche and colleague in the Cochrane database of systematic reviews in 2013. Seven eligible trials involving 600,000 women, aged 39 to 74 years were analysed. Four trials with suboptimal randomization showed that mammography was effective in reducing breast cancer mortality (RR: 0.75 (95% CI: 0.67 to 0.83) while the other three trials with optimal randomization did not show a statistically significant reduction in breast cancer mortality at 13 years (RR: 0.90 95% CI: 0.79 to 1.02). The RR was 0.81 (95% CI 0.74 to 0.87) for all seven trials combined. The trials with adequate

randomization found no reduction in all- cause mortality over 13 years (RR 0.99, 95% CI 0.95 to 1.03).[46]

In 2016, Nelson and colleagues published a systematic review/meta-analysis to update the 2009 U.S. Preventive Services Task Force Recommendation on breast cancer screening. The review included randomised controlled trials and observational studies up till June 2015. They concluded that screening reduced the risk of advanced breast cancer in women who were 50 years and above (RR, 0.62, CI: 0.46 to 0.83). This reduction was not seen in women 39 to 49 years who had a RR of 0.98 (CI: 0.74 to 1.37). They also found that screening prevented 8 deaths per 10,000 women and 21 deaths per 10,000 women over 10 years for women aged 50 to 59 years and 60 to 69 years respectively. The reduction in deaths observed was not statistically significant for younger women (39 to 49 years) and older women (70 to 74 years)[53] This study did not assess the quality of randomization of the included trials and so the estimated results may be biased by trials with suboptimal randomization.

A twenty-five year follow up was also published in 2014 for the Canadian National Breast Screening Study, a randomized control trial which began in 1980 and had a five-year screening period with 89,835 women randomised into mammography and no mammography arms. The screening arm had five annual mammography screens while the control arm had usual care in the community. During the five-year screening period 1.48% of women in the screening arm (n= 44925) and 1.17% of women in the control arm (n= 44 910) were diagnosed with invasive breast cancers. When comparisons were made between the two groups after 25 years, the hazard ratio for breast cancer deaths was 1.05 (95% CI: 0.85 to 1.30). The cumulative mortality rate for breast cancer was similar in both study arms. (hazard ratio 0.99, 95% CI: 0.88 to 1.12). The authors concluded that in a setting where

treatment was available mammography did not reduce mortality from breast cancer compared to usual care.[35]

An ecological study was conducted in the United States of America of 16 million women aged 40 years or older residing in 547 counties using data reported to the Surveillance, Epidemiology, and End Result (SEER) cancer registries data. During the year 2000, 53,207 women who were diagnosed with breast cancer were followed up for 10 years. Their exposure was the proportion of women who had a mammogram in the past two years in each county. They then made comparisons based on extent of exposure, between mortality outcome and tumour size at diagnosis. The researchers found that the extent of screening mammography was correlated with an increase in the incidence of small cancers (≤ 2cm) but no corresponding decrease in the incidence of larger cancers or mortality. In this study, a 10% increase in screening (e.g. from 60% -70%) was accompanied by 16% more breast cancer diagnosis but no significant reduction in breast cancer mortality (RR, 1.01; 95% CI, 0.96-1.06).[54]

This finding was similar to that found by a population-based, open cohort study[55] carried out in Norway involving 56,277 women, aged 20 years or older diagnosed with a first- time, invasive breast cancer from 1987 to 2010. Women 50 to 69 years were regarded as exposed to screening while those 20 to 49 years served as controls. Results showed that the introduction of the screening program more than doubled the incidence of localized stage cancers (from 63.9 to 141.2 per 100,000), while the incidence of more advanced stages did not change significantly among women aged 50–69 years, when compared to a younger control group ineligible for screening with a ratio of 1.02 (0.95-1.11).

Furthermore, other studies in the US [29], Australia [34] and Denmark [24], which used registry data to assess trends in the incidence of advanced breast cancers for over 20 year have shown that screening mammography only marginally reduced the rate at which women present with advanced cancer. The US study examined trends in the incidence of breast cancer from 1976 to 2008 in women ≥ 40 years using the Surveillance, Epidemiology, and End Results data. They found the rate of women presenting with late stage cancer had reduced by 8%. The Australian study observed trends from 1972 to 2012 as captured by the New South Wales Cancer registry and found that incidence of all stages of breast cancer was higher than pre-screening levels. They concluded that after 25 years of screening, detection of early stage breast cancer had not reduced incidence of late stage cancer. Results from the Denmark study which analysed data from the Danish Breast Cancer Group (DBCG) and the Danish Cancer Registry from 1980 to 2010 showed that screening reduced incidence of advanced cancer by 4% in women 50 to 69 years from 117 to 112.2 per 100,000 person years with an incidence rate ratio of 0 .96 (0.90 to 1.02).

2.8 Study justification

Evidence from the above studies shows varying estimates of the effectiveness of screening mammography with reductions in breast cancer mortality ranging from 15% to 25%. Consequently, this study examined trends in breast cancer incidence and mortality over the years and by birth cohorts, comparing incidence and mortality rates of female breast cancer by age and stage in Alberta. We considered the evolution of screening mammography over the years to see how it affected the observed trends.

Given a participation rate for mammography screening in Alberta of about 60%, if mammography reduces incidence of late stage cancer by 20%, this study should find a reduction of 12% with screening.

We set out to test our hypothesis using Alberta women and the Alberta breast cancer screening program.

Chapter Three: Methods

3.1 Study design

This study used secondary data analysis of Alberta Cancer Registry data to answer the research questions. We initially utilized trend analysis to determine the trends in incidence and mortality of breast cancer from 1982 to 2017 and then used a historical birth-cohort study design to compare incidence among five-year birth cohorts.

3.2 Exposure/outcome

The exposure of interest was screening mammography. Since information on individual exposure to screening was not available to the researcher, we used age group and time period as proxies for probability of exposure.

The main outcomes of interest were incidence of late stage breast cancer and mortality from breast cancer.

3.3 Study population

The study population comprised all women diagnosed with breast cancer as captured in the Alberta Cancer Registry from 1982 to 2017. This was the most recent available and complete data, since it takes about 2 years for data to be completely verified. Women were grouped into five-year birth cohorts. The target age was screen eligible women (50 to 74years)

3.4 Data source

Data for all cases of female breast cancer was obtained from the Alberta Cancer Registry (ACR). The ACR has been in existence since 1942, however only data from 1982 is considered to be complete and reliable. The registry has the mandate to collect data on diagnosis, initial treatment and mortality for patients with breast cancer in Alberta. Information is obtained from pathology reports, laboratories, physician reporting,

administrative booking systems, patients charts and vital statistics. Collaborative stage information for breast cancer is available from 2004. The registry also considers death from complications of cancer as a cancer death.

Breast cancer is coded in the Alberta cancer registry as C50 using the International Classification of Diseases (ICD-10) code. Over the years the ACR has achieved a completeness of over 95%[56]. This refers to the extent to which all new cases of cancer are captured in the Registries data bases. Cancer-related deaths are validated by the Registry. The Regional Health Authorities Act, Alberta Health Services policies and the Health Information Act ensure confidentiality and security of personal information within the Registry by making sure that those accessing information from the Registry follow rigorous confidentiality and security practices.

Population data was obtained from statistics Canada website. Table: 17-10-0005-01 (formerly CANSIM 051-0001).[57] Population of women in Alberta as at July 01 was extracted from 1971 to 2019. The data was already grouped into five-year age groups

Statistics Canada provides yearly sex and age specific population estimates for Canada. Data are revised yearly and after each census. The Census is conducted every five years using a modified de-jure method where counts are made of all Canadians present on the day of the census as well as those who are temporarily away. Postcensal estimates are calculated using data from the most recent census. Estimates are revised using birth, death and migration statistics as they become available. Statistics Canada follows scientific principles and professional ethics in all procedures used in collecting and presenting data.[57]

3.5 Data analysis

Total sampling of incident breast cancer cases from 1982 to 2017 was done. The year of birth was extracted for each woman and used in classifying women into five-year birth cohort groups. We then calculated the incidence and mortality from breast cancer across the years by age, stage of cancer and birth cohort. The introduction and evolution of mass screening mammography was taken into consideration while observing trends in incidence and mortality.

3.5.1 Incidence of breast cancer

Incident cases represent new cases of cancer in Albertan residents, thus, to be included as an incident case the woman was required to be resident in Alberta when the diagnosis was made. We included incident cases from 1988 to 2017 as data before 1988 was incomplete

Age specific incidence rate

The age specific incidence rate of breast cancer was calculated per 100 000 women by dividing the average number of new cases within each age group over the study period by the average number of women in Alberta in the corresponding age group during the same period

$$\frac{Average\ number\ of\ new\ cases\ of\ breast\ cancer\ in\ each\ age\ group}{Average\ population\ of\ Alberta\ woman\ in\ \ corresponding\ age\ group} X 100{,}000$$

Incidence rate

Incidence rates for breast cancer were calculated per 100,000 women by dividing the incidence counts by the population of women at risk of breast cancer in each index year and multiplying by 100,000. To obtain the population at risk, the number of women with breast cancer prior to the index year was subtracted from the population of women for that year.

$$\frac{Number\ of\ new\ cases\ of\ breast\ cancer\ in\ each\ age\ calendar\ year}{Population\ of\ Alberta\ woman\ at\ risk\ of\ breast\ cancer\ in\ each\ calendar\ year} X100{,}000$$

Age-standardized rates were then calculated by the direct standardization method. We used estimates of the 2011 July 1st Canadian population as the standard population. Age standardized rates were estimated as a weighted average of five-year age specific rates. The weights used were the calculated proportions of women in the corresponding age group of the standard population.

3.5.2 Incidence of breast cancer by stage

The ACR staged cancer using the AJCC 6th edition and women were classified as Stage 0, I, II, III or IV. Staging data was available from 2004 onwards. For this study, stage 0, I and II were regarded as early stage cancer while stage III and IV were regarded as late stage cancer. Breast cancer incidence by stage was calculated as:

$$\frac{Number\ of\ new\ cases\ of\ \ early\ or\ late\ or\ unstaged\ \ breast\ cancers\ \ per\ year}{Population\ of\ Alberta\ woman\ \ at\ risk\ of\ breast\ cancer\ in\ corresponding\ year} X100{,}000$$

Standardized rates were weighted averages of five-year age specific rates. The weights used were the calculated proportions of women in the corresponding age group of the standard population. (2011 Canadian population). We then compared incidence of early and late stage cancers among age groups.

Standardized rates were compared between time periods by estimating the standardized rate ratio (SRR) which estimates the relative risk of cancer at time A compared to time B to see whether the observed ratio is different from one[58]

3.5.3 Mortality from breast cancer

Mortality in the ACR included deaths from breast cancer in an Albertan woman regardless of where the woman died. We grouped deaths into breast cancer deaths and non-breast cancer deaths. Non breast cancer deaths included deaths from any cause other than breast cancer as well as deaths from other cancers. We included mortality data from 1993 to 2018 as data before 1993 was incomplete.

Age specific mortality rate

The age-specific mortality rates of breast cancer were calculated per 100 000 women by dividing the average number of deaths within each age group over the study period by the average number of women in Alberta in the corresponding age group during the same period

$$\frac{Average\ number\ of\ deaths\ from\ breast\ cancer\ in\ each\ age\ group}{Average\ population\ of\ Alberta\ woman\ in\ \ corresponding\ age\ group} X100{,}000$$

Cause specific mortality rate from breast cancer

The cause-specific mortality rates for breast cancer were calculated per 100,000 women by dividing the number of deaths from breast cancers by the population of women at risk of dying from breast cancer in each index year. To obtain the population at risk, the number of women who had died from any cause was subtracted from the denominator since they are no longer at risk of dying

$$\frac{Number\ of\ Alberta\ women\ who\ died\ from\ breast\ cancer\ in\ each\ calendar\ year}{Number\ of\ Alberta\ women\ at\ risk\ of\ dying\ from\ breast\ cancer\ in\ that\ year}\ X100\ 000$$

Age-standardized mortality rate for breast cancer was calculated using the direct standardization approach. We used estimates of the July 1st Canadian population as the standard population. Age standardized rates were estimated as a weighted average of five-

year age specific mortality rates from breast cancer. The weights used were the estimated proportions of women in the same age group of the standard population. We also compared cause specific mortality by age group.

All-cause mortality rate

The all-cause mortality rates for breast cancer were calculated by dividing the number of total deaths by the population of women alive in each index year and multiplying by 100,000. To obtain the population at risk, the number of women who had died from any cause was subtracted from the denominator since they are no longer at risk of dying.

$$\frac{Number\ of\ Alberta\ women\ who\ died\ in\ each\ calendar\ year}{Number\ of\ Alberta\ women\ at\ risk\ of\ dying\ from\ breast\ cancer\ in\ that\ year}\ X100\ 000$$

The standardized rates were estimated using the same standardization approach as described previously and comparisons were made among age groups.

3.5.4 Birth cohort analysis

Age-specific incidence rates for birth cohorts

Age-specific incidence of breast cancer per 100,000 women was calculated by dividing the average incidence counts in each five-year age group for each birth cohort by the population at risk of breast cancer in each age group for each cohort.

$$\frac{Average\ number\ of\ new\ cases\ of\ breast\ cancer\ in\ each\ age\ group\ for\ each\ birth\ cohort}{Population\ of\ Alberta\ woman\ at\ risk\ of\ breast\ cancer\ in\ each\ age\ group\ for\ each\ cohort}\ X100{,}000$$

For example, what was the incidence of breast cancer per 100,000 women born between 1945 to 1949 when they were aged 50 to 54 years?

In this example, women in birth cohort (1945 to 1949) were aged 50 to 54 years from calendar year 1995 to 2003.

The total number of new cases of breast cancer diagnosed in this birth cohort when they were aged 50 to 54 years was 1135 over the span of 9 years. The numerator here was 1135 divided by 9, which was the average number of new cases of breast cancer diagnosed in this birth cohort when they were aged 50 to 54 years.

The denominator was 81,883 which was the population of women at risk of breast cancer in this birth cohort when they were aged 50 to 54 years. The population at risk was derived by subtracting the cumulative cases already diagnosed with breast cancer for each year.

Table 3.1: Population of women in Alberta aged 50-54 years from 1995 to 2003

Calendar year	Population of Alberta woman*	Population at risk **
1995	64,921	64040
1996	68,137	67094
1997	74,090	72868
1998	79,546	78110
1999	84,298	82654
2000	89,450	87578
2001	94,065	91959
2002	96,988	94667
2003	100,586	97973

*the population of Albertan women aged 50 to 54 years from 1995 to 2003 as captured by statistics Canada

**The population at risk: after subtracting those diagnosed with breast cancer in previous years

The average population at risk for all nine years from 1995 to 2003 (81882.56) was used as the denominator for this birth cohort. This was repeated for all birth cohorts.

*All calculations for women at risk utilized this same approach.

Exposure to mammography among birth cohorts

For better understanding of the incidence trends among birth cohorts, we categorised birth cohorts based on their screening experiences using timelines from the Alberta breast cancer screening program (ABCSP) we used the period between 1990 and 2017 as a period of possible exposure when women were between 50 to 74 years old.

Table 3.2 Estimated exposure to mammography among birth cohorts

	Mammography screening exposure	Older birth cohort	Younger birth cohort
1	No screening (NS)	<1900	1915-1919
2	Partial screening (PS)* starting from oldest ages.	1920-1924	1945 -1949
3	Full screening (FS)	1950-1954	1960-1964
4	Not yet screen eligible (NE)	1965-1969	1990-1994

*****Birth cohorts with partial screening would have been exposed to screening at older ages

Incidence of early and late stage cancers

We calculated the incidence of early stage cancers among birth cohorts per 100,000 by dividing the average number of early stage cancers diagnosed within each age group for each birth cohort by the population of women at risk for the same age group.

$$\frac{Average\ number\ of incident\ early\ or\ late\ \ cancer\ in\ each\ age\ group\ for\ each\ birth\ cohort}{Population\ of\ Alberta\ woman\ at\ risk\ of\ breast\ cancer\ in\ each\ age\ group\ for\ each\ cohort}\ X100{,}000$$

Proportion of early/late/unknown cancers

We calculated the proportion of women presenting with early or late or unknown stages of breast cancer across birth cohorts. This was done by computing the proportion of incident early/late/unknown stage breast cancer in each birth cohort as follows:

$$\frac{Number\ of\ early/late/unknown\ stage\ breast\ cancer\ in\ \ each\ birth\ cohort}{Total\ number\ of\ breast\ cancer\ cases\ in\ each\ birth\ cohort}\ X100$$

We compared these proportions across birth cohorts.

Proportion of deaths caused by breast cancer that might be helped by mammography

We compared the proportion of deaths from breast cancer across birth cohorts

$$\frac{Number\ of\ deaths\ from\ breast\ cancer\ in\ each\ cohort}{Number\ of\ women\ diagnosed\ with\ breast\ cancer\ in\ that\ cohort}\ X100$$

Here we excluded deaths before age 50 and after 80 years as it is unlikely these would be helped by screening mammography.

3.5.5 Joinpoint regression

Statistical significance of trends was assessed using Joinpoint regression analysis (Joinpoint regression program, version 4.7.0.0.) which is a Windows based statistical software package that can be used to assess changes in observed trends and determine their statistical significance. The test of significance uses a Monte Carlo Permutation method (i.e., it finds the line of best fit for each segment.).[59]

We set the minimum number of joinpoints at zero and the maximum number at five.

We identified the time point in which the trend changed significantly and also determined if the annual percent change (APC) was significantly different from zero (trend in cancer rate was neither increasing nor decreasing) at an alpha level set at 0.05.

3.6 Power calculation

We determined whether our study had the statistical power to detect a difference between two proportions. Women in both groups (screened and unscreened) were assumed to be same and that nothing else differed except their participation in screening

Given that the proportion of late stage cancer in the unscreened group was 0.2 and the proportion in the screened group approximately 0.15, we determined that our study had sufficient power to detect a difference of 0.05 (an absolute decrease of 25%) with a sample size of 1000 if the true late stage without screening was 0.2 and the proportion of late stage with screening was 0.15.

Calculations were made using the Power Analysis and Sample Size Software (P.A.S.S 2019) and the two-proportions tests which assumes that the difference between two proportions is zero or their ratio is one under the null hypothesis[60–65]

3.7 Ethical considerations

Ethical approval was received from the Health Research Ethics Board of the Alberta Cancer Committee (HREBA-CC), HREBA.CC-19-0239. Encrypted data was received from the Alberta Cancer Registry and was assessible only to the researchers. All study subjects had a unique identifiable number and no personal identifiable information was received from the registry. De-identified data elements received were

- Date of birth
- Age at diagnosis
- Stage at diagnosis
- Date of diagnosis
- Date of death
- Cancer topography
- Cancer morphology
- Cancer site or tumour group
- Behaviour of cancer
- Regional node status

Security of this data was assured by ensuring that the computer containing the data set was always kept safe and password protected. We used a section of the “Hydrogen drive” which is a secure drive at the University of Calgary that can be used to store restricted and confidential data.

Chapter Four: Results

There was a total of 61,872 cases of female breast cancer reported to the Alberta cancer registry over the study period (1982 to 2017), of which 56,972 (92.1%) were incident cases. The mean age at diagnosis was 60.3 (SD:14.1) years with majority (82.3%) diagnosed at early stage. Over twenty-one thousand (37.2%) had died, of which 46.5 % died from breast cancer. The mean age at death was 74.5 years.

Table 4.1: Sample characteristics

Summary data		
Total number of cases reported to the ACR from 1982 to 2017	61,872	
Number of incident cases	56972 (92.1%)	
Mean age at first diagnosis	60.3 (SD-14.1) Years	
	N	**%**
Stage at first diagnosis (from 2004)		
Insitu (0)	3917	12.0
Early (I, II)	22956	70.3
Late (III, IV)	5,052	15.5
Unknown	727	2.2
Vital statistic (as at 2018)		
Alive	35,756	62.8
Dead	21,216	37.2
Cause of death		
Breast cancer	9,866	46.5
Non breast cancer	11,350	53.5
Mean age at death	74.5 (SD-15.4) years	

4.1 Overall incidence of breast cancer

Table 4.2: Age distribution of incident cases of breast cancer reported to the Alberta Cancer Registry from 1982 to 2017

Age group (years)	Frequency	Percent
≤24	51	0.1
25-29	279	0.5
30-34	942	1.7
35-39	2,113	3.7
40-44	4,350	7.6
45-49	6,431	11.3
50-54	7,144	12.5
55-59	6,767	11.9
60-64	6,743	11.8
65-69	6,471	11.4
70-74	5,637	9.9
75-79	4,418	7.8
80-84	3,028	5.3
85-89	1,715	3.0
90-94	690	1.2
95-99	165	0.3
100+	28	0.1
Total	56,972	100

The highest number of women 7144 (12.5%) were diagnosed with breast cancer when they were aged 50 to 54 years. Those 100 years and above had the lowest number of incident cases 28 (0.1%).

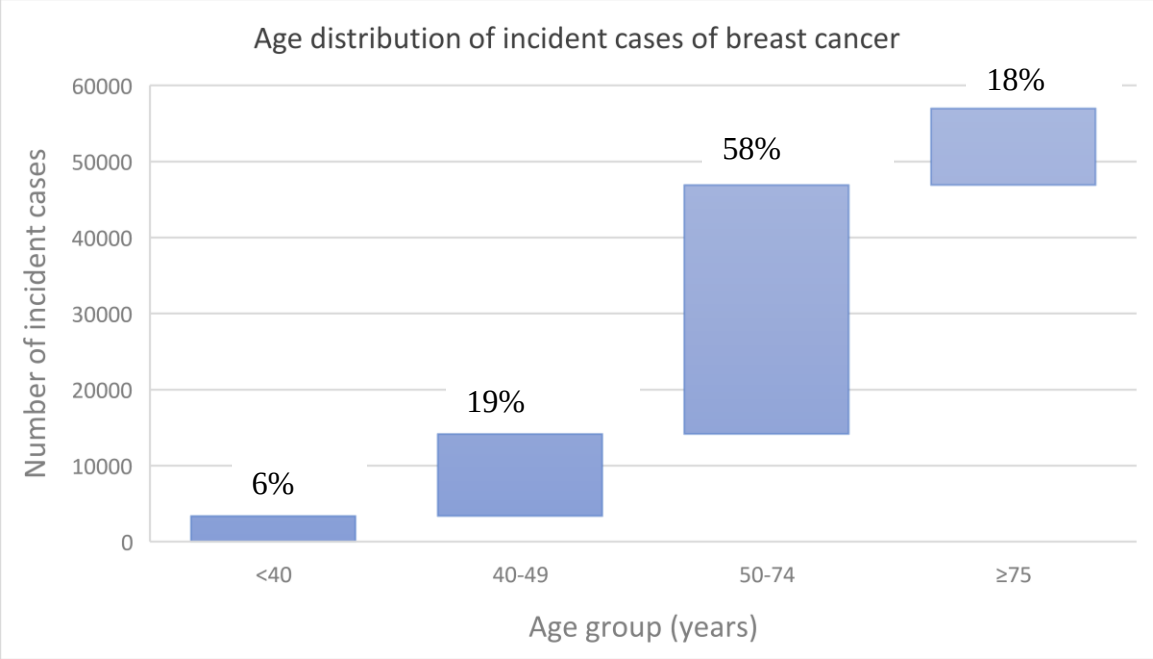


Figure 4.1: Age distribution of incident cases of breast cancer

Majority (58%) of the incident cases of breast cancer reporting to the ACR from 1982 to 2017 were in screen eligible women (50 -74 years) while 6% of incident cases were in women less than 40 years. Those between 40 and 49 years accounted for 19% while elderly >75 years accounted for 18% of the incident cases.

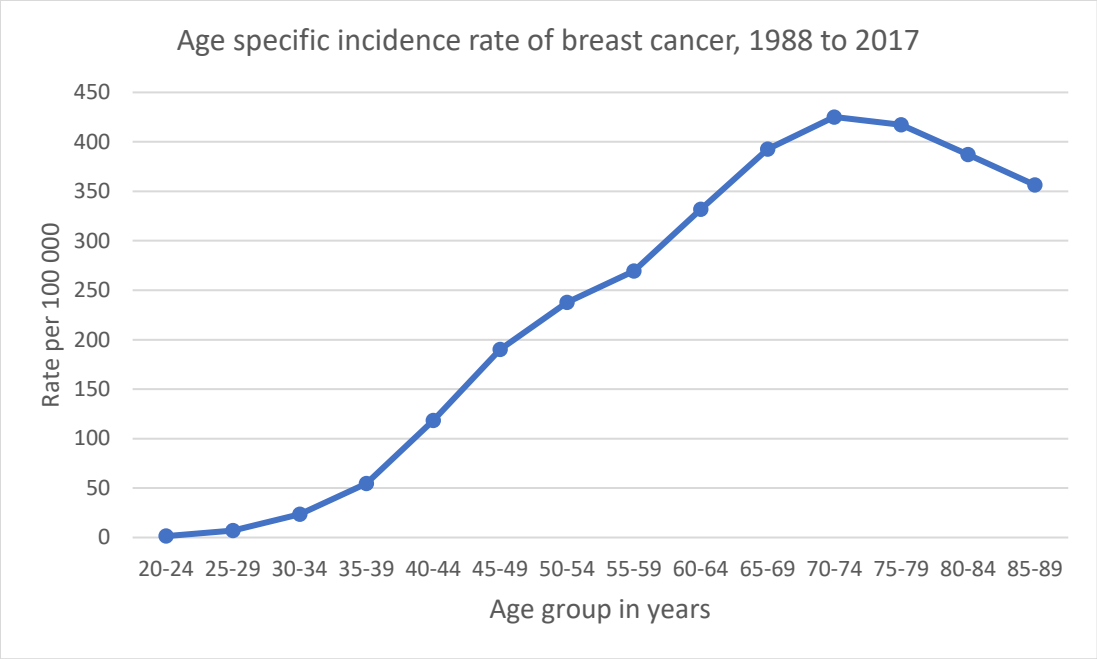


Figure 4.2: Age specific incidence of breast cancer from 1988 to 2017

Incidence of breast cancer increases with age. It begins to rise between 25 to 29 years (7 per 100 000), reaches a peak at 70 to 74 years (425 per 100,000) and declines afterwards

This was calculated using the formula:

$$\frac{Average\ number\ of\ new\ cases\ of\ breast\ cancer\ in\ each\ age\ group}{Average\ population\ of\ Alberta\ woman\ at\ risk\ of\ breast\ cancer\ in\ corresponding\ age\ group} X100{,}000$$

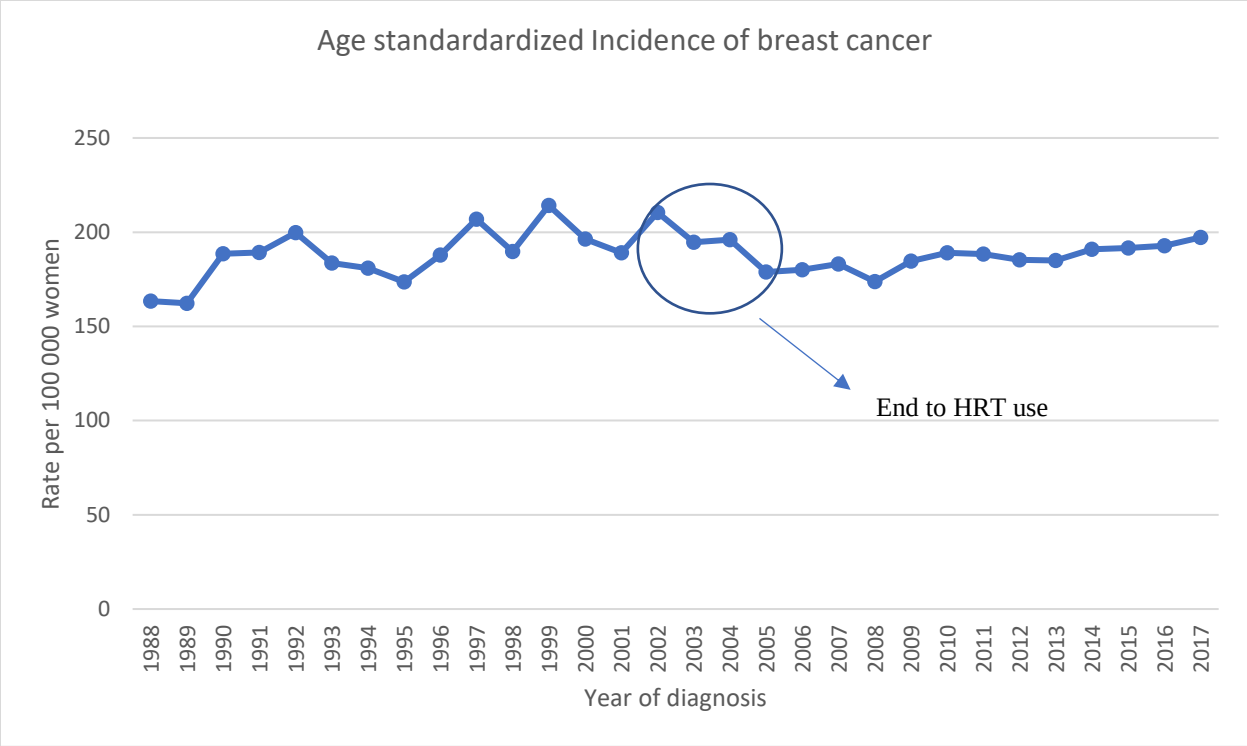


Figure 4.3: Age standardized incident rates of breast cancer from 1988 to 2017

The age standardized incidence of breast cancer ranged from 163.4 per 100,000 women in 1988 to 197.2 per 100,000 women in 2017. The highest incidence in this period was in 1999 (214.2 per 100,000 women)

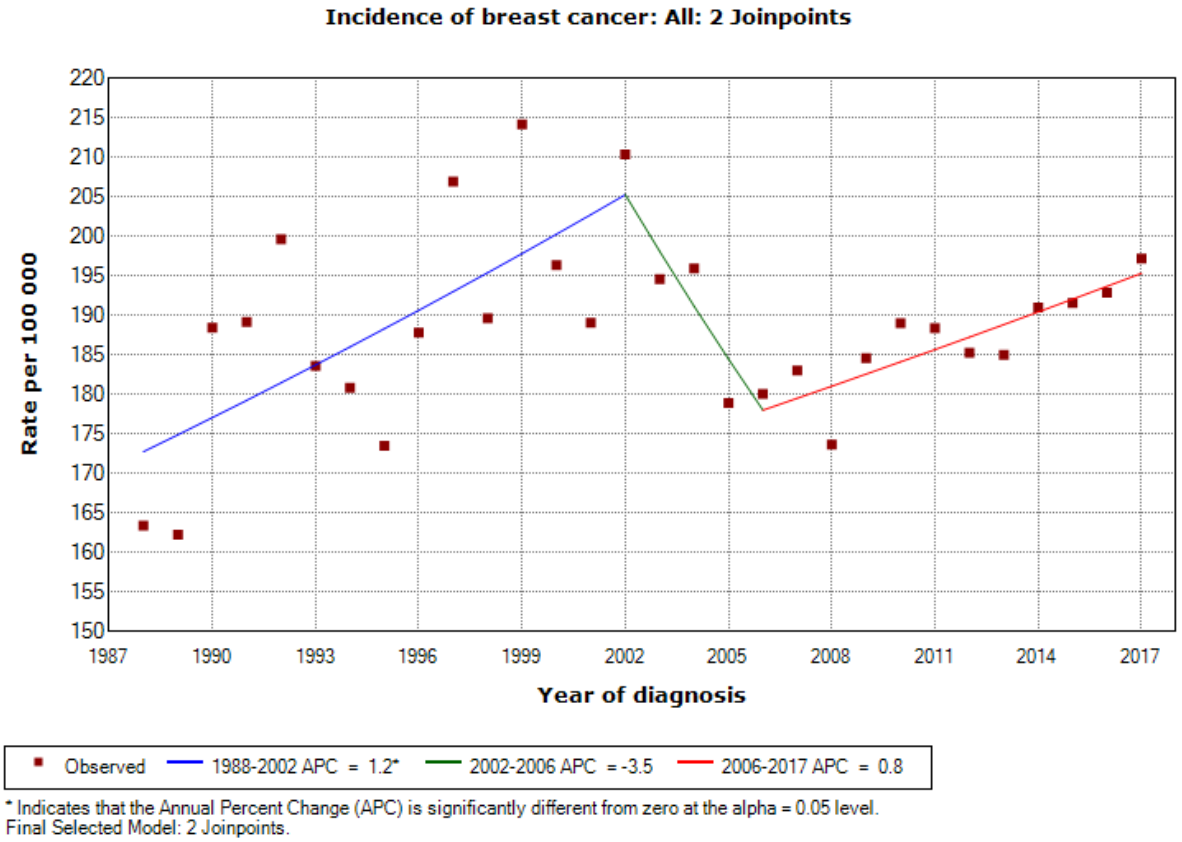


Figure 4.4: Joinpoint analysis showing trends in the age standardized incidence of breast cancer from 1988 to 2017

The graph above has two joinpoints, one at 2002 and the other at 2006. The incidence of female breast cancer therefore significantly changed twice between 1988 and 2017

Incidence for breast cancer was on the rise from 1988 to 2002 with an annual percent change (APC) of 1.2 (95% CI: 0.5 to 1.9, p <0.001)

The incidence decreased from 2002 to 2006 at 3.5% per year (95% CI: -10.3 to 3.8, p = 0.3) and then has been rising since 2006 with an APC of 0.8 (95% CI: -0.1 to 1.8, p = 0.1)

The average annual percent change (AAPC) was 0.4 (95% CI: -0.6 to 1.5, p = 0.4)

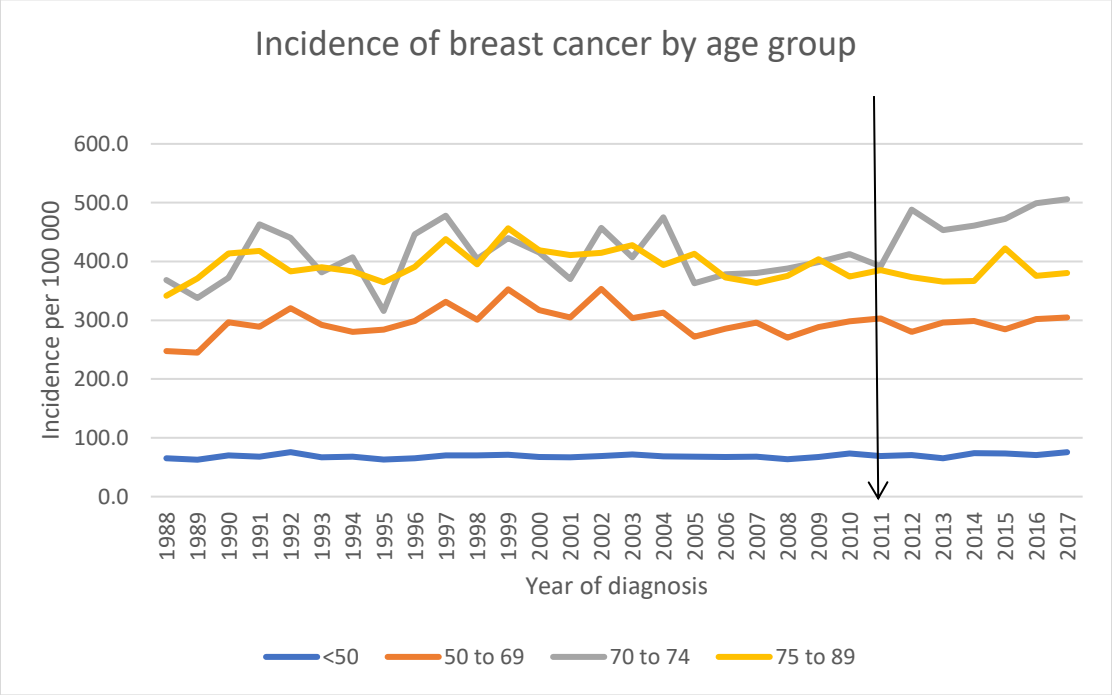


Figure 4.5 Incidence of breast cancer by age group

The above figure shows the effect of the addition of women aged 70 to 74 years to the screen eligible age in 2011 by the Canadian Task Force on Preventive Health care. The Incidence rose by 97 per 100,000 between 2011 and 2012 in women 70 to 74 years.

4.2 Incidence of breast cancer by stage

Table 4.3: Stage at diagnosis of breast cancer by age group from 2004 to 2017

Age at diagnosis (years)	Stage of breast cancer						Total n (%)
	0 n (%)	I n (%)	II n (%)	III n (%)	IV n(%)	Unknown n (%)	
<40	155 (8.8)	394 (22.4)	790 (45.0)	316 (18.0)	83 (4.7)	19 (1.1)	1,757 (100.0)
40-49	870 (14.8)	1,895 (32.1)	2,091 (35.5)	778 (13.2)	194 (3.3)	69 (1.2)	5,897 (100.0)
50-74	2,485 (12.8)	8,138 (42.0)	5,796 (30.0)	1886 (9.7)	836 (4.3)	238 (1.2)	19,379 (100.0)
>75	407 (7.2)	2,021 (36.0)	1,831 (32.6)	564 (10.0)	395 (7.0)	401 (7.1)	5,619 (100.0)
Total	3,917 (12.0)	12,448 (38.1)	10,508 (32.2)	3544 (10.9)	1508 (4.6)	727 (2.2)	32652 (100.0)

Over 75 % of breast cancer was diagnosed at early stages (stage 0, I and II) across all age groups of women.

Most of the younger women were diagnosed at stage II, 45% for women <40 years and 35.5% for women 40 to 49 years.

Among screen eligible women (50 to 74 years), 42% were diagnosed at stage I and 30% at stage II.

For women over 75 years who have passed the age of screening, 75.8% of cancers were diagnosed at early stages. The largest proportion of unknown stage (7.1%) were in women above 75 years

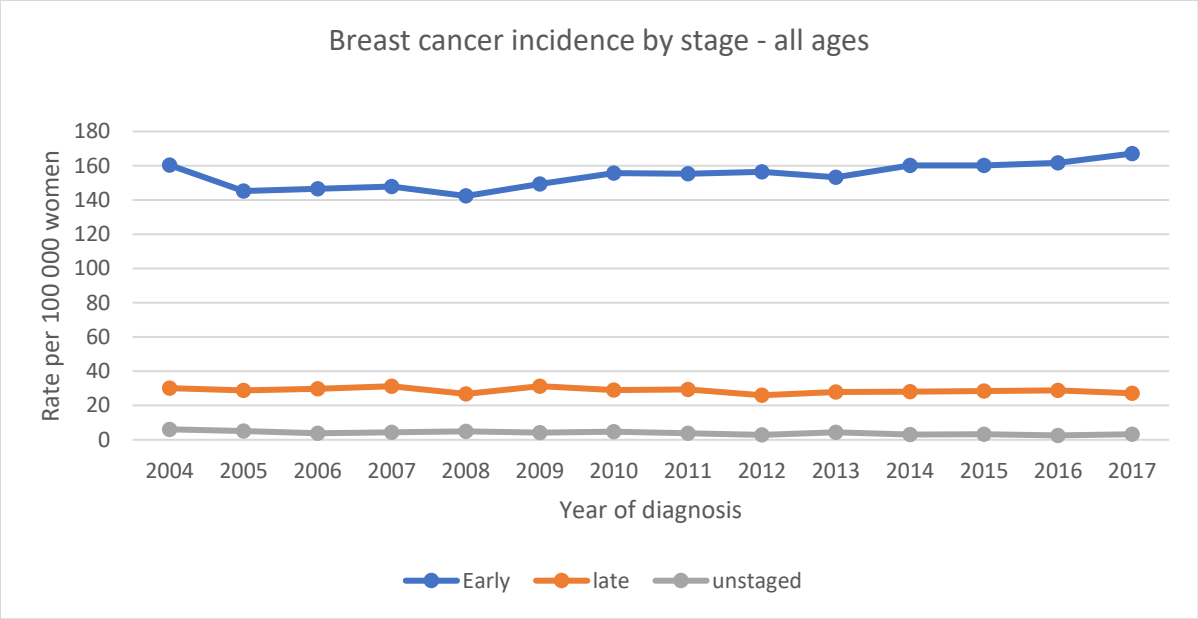


Figure 4.6: Age standardized incidence of breast cancer per 100,000 women by stage at diagnosis

Table 4.4: Joinpoint analysis for age standardized incidence of breast cancer per 100,000 women by stage at diagnosis

Stage	Joinpoint	Year	APC	95% CI	p-value
Early	1 (2006)	2004 to 2006	-4.4	-10.2 to 1.8	0.1
		2006 to 2017	1.3	0.8 to 1.7	<0.001
Late	0	2004 to 2017	-0.65	-1.4 to 0.1	0.1
Unstaged	0	2004 to 2017	-4.75	-6.8 to -2.6	<0.001

The incidence of early stage cancer among women of all ages increased from 160 per 100,000 in 2004 to 167 per 100,000 women in 2017 and was higher than the incidence of late stage which remained below 40 per 100,000 women throughout the same period. The incidence of early stage cancer reduced by 4.4% annually between 2004 to 2006 (This is the period around the end to the use of HRTs) and has been rising by 1.3% per year since 2006 ($p<0.001$).

There was no significant change in trend for late stage cancer from 2004 to 2017(zero joinpoint) with its incidence decreasing minimally by 0.65% per year ($p=0.1$). The unstaged cancers have been decreasing significantly over the years at a rate of 4.75 per year.

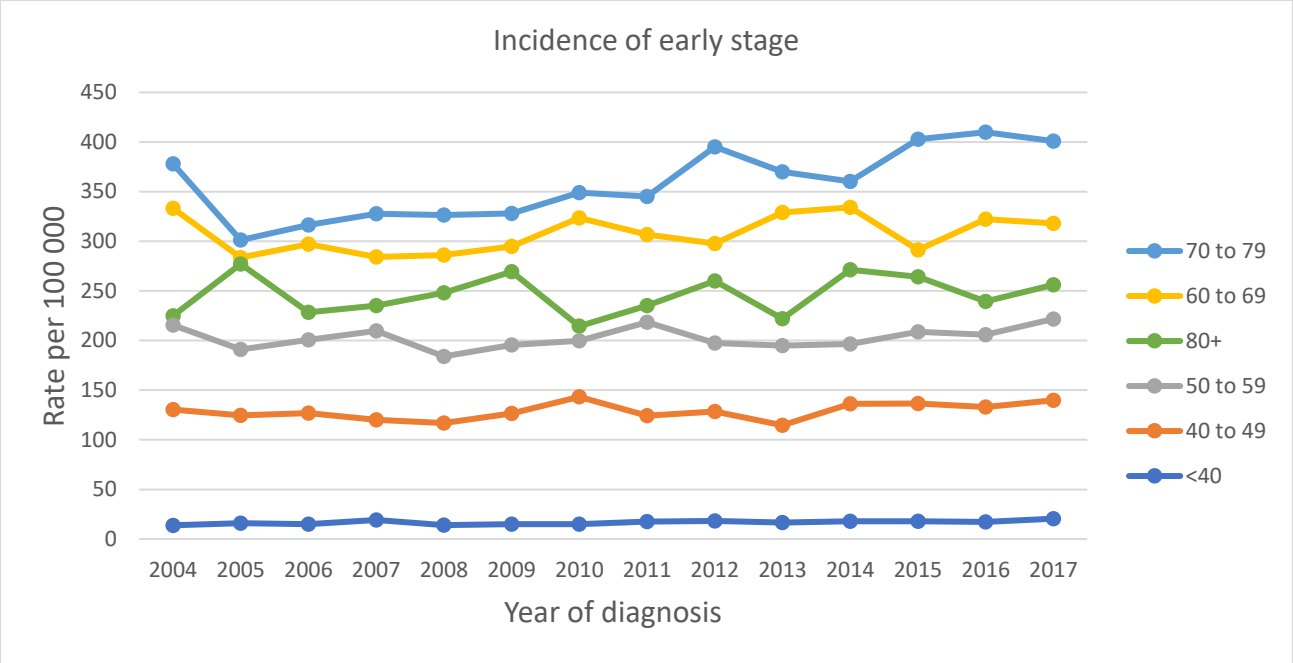


Figure 4.7: Incidence of early stage breast cancer by age group per 100,000 women

Table 4.5: Joinpoint analysis for the incidence of early stage breast cancer by age per 100,000 women

Age group	Joinpoint	APC	95% CI	p-value
<40	0	1.9	0.6 to 3.2	<0.001
40 – 49	0	0.7	-0.3 to 1.6	0.1
50 – 59	0	0.3	-0.5 to 1.1	0.4
60 – 69	0	0.5	-0.3 to 1.4	0.2
70 – 79	0	1.8	0.8 to 2.8	<0.001
80+	0	0.4	-0.8 to 1.6	0.5

The incidence of early stage breast cancer was rising for all age groups. Women less than 40 years and women 70 to 79 years had incidence rising significantly

The lowest incidence of early stage cancer was in those less than 40 years and the highest incidence was in those 70 to 79 years

There was no significant change in trend for all ages of early breast cancer from 2004 to 2017. (zero join points).

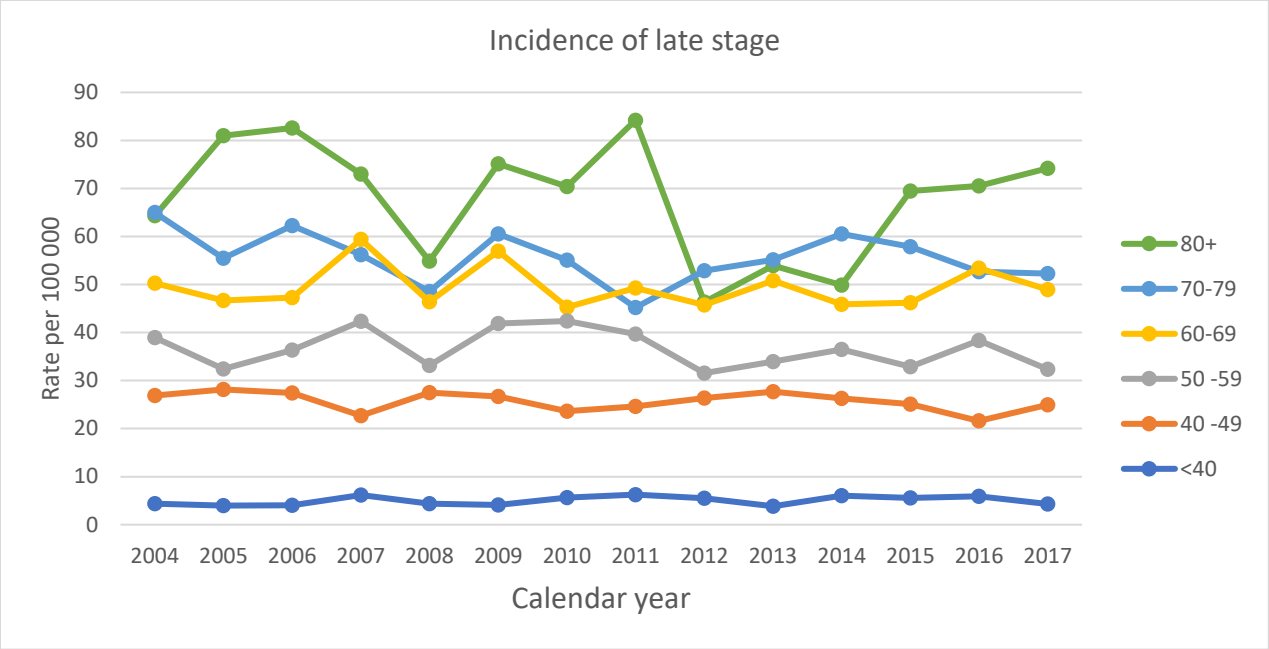


Figure 4.8: Incidence of late stage breast cancer by age group per 100,000 women

Table 4.6: Joinpoint analysis for the incidence of late stage breast cancer by age group per 100,000 women

Age group	Joinpoint	APC	95% CI	p-value
<40	0	1.6	-0.1 to 4.3	0.2
40 – 49	0	-0.8	-1.9 to 0.3	0.1
50- 59	0	-0.7	-2.3 to 0.8	0.3
60-69	0	-0.2	-1.5 to 1.1	0.7
70-79	0	-0.8	-2.1 to 0.6	0.3
80+	0	-1.1	-3.9 to 1.7	0.4

The incidence of late stage breast cancer was higher among older age groups with women over 80 years having the highest incidence

The incidence of late stage breast cancer was decreasing (not statistically significant) for all age groups except for women less than 40 year where the incidence was increasing by 1.6% annually (p=0.2).

In women from 40 years to 80+ years, incidence of late stage breast cancer was decreasing annually from between 0.2% to 1.1%.

There were no significant changes in trend for all ages of late breast cancer from 2004 to 2017. (zero join points).

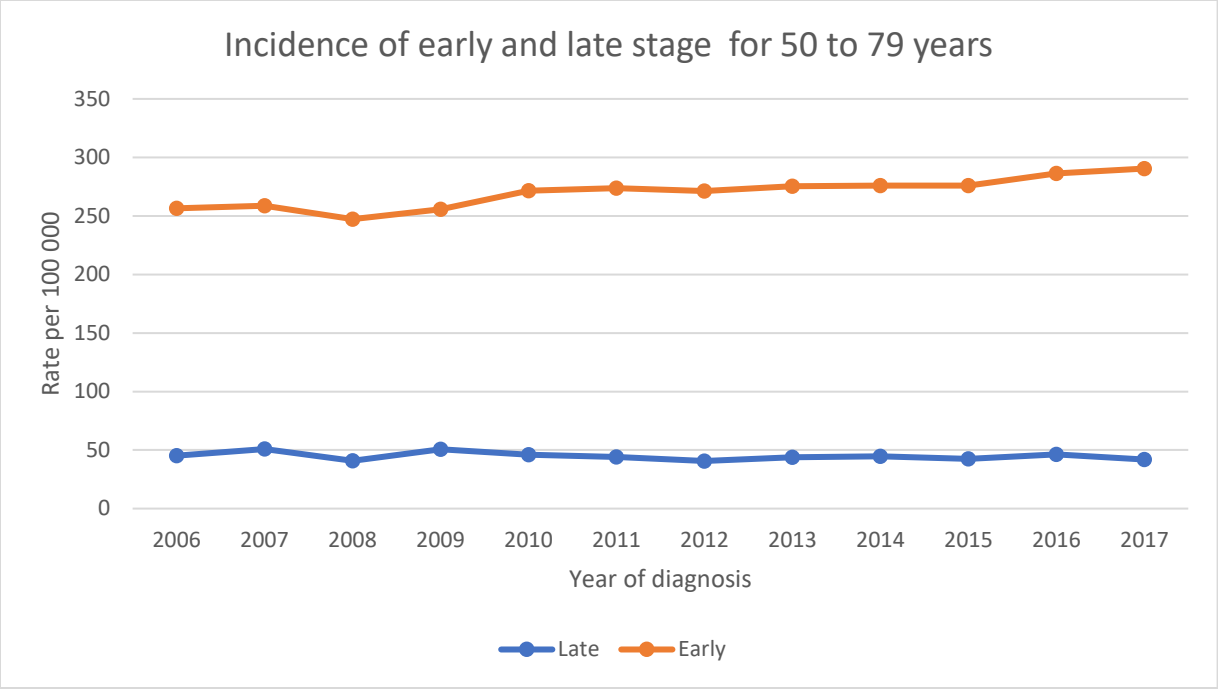


Figure 4.9: Incidence of early and late stage breast cancer in women 50 to 79 years per 100,000 women

Table 4.7: Joinpoint analysis for the incidence of late stage breast cancer by age group per 100,000 women

Stage	Joinpoint	APC	95% CI	p-value
Early	0	1.2	0.8 to 1.6	<0.001
Late	0	-0.8	-2.1 to 0.5	0.2

From 2006 to 2017 (excluding the effect of Hormone replacement therapy), the incidence of early stage breast cancers among women aged 50 to 79 years increased by 33 per 100,000 women (257 per 100 000 women in 2006 to 290 per 100,000 women in 2017) at an average rate of 0.8% per annum. (12.8% increase). This rise was statistically significant with a p value less than 0.001. On the other hand, the incidence of late-stage cancer decreased by 6.6% from 45 per 100,000 women to 42 per 100,000 women at a lower rate of 0.8 per annum. This reduction was not statistically significant (p=0.2)

Incidence of late stage cancer in women 50 to 79 years in 2006 was 45.3 per 100,000 (95% CI-38.8 to 51.8) and in 2017, it was 42.0 per 100,000 (95% CI-36.8 to 47.2), giving a standardized rate ratio of 0.93 (95% CI 0.77 to 1.12). This interval includes one and so the reduction in late stage cancer in women 50 to 79 from 2006 to 2017 is not statistically significant.

4.3 Breast cancer mortality

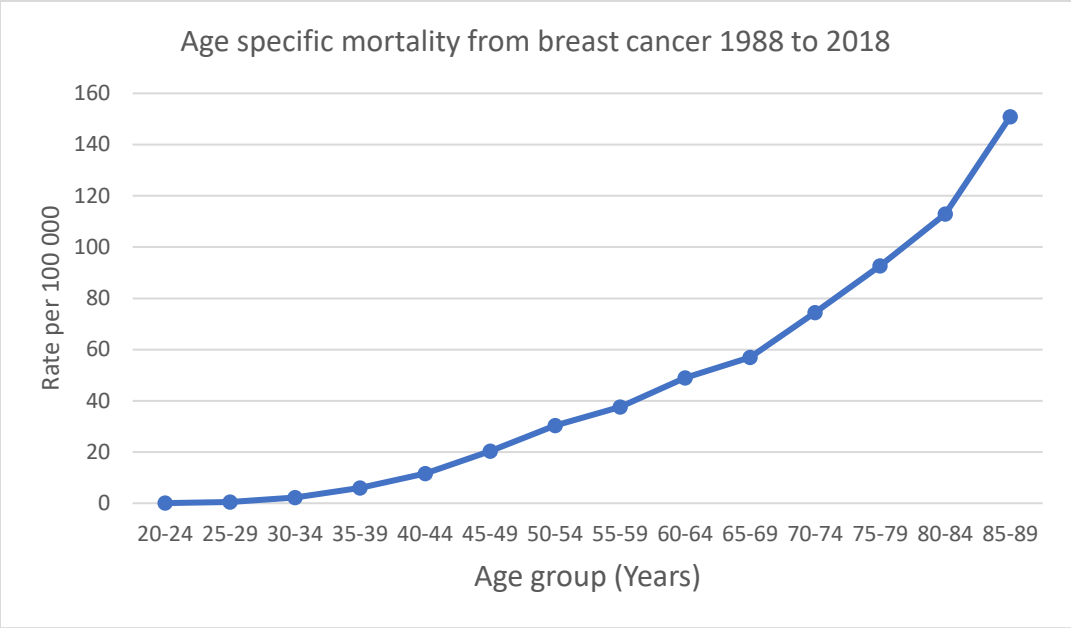


Figure 4.10: Age specific mortality from breast cancer from 1988 to 2018

Deaths from breast cancer increases with increasing age. The rate at 40 to 45 years was 11.6 per 100,000 women and was 150.9 per 100 000 women at 85 to 89 years.

This was calculated using the formula:

$$\frac{Average\ number\ of\ deaths\ from breast\ cancer\ in\ each\ age\ group}{Average\ population\ of\ Alberta\ woman\ at\ risk\ of\ \ dying\ from\ breast\ cancer\ in\ \ corresponding\ age\ group} X100{,}000$$

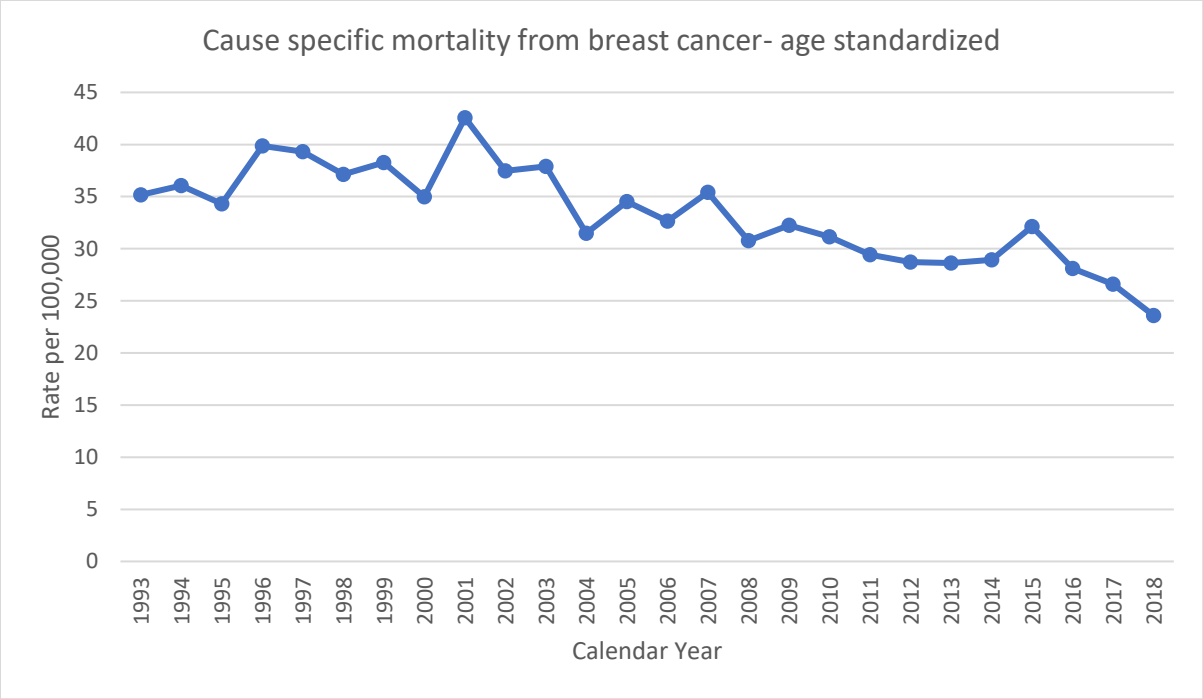


Figure 4.11: Cause specific mortality from breast cancer from 1993 to 2018 (All ages)

Deaths caused by breast cancer decreased by 11 per 100,000 women from 35 per 100,000 in 1993 to 24 per 100,000 in 2018

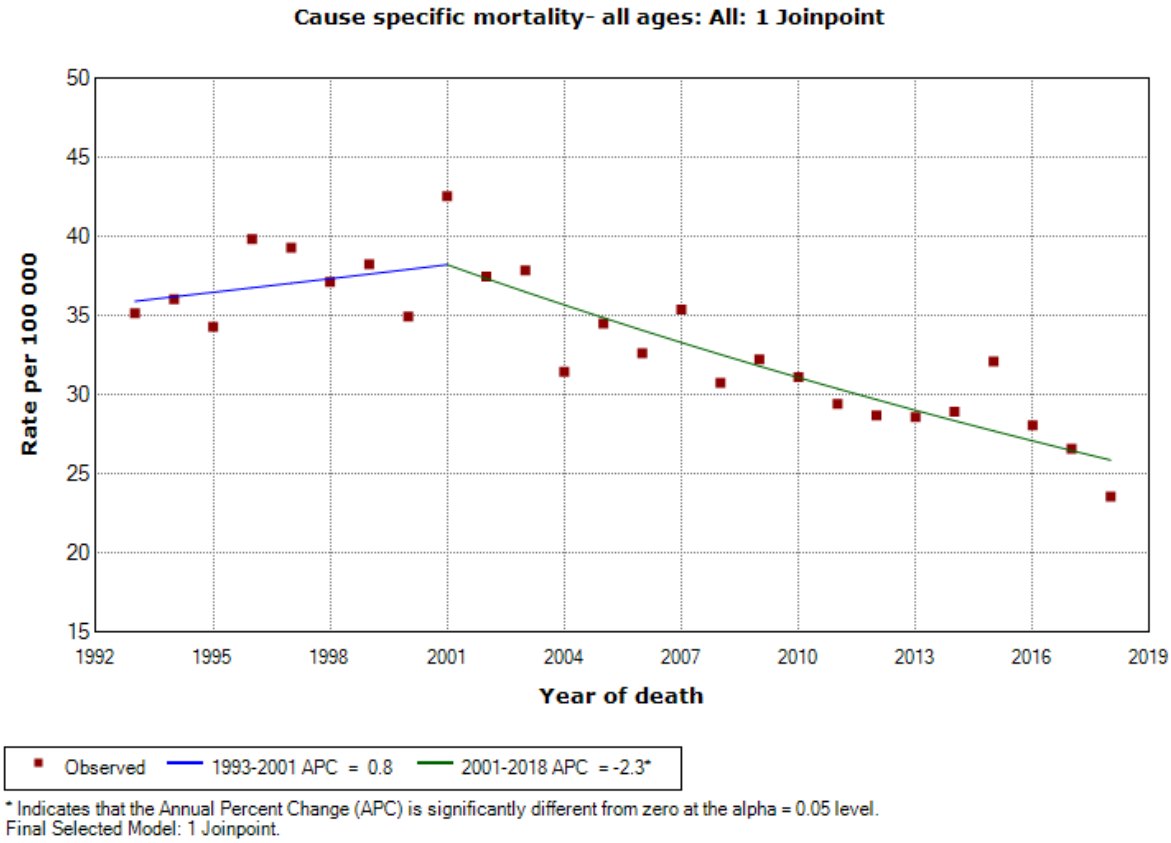


Figure 4.12: Joinpoint analysis for the cause specific mortality from breast cancer from 1993 to 2018

This graph has one joinpoint at 2001, showing a gradual rise in mortality from 1993 to 2001 at 0.8% per year (95% CI: -1.2 to 2.8, p=0.4) and then a decrease from 2001 to 2018 at 2.3 per year. (95%CI: -2.3 to -1.6, p<0.001) The average annual percent change (AAPC) was -1.3 (95%CI: -2.0 to -0.6, p<0.001)

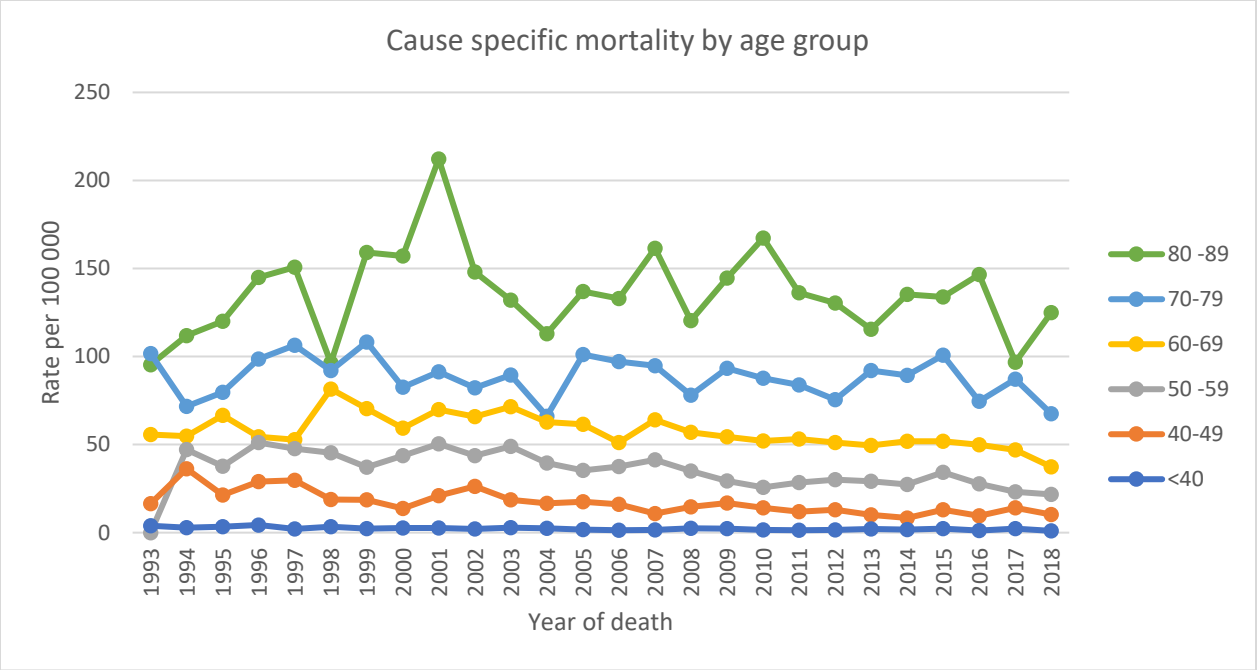


Fig 4.13: Cause specific mortality by age group

Table 4.8: Joinpoint analysis for cause-specific mortality by age group

Age group	Joinpoint	AAPC*	95% CI	p-value
<40	0	-3.3	-4.7 to -2.0	<0.001
40-49	0	-3.8	-4.9 to -2.6	<0.001
50 -59	0	-2.9	-3.6 to-2.2	<0.001
60 -69	1 (1999)	-0.8	-2.1 to 0.6	0.3
70 -79	0	-0.5	-1.2 to 0.3	0.2
80-89	0	0.0	-1.0 to 1.1	0.9

*AAPC- Average annual percent change

Cause specific mortality has been on the decline for all age groups except women 80 to 89 where there has been no change. The decline was statistically significant for women less than 60 years.

Figure 4.14 to 4.16 below show the mortality from all causes among women diagnosed with breast cancer

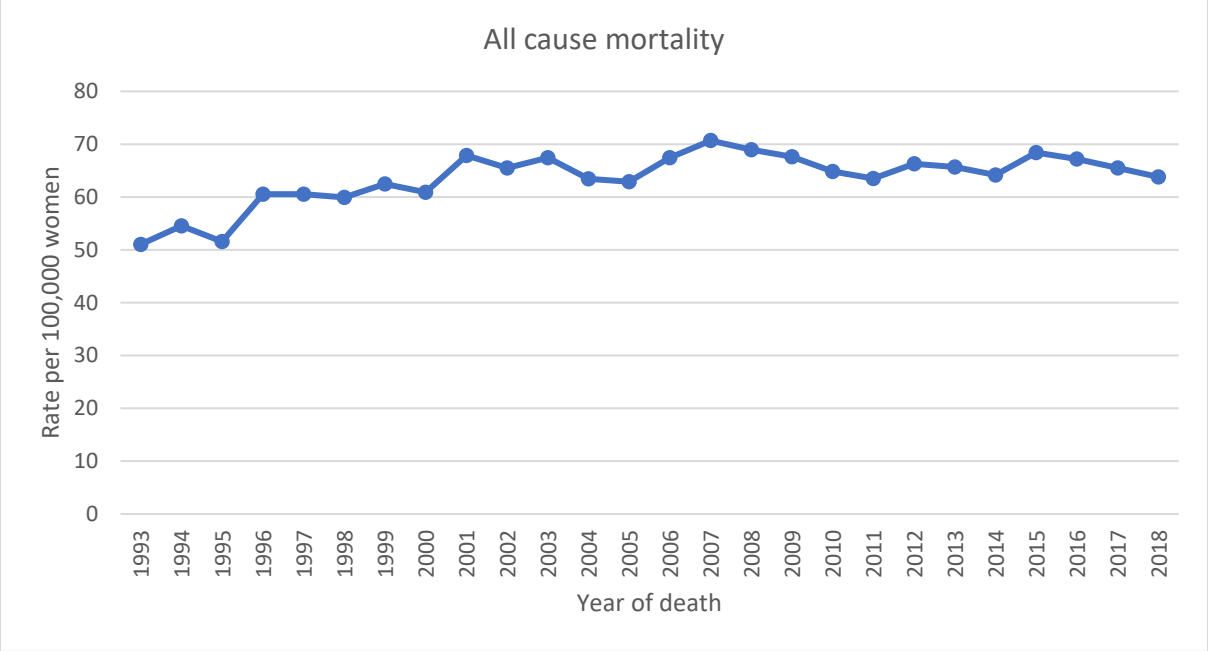


Figure 4.14: All cause mortality from 1993 to 2018

Deaths from all causes among women of all ages who had been diagnosed with breast cancer was 51 per 100,000 in 1993 and increased to 63.8 per 100,000 women in 2018.

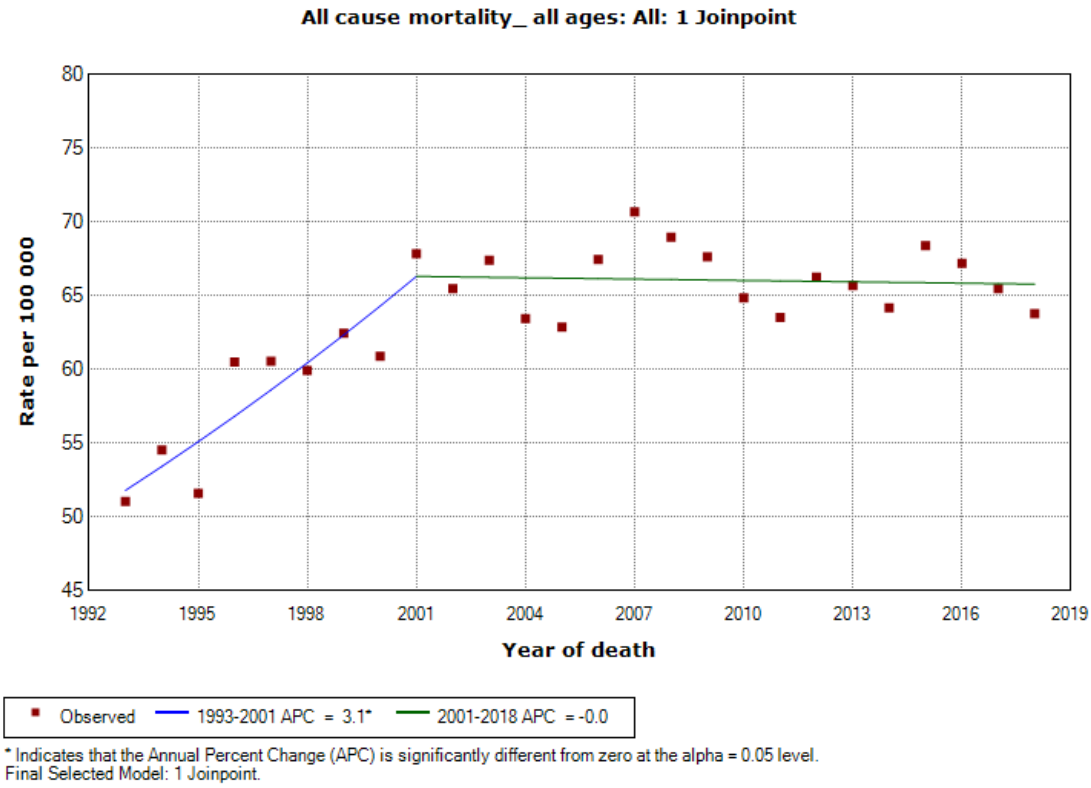


Figure 4.15: Joinpoint analysis for the all-cause mortality from 1993 to 2018

This graph has one joinpoint at 2001. There was a rise in mortality between 1993 to 2001 (APC: 3. 1% CI: 1.9 to 4.4, p<0.001)

All-cause mortality remained stable from 2001 to 2018 (APC: -0.0, 95% CI: -0.4 to 0.3, p= 0.8)

The average annual percent change (AAPC) was 1.0 (95%CI: 0.5 to 1.4, p<0.001)

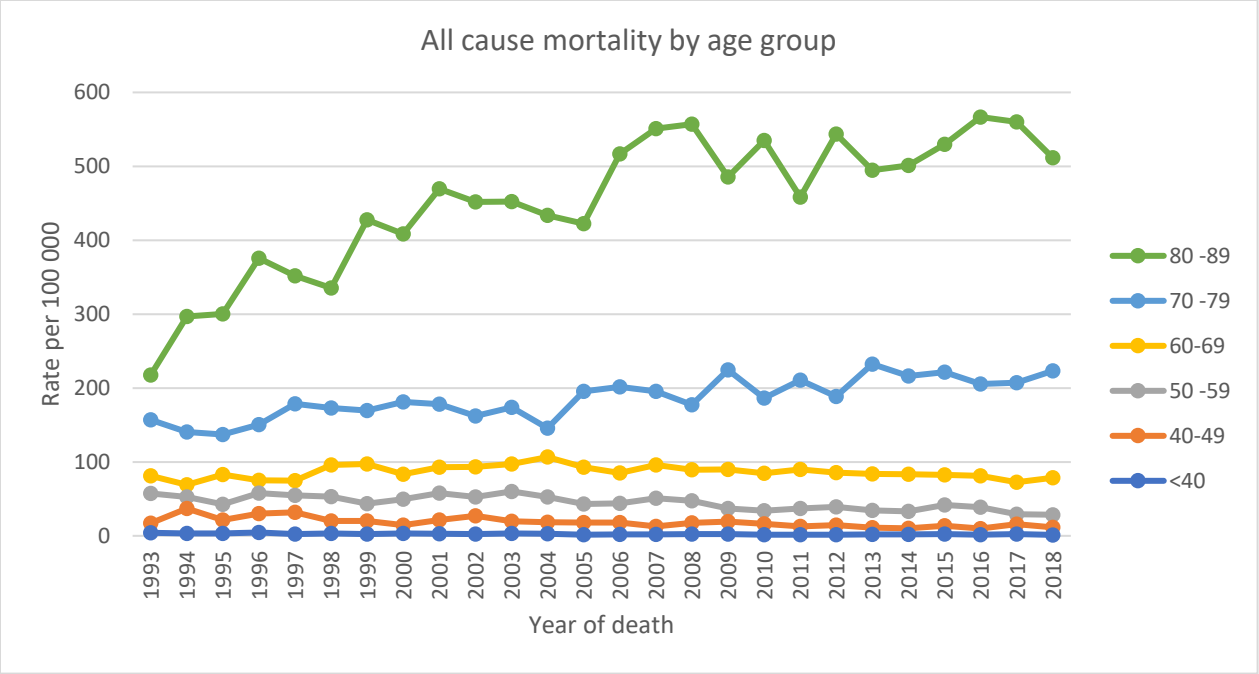


Fig 4.16: All cause mortality among women diagnosed with breast cancer, by age group

Table 4.9: Joinpoint analysis for All cause mortality by age group

Age group	Joinpoint	AAPC	95% CI	p-value
<40	0	-3.2	-4.3 to -2.1	<0.001
40-49	0	-3.4	-4.5 to -2.3	<0.001
50 -59	0	-2.3	-3.0 to -1.6	<0.001
60 -69	1 (2003)	0.1	-0.6 to 0.9	0.7
70 -79	0	1.7	1.2 to 2.1	<0.001
80-89	1 (2001)	3.1	2.0 to 4.2	<0.001

Death from all causes in women previously diagnosed with breast cancer has been decreasing significantly for women less than 60 years and has been increasing for women 60 years and above, most marked in women 80 to 89 years.

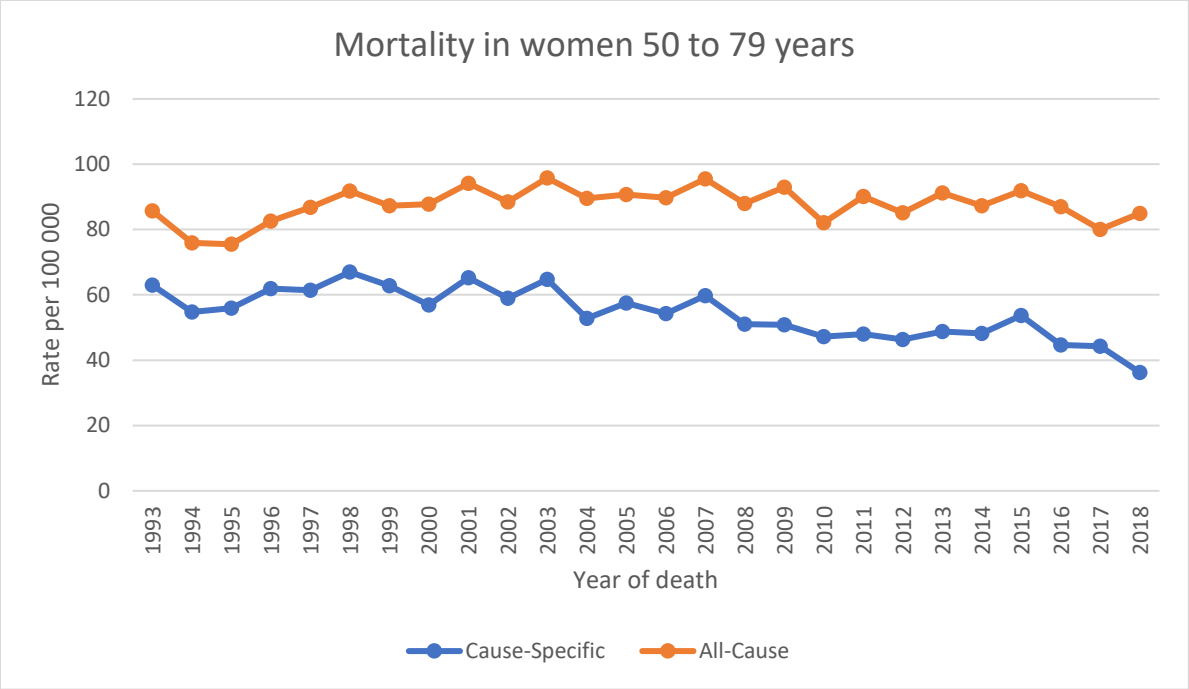


Fig 4.17: Breast cancer mortality and all cause mortality in women 50 to 79 years

Table 4.10: Joinpoint analysis for breast cancer mortality and all cause mortality in women 50 to 79 years

Mortality	Joinpoint	Year	APC	95% CI	p-value
Cause specific	1 (2001)	1993 to 2001	0.7	-1.7 to 3.3	0.5
		2001 to 2018	-2.3	-3.1 to 1.5	<0.001
All cause	1 (2001)	1993 to 2001	2.1	0.5 to 3.7	<0.001
		2001 to 2018	-0.5	-1.0 to 0.0	0.1

The mortality rate from breast cancer in women 50 to 79 years reduced by 29 per 100 000 from 65 per 100 000 in 2001 to 36 per 100 000 in 2018. This decrease occurred at 2.3% per year $p < 0.001$

Death from all causes among women diagnosed with breast cancer reduced by 9 per 100,000 from 94 per 100 000 in 2001 to 85 per 100,000 in 2018. This decrease occurred at 0.5% per year ($p=0.1$)

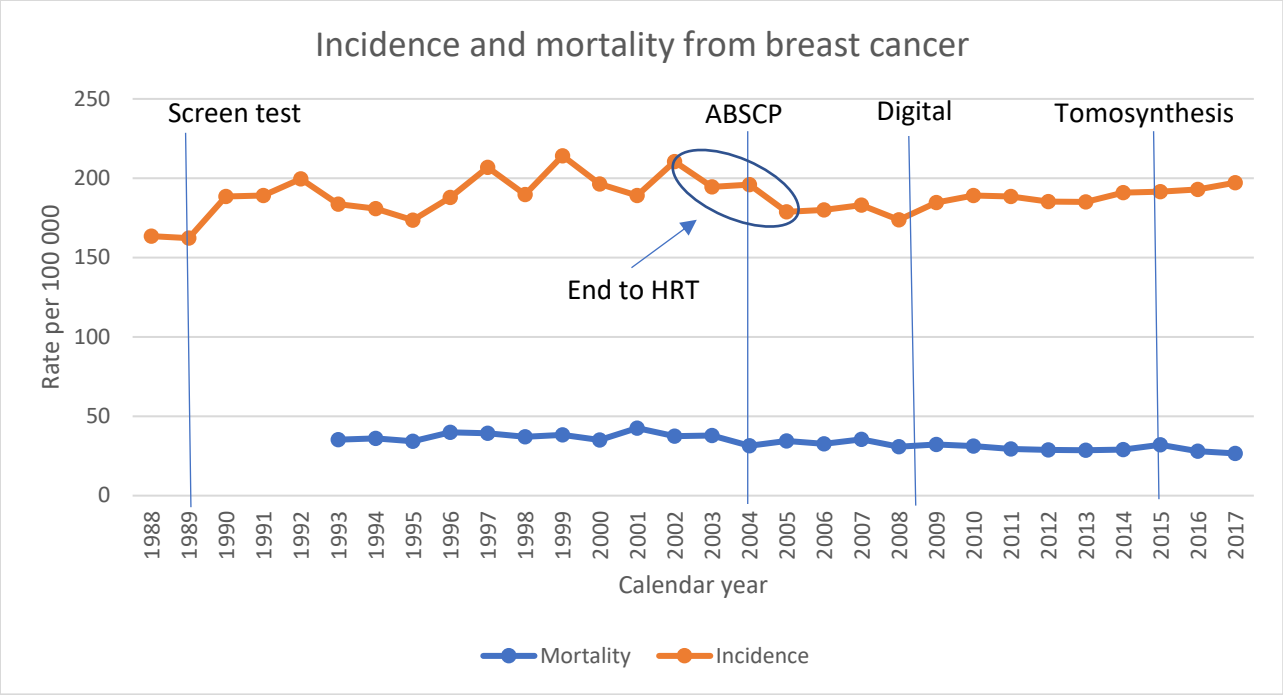
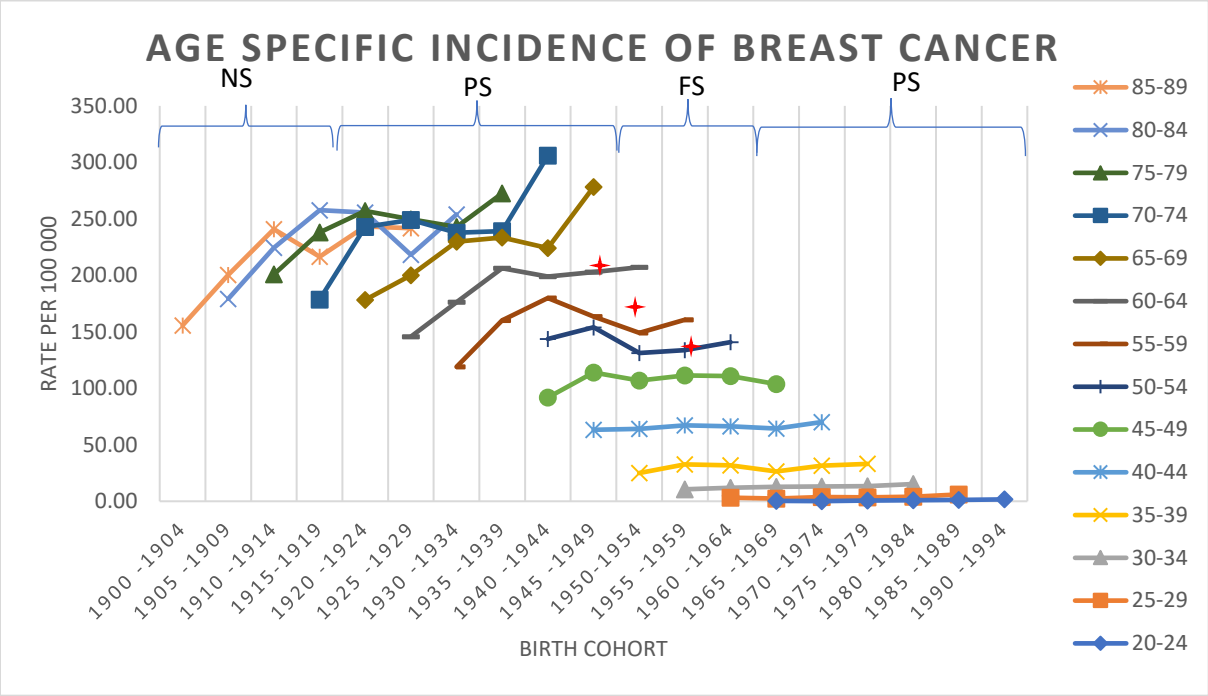


Figure 4.18: Incidence and mortality from breast cancer from 1988 to 2017

The above graph has four vertical lines which indicate changes to the screening program in Alberta. The first line at 1989, is when screening mammography was introduced. The second line at 2004 represents the beginning of the organised screening program. The third line about 2009 represents when the entire province is using digital mammography. The fourth line at 2015 represent when tomosynthesis became available.. After screen test was introduced, the incidence increased from 163 per 100,000 in 1988 to 210 per 100,000 in 2002 and then reduced by 31 per 100,000 from 2002 to 2005 and has been on the rise thereafter with the introduction of digital mammography and tomosynthesis. Deaths from breast cancer have reduced from 35 per 100,000 in 1993 to 27 per 100,000 in 2017. However, the total death rate in those diagnosed with breast cancer has not changed concomitantly.

4.4 Birth cohort analysis

The birth cohort analysis shows incidence and mortality trends from breast cancer as women in the same birth cohort move upward from one five- year age group to the next. It also shows incidence rates for specific five-year age groups across birth cohorts.



*NS: No screening, PS: Partial screening, FS: Full screening, NE: Not yet eligible

✦ Red stars represent rapid reduction in the use of HRT between 2002 and 2006

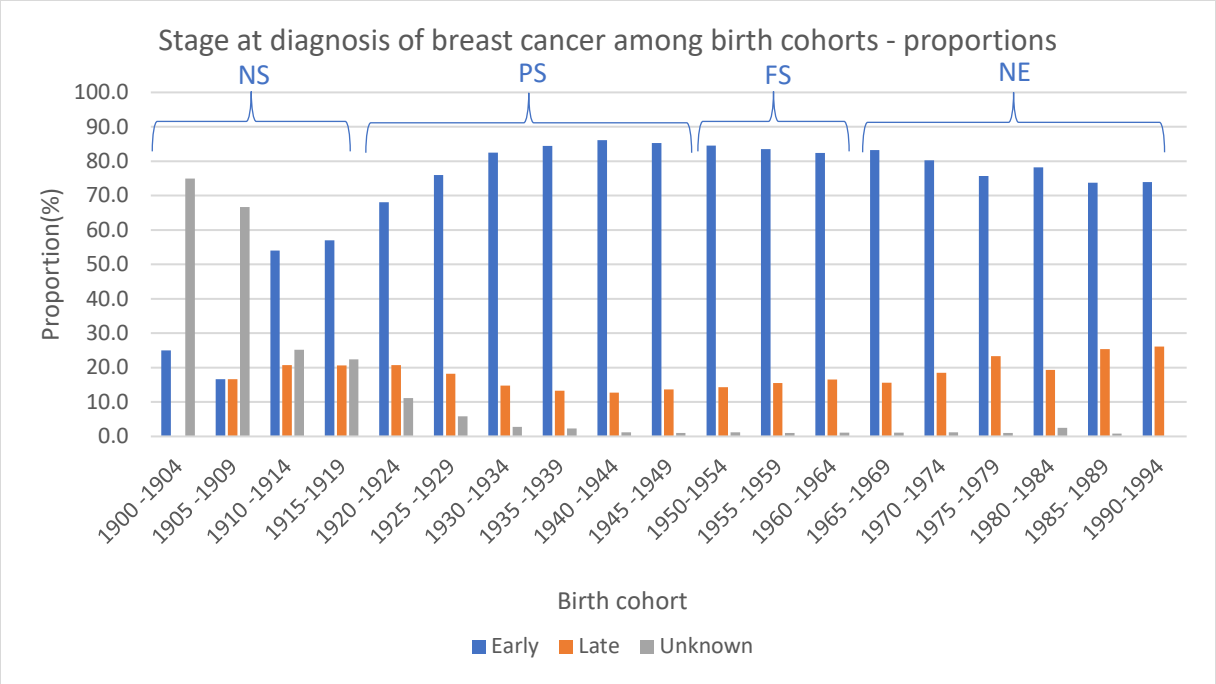
Figure 4.19: Age -specific incidence of breast cancer per 100,000 women among birth cohorts

The above graph was derived using the formula:

$$\frac{Number\ of\ new\ cases\ of\ breast\ cancer\ in\ each\ age\ group\ for\ each\ birth\ cohort}{Population\ of\ Alberta\ woman\ at\ risk\ of\ breast\ cancer\ in\ each\ age\ group\ for\ each\ cohort} X100{,}000$$

As women grew older, the incidence of breast cancer increased. This trend was consistent across birth cohorts. For example, for women in cohort “1950 -1954”, the incidence rose from 25 per 100,000 women at 35-39 years to 149 per 100,000 women at 55 -59 years.

The incidence of breast cancer at specific ages was higher among recent birth cohorts. This trend was transiently reversed at a time which coincided with the end to the use of HRT, and then continued afterwards.



*NS: No screening, PS: Partial screening, FS: Full screening, NE: Not yet eligible

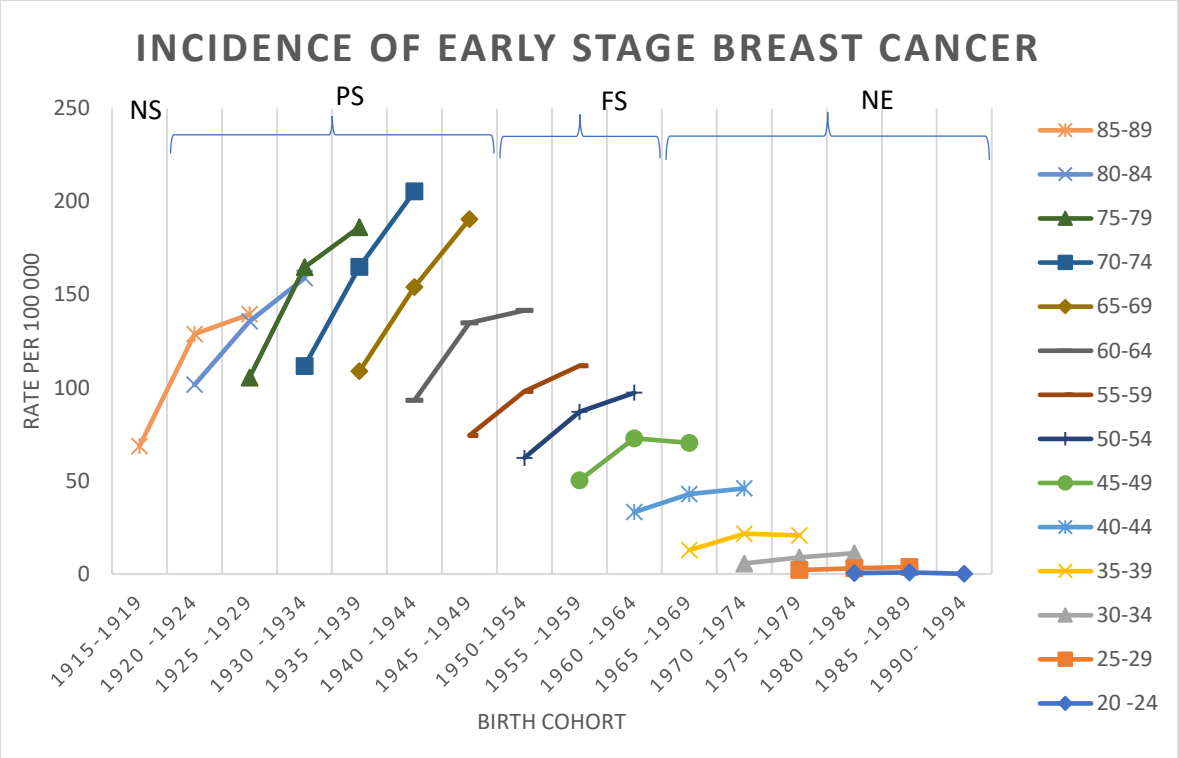
Figure 4.20: The proportion of women presenting at various stages of breast cancer among birth cohorts

This graph shows the proportion of early, late or unknown cancers that were diagnosed among women in each birth cohort

This was calculated using the formula:

$$\frac{Number\ of\ early/late/unknown\ stage\ breast\ cancer\ in\ \ each\ birth\ cohort}{Total\ number\ of\ breast\ cancer\ cases\ in\ each\ birth\ cohort}\ X100$$

Across all birth cohorts, most cancers were diagnosed at early stages. except those born from 1900 to 1909 who had more of their cancers as unstaged. The proportions of early stage were higher for birth cohorts who had some exposure to screening mammography. Unknown stages were highest in the historic cohorts, accounting for 75% of cases in birth cohort '1900 to 1904' and reduced with each recent birth cohorts up till 0.0 % in birth cohort '1990 to 1994'



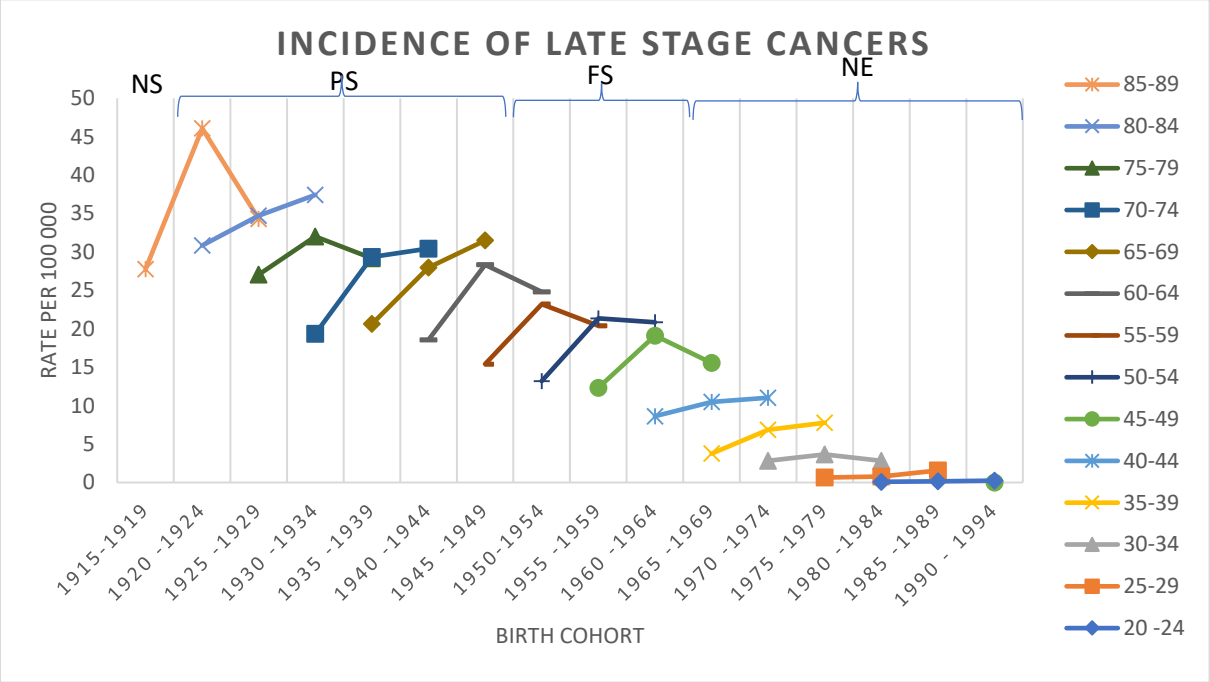
* NS: No screening PS: Partial screening, FS: Full screening, NE: Not yet eligible

Figure 4.21: Incidence of early stage breast cancer per 100,000 women among birth cohorts

The above graph was derived using the formula:

$$\frac{Number\ of\ new\ cases\ of\ early\ stage\ breast\ cancer\ in\ each\ age\ gruop\ for\ each\ birth\ cohort}{Population\ of\ Alberta\ woman\ at\ risk\ of\ breast\ cancer\ in\ each\ age\ group\ for\ each\ cohort} X100{,}000$$

Across all birth cohorts, the incidence of early stage breast cancer was generally higher with age. Recent birth cohorts had higher rates of breast cancer at specific ages.



*PS: Partial screening, FS: Full screening, NE: Not yet eligible

Figure 4.22: Incidence of late stage breast cancer per 100,000 women among birth cohorts from 2004 to 2017

The above graph was derived using the formula:

$$\frac{Number\ of\ new\ cases\ of\ late\ stage\ breast\ cancer\ in\ each\ age\ group\ for\ each\ birth\ cohort}{Population\ of\ Alberta\ woman\ at\ risk\ of\ breast\ cancer\ in\ each\ age\ group\ for\ each\ cohort}\ X100{,}000$$

Across all birth cohorts, the incidence of late stage breast cancer was higher with age. At specific ages, the incidence was initially rising among recent cohorts and then reduced.

Table 4.11 Incidence of early and late stage cancers per 100,000 women among birth cohorts with full screening exposure

Stage	Age group (Years)	Incidence per 100 000 among birth cohorts		
		1950 -1954	**1955 -1959**	**1960 -1964**
Early	50 -54	-	87.2	97.3
	55-59	98.0	111.8	-
Late	50-54	-	21.4	20.8
	55-59	23.2	20.4	-

This table was derived from figure 4.16 and 4.17 and shows the increase in incidence of early stage and the decrease in incidence of late stage among birth cohorts exposed to full screening.

When women were aged 50 to 54 years the incidence of early stage cancer increased by 10 per 100 000 from 87.2 per 100 000 women in birth cohort "1955-1959" to 97.3 per 100 000 women in birth cohort "1960 -1964" (11.6% increase) while the incidence of late stage cancer decreased by 0.6 per 100 000 from 21.4 to 20.8 per 100,000 women. (2.8% decrease)

Also, when women were aged 55 to 59 years the incidence of early stage cancer increased by 14 per 100 000 from 98.0 per 100 000 women in birth cohort "1950-1954" to 111.8 per 100,000 women in birth cohort "1955-1959" (14% increase) while the incidence of late stage cancer decreased by 3 per 100 000 from 23.2 to 20.4 per 100 000 women. (12% decrease)

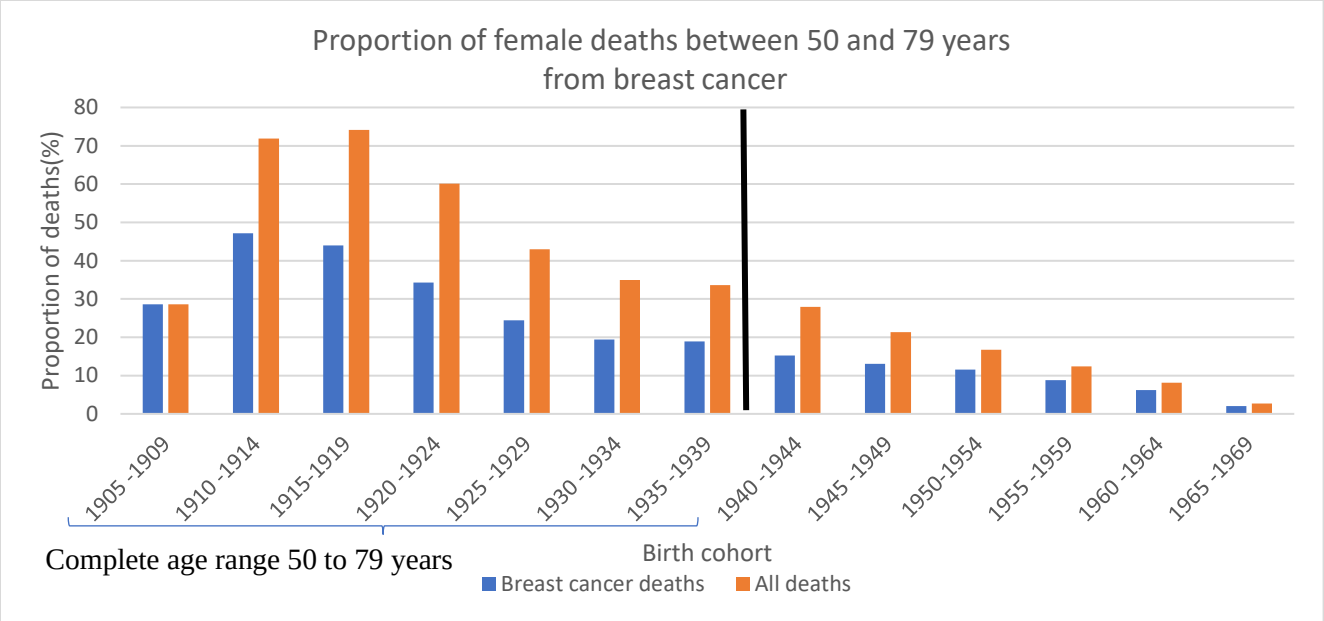


Figure 4.23: Proportion of women diagnosed with breast cancer who died from breast cancer/ any cause when they were aged 50 to 79 years

This was derived using the formula:

$$\frac{Number\ of\ deaths\ from\ breast\ cancer or\ any\ cause\ between\ 50\ to\ 80\ years\ in\ each\ cohort}{Number\ of\ women\ diagnosed\ with\ breast\ cancer\ in\ that\ cohort} X100$$

In the above graph, deaths before age 50 and after age 79 were excluded as they would unlikely be helped by screening mammography. The graph ranges from birth cohort "1905 - 1909" to birth cohort "1965 to 1969". The black vertical line divides the graph into complete and incomplete age ranges as only birth cohorts to the left of the black line contain women who had reached 79 years

For the complete data, the proportion of women dying from breast cancer as well as any cause is generally lower for more recent birth cohorts. The highest proportion (47%) was in birth cohort "1910 to 1914"

Chapter Five: Discussion

5.1 Age standardized incidence

Our study found that the incidence of breast cancer in Alberta is on the rise. The highest proportion was among screen eligible women aged between 50 and 74 years (58%) while those aged 40 to 49 years accounted for 19% of incident cases. Breast cancer incidence begins to rise from 25 to 29 years, reaches a peak between 70 to 74 years and then declines. The age standardized incidence increased at a rate of 1.2% per year between 1988 and 2002 and has been increasing gradually at a rate of 0.85% per year since 2006. There was a short-lived drop between 2002 and 2006, when the incidence of breast cancer decreased by 3.5% per year.

Screening may be responsible for this rise in incidence of breast cancer as it is known to identify cases that would have remained inapparent.[3] Participation rates increased by about 10% after the Canadian task force on Preventive Health Care updated its guidelines to include women 70 to 74 years in the screen eligible age in 2011 and incidence continued to rise afterwards, especially in this age group in which the incidence increased by 97 per 100,000 a year after the change was made (figure 4.5). The introduction of more sensitive screening techniques, including digital mammography and tomosynthesis, may have contributed to a further increase in breast cancer incidence, as a recently published systematic review, which included 24 studies comparing film to digital mammography showed an increase of 0.51 per 1000 screens (10% relative increase) with no associated reduction in interval cancer rates [66] Other factors such as obesity which has been changing gradually for many years, may also play a role in the increasing incidence of breast cancer, as postmenopausal obese women are more likely to have higher levels of estrogen which can

increase their risk of breast cancer,[67] and obesity rates in Alberta and Canada in general have been on the rise.[68,69]

The reduction in breast cancer incidence between 2002 and 2006 coincides with the rapid reduction of hormone replacement therapy following a publication of the Women's Health Initiative trial which linked hormone replacement therapy to increased incidence of breast cancer.[28] This would have likely affected women in the post menopausal age group (over 50 years). Women aged 50 to 74 years are within the screening age bracket and their participation in screening may have contributed to the high proportion of breast cancers diagnosed in this age group. The Canadian Task Force for Preventive Health care recommends that they be screened every 2 to 3 years, and this decision is conditional on the relative value the woman places on the possible benefits and harms from screening. [42] The screening recommendation in women 40 to 49 years remains controversial. The task force does not recommend screening in this age group, but radiologists say that these women should be screened every 1 to 2 years beginning at 40 years. [42,44] Cancers in younger women are usually more aggressive, having worse prognosis and screening may not be helpful in preventing mortality from these types of cancers as most of them may occur between screening intervals. [18,19]

The incidence rates observed in our study are similar to those reported by the 2019 report on cancer statistics in Alberta.[2] This is expected as data was also obtained from the Alberta Cancer Registry. Our findings however differ from the general Canadian population where incidence rates have shown a small but statistically significant decrease of 0.2 per year between 1991 and 2015. This may be due to the use of tomosynthesis, a more sensitive techniques being used in Alberta, compared to other provinces.[70]

5.2 Stage specific incidence of breast cancer

Screening mammography is meant to detect breast cancer early and, if effective should reduce the incidence of late stage cancers. Our study found that most breast cancers in Alberta were diagnosed at early stages (0, I & II), across all age groups, including women aged 75 years or older. There was a 14% increase in the incidence of early cancers by 20 per 100,000 from 147 to 167 per 100,000 women and a 10% decrease in the incidence of large tumors by 3 per 100,000 from 30 to 27 per 100,000 (among all ages combined from 2006 to 2017). The incidence of early stage breast cancer was rising for all age groups. This rise was statistically significant for women less than 40 years and those 70 to 79 years: women not usually being screened.

Looking closely at women 50 to 79 years (likely exposed to screening), the incidence of early stage breast cancers increased by 12.8% from 257 per 100,000 women to 290 per 100,000 women at an average rate of 1.2% per annum. This rise was statistically significant with a p value less than 0.001. On the other hand, the incidence of late-stage cancer decreased by 6.6% from 45 per 100,000 women to 42 per 100,000 women at a lower rate of 0.8 per annum. (p=0.2) with a standardized rate ratio of 0.93 (95% CI- 0.77 to 1.12) and so the reduction in late stage cancer in women 50 to 79 years, from 2006 to 2017 was not statistically significant. This downward trend in late stage cancers was observed among all age groups except in women under 40 years for whom incidence of late stage cancers increased by an average of 1.6% per year. (not statistically significant). Most of the unstaged cancers were found in women over 75 years.

After comparing the incidence of early and late stage cancers in women exposed to screening, where screening participation ranged from 55% to 64% during this period, we see

that screening may have some effect in reducing the incidence of late stage cancer (by 3 per 100,000) and this decrease is associated with an increase in incidence of early stage cancers (by 33 per 100,000). This excess incidence may be due to overdiagnosis which identifies cancers that were never going to cause harm. These women would have undergone many unnecessary procedures including surgeries, chemotherapy and radiations, all of which could have resulted in more harm than good. So, 11 women were treated for one to possibly not get a late stage cancer.

Screening may not be beneficial in women less than 40 years even though the incidence of late stage cancers was increasing in this age group. These are young women who have not yet reached routine screening age, and late stage cancers occurring in these young women are likely due to fast growing and aggressive cancers commonly found in this group. One might then argue that screening should be offered to these younger women. However, these women represented less than a quarter of the total cases of breast cancer in our sample and screening in this age group would likely be inefficient, as screening should be done when the prevalence of the disease is high enough to justify the effort and costs of screening. [71,72] Also, women in this age group usually have dense breasts which makes it more difficult to interpret their screening mammogram as both cancers and dense tissue appear white on mammogram. It has been suggested that ultrasound may be more beneficial in these women as cancer is hypoechoic while dense tissue is echogenic on ultrasound.[73]

Breast cancers diagnosed in women 75 years and over in Alberta are not likely to be detected by screening mammography, since these women are past the screening age. These women still had over three-quarters of cancers detected at early stages, which may therefore imply that screening mammography may not be a requirement for early detection of breast cancer.

These women over 74 years also had the largest proportion of breast cancers with unknown stages. A possible explanation for this is that these women are likely to have other comorbidities and further testing /procedures may do more harm than good. Over the years, unstaged cancers have also declined probably due to advances in staging techniques and also because the cancer registry has improved access to health records and therefore leaves fewer cases unstaged.

Our findings are similar to findings of a US study published by Bleyer and colleague in 2012, which also found that the rise in the incidence of early cancers far exceeded the decrease in the incidence of large tumors. [29] They found that the incidence of early stage cancers had doubled from 112 to 234 per 100,000 women between 1976 and 2008 while the incidence of late stage cancers had decreased by 8% from 102 to 94 per 100,000 women. Their figures were based on data from the Surveillance, Epidemiology, and End Results (SEER) program from 1976 to 2008. (The SEER program is the population- based registry for incident cancers in the United states).

Our findings are also similar to an ecological study in the United States that found an increase in incidence of small cancers, not matched by a reduction in large cancers. [54] They used data reported to the Surveillance, Epidemiology, and End Result (SEER) program and compared incidence of stage-specific cancers to extent of screening in 547 counties. They found that a 10% increase in extent of screening (e.g. from 60% -70%) was accompanied by 16% more breast cancer diagnosis but no significant reduction in breast cancer mortality (RR, 1.01; 95% CI:0.96-1.06)

5.3 Mortality in women previously diagnosed with breast cancer

Death from breast cancer is known to increase with age and this trend has also been shown in our study with women aged 20 to 24 years having rates as low as 0.05 per 100,000 and women 85 to 89 years at rates as high as 150.9 per 100,000.

Looking at all age groups combined, breast cancer mortality reduced by 19 per 100,000 from 43 per 100,000 in 2001 to 24 per 100,000 in 2018 at 2.3 per year ($p<0.001$) while all-cause mortality among women diagnosed with breast cancer, decreased by 4 per 100,000 from 68 per 100,000 women to 64 per 100,000 during the same time period.

For specific age groups, breast cancer mortality reduced across the years except in those 80 to 89 years where it remained stable. This reduction was statistically significant in those less than 60 years. from 1993 to 2018, All-cause mortality in women previously diagnosed with breast cancer decreased significantly between 2.3 to 3.4% per year in women less than 60 years and increased for women 60 years and above between 0.1 and 3.1% per year. Among women 50 to 79 years (exposed to screening), death from breast cancer reduced by 2.3% per year from 65 per 100,000 women in 2001 to 36 per 100,000 women in 2018 (45% reduction) while death from all causes decreased from 94 per 100,000 in 2001 to 85 per 100,000 in 2018 with an annual percent decrease of 0.5.

This reduction in mortality from breast cancer was occurring despite the increase in the incidence of breast cancer and so the reduction in deaths was not as a result of fewer breast cancer cases. A greater awareness of the disease, improvements in treatment options, as well as screening mammography could all have contributed to the observed reduction in deaths from breast cancer over the years. A study using modelling methods in the United States to determine the relative and absolute contribution of screening mammography and adjuvant

therapy to the reduction in breast cancer mortality from 1975 to 2000 found that about half of the observed decline in mortality was causally linked to mammographic intervention itself, whereas the other half was due to improved management.[74] So, if same is applied to Alberta's data, screening may have reduced deaths from breast cancer by 22.5%.

The process of classifying the cause of death can lead to some misclassification bias and so all-cause mortality is likely to be a better endpoint for this assessment, and our results show that all-cause mortality has remained fairly stable over the last 17 years. Women over 60 years who have been diagnosed with breast cancer, had increasing all-cause mortality over the years, even though mortality among women in the general population has decreased. In the general population deaths from all causes in women 80 to 89 years decreased from 76 per 1000 women in 1993 to 55 per 1000 women in 2018. (see figure 5.1) Perhaps women previously diagnosed with breast cancer have a higher chance of dying from all causes as they get older. Exposure to treatment such as chemotherapy and radiotherapy has been associated with higher risk of cardiovascular disease while hormone therapy (tamoxifen) has been associated with thromboembolic events and stroke.[75] Treatments may offer some temporary solution to their cancers, but they may eventually die from treatment complications.

Our findings are consistent with previous findings such as the 2019 Canadian Cancer Statistics, which also showed that deaths from breast cancer have been declining and have fallen by 48% since 1986.[1] Also, the Canadian National Breast Screening Study, a randomized control trial which began in 1980 found that after 25 years, mammography did not reduce mortality from breast cancer compared to usual care in a setting where treatment is available.[35] Narod and colleagues analyzed incidence rates, mortality rates and survival

from breast cancer from the Surveillance, epidemiology and end results (SEER) database. They found that breast cancer mortality reduced from 32 per 100,000 in 1975 to 21 per 100,000 in 2011 (34% reduction). They also found that breast cancer survival increased by 28% from 64.9% to 82.2%, which led to their conclusion that the drop in mortality rate was most likely due to increased survival from a lower case fatality rate which stemmed from increased used of adjuvant chemotherapy over the period[37]

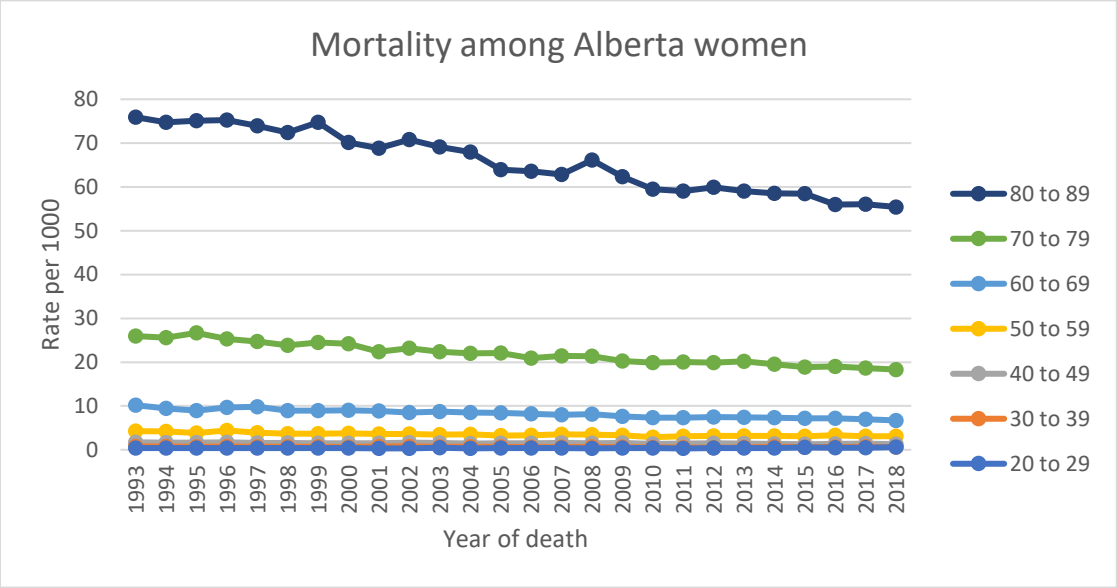


Figure 5.1: All Cause Mortality among Alberta women for 1993 to 2018

5.4 Birth cohort analysis

The birth cohort analysis also had similar findings as the trend analysis. These analyses show incidence and mortality trends from breast cancer as women in the same birth cohort move from one five- year age group to the next. It also shows how incidence rates for specific five-year age groups evolve across different birth cohorts. We observed trends among birth cohorts and five-year age groups, keeping in mind that women in the same birth cohort would likely have similar mammography screening experiences.

As women in each birth cohort grew older, the incidence of breast cancer increased. Also, the incidence of breast cancer among subsequent recent birth cohorts was higher at specific ages. So, more cancers were being detected in similar age groups, in recent birth cohorts. This trend was transiently reversed at a time that coincided with the end of the use of HRT, and then continued afterwards.

In terms of stage, most cancers were diagnosed at early stages across all birth cohorts. Each subsequent recent birth cohort had higher rates of early breast cancer at specific ages while the incidence of late stage cancers reduced with recent cohorts at specific ages. For birth cohorts exposed to full screening and excluding the effect of hormone replacement therapy, the incidence of early stage cancer increased by 10 per 100,000 (11.6% increase) from birth cohort "1955-1959" to birth cohort "1960 -1964" when women were aged 50 to 54 years while the incidence of late stage cancer decreased by 0.6 per 100 000 (2.8% decrease). Also, when women were aged 55 to 59 years the incidence of early stage cancer increased by 14 per 100,000 from birth cohort "1950-1954" to birth cohort "1955-1959" (14% increase) while the incidence of late stage cancer decreased by 3 per 100,000 (12% decrease). This translated to an average increase in early stage of 13% and an average decrease in late stage incidence of 7% when they were aged 50 - 59 years.

The proportion of women diagnosed at late stage increased in post-1970-born cohorts, and more unstaged cancers were found in women born before 1909. Also, the proportion of women dying from breast cancer was also seen to be lower among more recent birth cohorts.

The higher proportion of unstaged cancers in women born before 1909 is likely because these women would not have undergone further testing and procedures as they were all diagnosed when they were over 70 years. These unstaged cancers would have reduced the

proportion that was meant to represent early or late stages, but since unstaged cancers accounted for only 2.2 %, it would unlikely affect our estimates. Aggressive type cancers are usually found in young women who have not yet reached screening age. This may explain the higher proportion of late stage cancers in these women compared to women in historic birth cohorts.

Screening is intended to detect early stage cancers and therefore may have contributed to the higher incidence of early stage cancers in recent birth cohorts relative to historical birth cohorts at similar ages, as screen eligible women in recent birth cohorts are more likely to be exposed to screening. Also, the increase in incidence of early cancer in birth cohorts exposed to screening without a corresponding decrease in the incidence of late stage cancer is likely from a stage shift from overdiagnosed cases.

The proportion of women dying from breast cancer was also noticed to be lower among younger birth cohorts which further confirms our earlier finding in this study that breast cancer mortality has reduced with time. However, there may have merely been substitution of ascribed causes, since they eventually died of other causes at higher rates compared to the general population.

5.5 Strengths/limitations of study

The Alberta Cancer Registry (ACR) which was our data source, is a very robust data set but had some limitations. The ACR is a large database spanning over 35 years and has a high rate of histological confirmation. Reporting is mandatory which should lead to high coverage. The Registry excludes cancers without histological confirmation of breast cancer,

thereby contributing to the reliability of the data. It also performs multiple data editing to ensure that all information is entered as precisely as possible, for example, the diagnosis date must be after birth date. We did a power calculation which showed that our study was adequately powered to detect any differences in observed proportions.

Population based screening mammography began in Alberta in the early1990s, and an observable increase in early stage incidence would likely have followed closely, and if effective, a decrease in late stage cancer would then follow about five year after. Staging was only captured by the cancer registry from 2004 onwards and so we do not have stage information for the entire study cohort, which made it impossible to compare stage trends before and after the introduction of screening mammography. The Alberta Breast Cancer Screening Program (ABCSP) was established in 2004 as a cooperation between Screen Test and the Alberta Society of Radiologists (ASR) and has been ensuring quality in mammography screening. It has also evolved over the years with advances in mammography techniques which should detect more early cancers and prevent late cancers. We observed incidence trends in breast cancer stage for 13 years from 2004 to 2017, which was 14 years after screening mammography began in Alberta and could have been several years after the incidence reached a steady state,. However, our study should pick up any observable changes between 2004 and 2017, which included periods with more sensitive screening techniques like tomosynthesis (see figure 5.2),

Our study findings are based on population estimates and may not reflect individual risks, as we did not have access to individual screening exposure and therefore used screening program timelines in Alberta and age of women as proxies for probability of exposure to

mammography. Also, data on treatments received by each woman was not available to the researcher, so we couldn't assess the direct effect of treatment on mortality.

It may have been worthwhile to compare stage specific incidence and mortality of a cohort of women who are being screened and the cohort of women who are not participating in screening, to see if screening is effective but this would likely lead to a healthy user bias as these women would unlikely be comparable with differing underlying characteristics

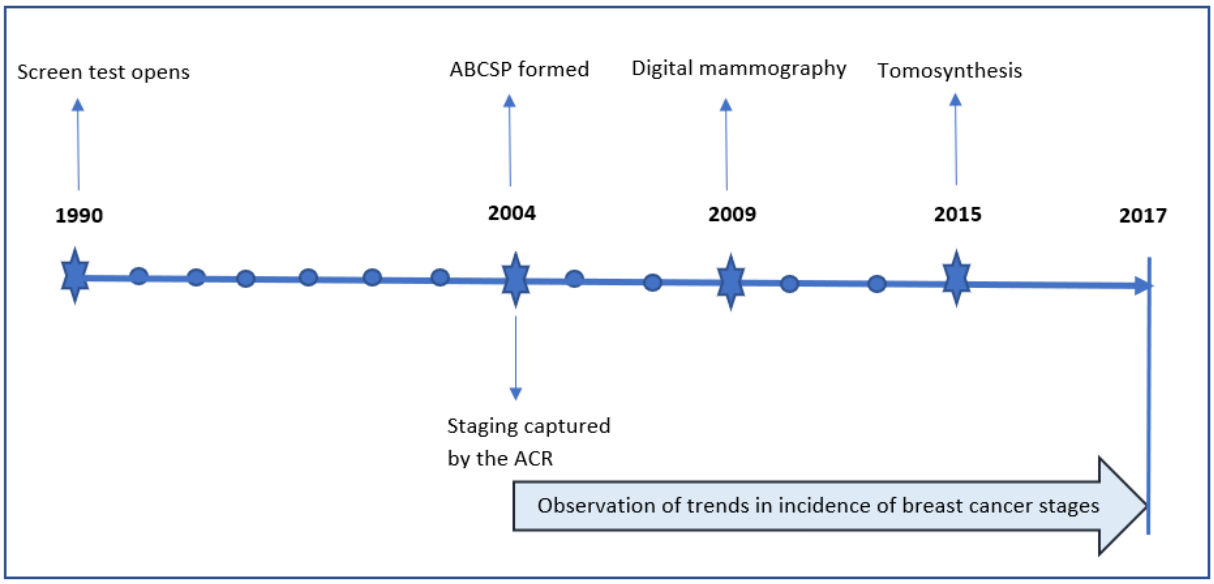


Figure 5.2 Period of observation of incidence of breast cancer by stage versus timelines of screening mammography in Alberta

5.6 Cost of screening

The implementation of this population-based screening program in Alberta has budget implications for the publicly funded health care system. Mittmann et al [76] estimated the lifetime overall cost for biennial screening per woman aged 50 to 69 years in Canada at about $6,100. By comparison, the cost associated with no screening was $3,000. Reducing the screening age to 40 years added $1,300 -$2,400 per woman to the screening cost. This estimate included costs of treatment, additional tests and procedures, and recall mammography for positive results. The Costs of Breast Cancer Screening in women 40 to 49 years in the United States of America was estimated by analyzing claims data from a Private Insurance company in 2017. The mean cost per person screened was estimated after taking into consideration the subsequent procedures in the immediate 4 months following screening and then extrapolated national costs from these estimates. They found that the cost for total screening and subsequent evaluation per beneficiary screened was $353 (SD:539) which came to $2.13 billion per year in national cost. The authors did not estimate the average cost per life saved. (Full table in appendix 1) [77]

Chapter Six: Conclusion

There has been some reduction in the incidence of late stage breast cancer by 3 per 100,000 from 2006 to 2017 and breast cancer deaths (by 29 per 100,000) from 2001 to 2018 with screening mammography. This has been associated with an increase in early stage cancers (by 33 per 100,000), which may be explained by overdiagnosis.

Increased incidence of early cancers typically follows screening and can be a consequence of both effective screening and overdiagnosis. If screening is effective, the increase in early cancers should be accompanied by a reduction in the incidence of late stage cancers over time, as these late tumors would have been detected earlier by screening and would have yielded better outcomes, including a reduction in mortality From our hypothesis, given a participation rate for mammography screening in Alberta of about 60%, if mammography reduces incidence of late stage cancer by 20%, our study should find a total population reduction of 12% with screening, leaving 88% (0.88) behind. Our study found a reduction of 7% and a standardized rate ratio of 0.93 (95% CI: 0.77 to 1.12) whose confidence limit includes 0.88, so our study did not have enough power to detect a 12% reduction. However, our study observed incidence of late stage from 2004, when women were already being screened at a steady state, making it difficult to appreciate the full effect of screening mammography on incidence of late stage breast cancers.

Breast cancer mortality in women 50 to 79 years which reduced by 45% between 2001 and 2018, could be due to both screening mammography and improved treatment options. Also, all cause mortality in women over 60 years who had previously been diagnosed with breast cancer has been increasing, and so, while women may not have died from breast cancer, they may have died from its treatment or complications.

In 2018, following a systematic review and a modified delphi consensus process, Dobrow and colleagues presented a set of screening principles which should guide screening decisions. One of the principles identified is that : “The expected range and magnitude of benefits (e.g., increased functioning or quality of life, decreased cause-specific mortality) and harms (e.g., overdiagnosis and overtreatment) for screening participants and society should be clearly defined and acceptable, and supported by existing high-quality scientific evidence (or addressed by ongoing studies) that indicates that the overall benefit of the screening program outweighs its potential harms”.[72]Screening mammography does not clearly meet these criteria. The WHO also recommends that screening programs should only be undertaken when their effectiveness has been clearly demonstrated.[71] This may not be the case for screening mammography.

Recommendation/next steps

Screening mammography may not be so effective in reducing the burden of breast cancer in Alberta. Women need to be educated on the effectiveness of screening mammography and guided in making informed decisions regarding their screening practices based on individual risk and belief systems.

More studies that could link the actual screening practises in these women would need to be done in order to understand the direct impact of screening on these trends. With the recent COVID-19 pandemic and a pause for routine screening, future studies can also assess whether there are any changes to the incidence and mortality from breast cancer during this period. Also, future research could explore perspectives of women who have been diagnosed with breast cancer with regards to overdiagnosis and treatment options, to determine what role, if any, informed choices played in their screening decisions.

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Appendix 1 Estimated cost of screening mammography

Table. Annual Breast Cancer Screening Cost and Use Among Women in Their 40s With Private Insurance

Screening-associated procedures	Screening cost, $		Total national cost, $ millions[a]	Use, No. (%)[b]
	Cost per beneficiary screened			
	Mean (SD)	Median (IQR)		
Screening mammography				
Total	249 (125)	226 (164-312)	1498	930 526 (41.2)
2-Dimensional	125 (133)	120 (0-213)	750	543 380 (24.1)
Screening digital breast tomosynthesis[c]	124 (170)	0 (0-250)	749	387 146 (17.2)
Supplementary screening ultrasonography	3 (35)	0 (0-0)	21	12 607 (1.4)
Recall				
Total	56 (172)	0 (0-0)	337	137 764 (14.8)
Diagnostic 2-dimensional mammography	21 (81)	0 (0-0)	125	79 064 (8.5)
Diagnostic digital breast tomosynthesis[c]	8 (56)	0 (0-0)	47	22 388 (2.4)
Diagnostic ultrasonography	27 (100)	0 (0-0)	165	103 388 (11.1)
Other diagnostic tests				
Total	45 (421)	0 (0-0)	273	20 229 (2.2)
Biopsy	39 (375)	0 (0-0)	234	18 085 (1.9)
Magnetic resonance imaging	6 (118)	0 (0-0)	39	4434 (0.5)
Total screening and subsequent evaluation[d]	353 (539)	250 (174-367)	2128	NA