Cost-effectiveness of the Norwegian Breast cancer screening program.

P.A. van Luijt, M.D. (corresponding author)

E.A.M. Heijnsdijk, PhD.

H.J. de Koning, Prof.

Affiliations:

Erasmus MC

Department of Public Health

P.O. box 2040

3000 CA Rotterdam

E-mail correspondence through: p.vanluijt@erasmusmc.nl

Telephone: +31 (0) 10 7 04 43 22

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Summary statement: There have been remarkable trends in breast cancer incidence in Norway in the last decades. These trends partially coincide with the introduction of mammography screening in general and the Norwegian Breast Cancer Screening Program in particular. Novelty and impact: This paper evaluates the cost-effectiveness of the NBCSP in terms of mortality reduction and costs for diagnosis and treatment, while taking into account the different possible explanations for these trends.

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Abstract

The Norwegian Breast Cancer Screening Programme (NBCSP) has a nation-wide coverage since 2005. All women aged 50-69 years are invited biennially for mammography screening. We evaluated breast cancer mortality reduction and performed a cost-effectiveness analysis, using our microsimulation model, calibrated to most recent data. The microsimulation model allows for the comparison of mortality and costs between a (hypothetical) situation without screening and a situation with screening. Breast cancer incidence in Norway had a steep increase in the early 1990s. We calibrated the model to simulate this increase and included recent costs for screening, diagnosis and treatment of breast cancer and travel and productivity loss. We estimate a 16% breast cancer mortality reduction for a cohort of women, invited to screening, followed over their complete lifetime. Cost-effectiveness is estimated at NOK 112,162 per QALY gained, when taking only direct medical costs into account (the cost of the buses, examinations, and invitations). We used a 3.5% annual discount rate. Cost-effectiveness estimates are substantially below the threshold of NOK 1,926,366 as recommended by the WHO guidelines. For the Norwegian population, which has been gradually exposed to screening, breast cancer mortality reduction for women exposed to screening is increasing and is estimated to rise to approximately 30% in 2020 for women aged 55-80 years. The NBCSP is a highly cost-effective measure to reduce breast cancer specific mortality. We estimate a breast cancer specific mortality reduction of 16 to 30%, at the cost of 112,162 NOK per QALY gained.

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Introduction

The Norwegian Breast Cancer Screening Program (NBCSP) was initiated in 1996 and gradually expanded to provide nation-wide coverage in 2005.[1] All women aged 50-69 years, based on the Central Population Register, are invited every other year for mammography screening. Breast cancer incidence increased in the early 1990s, as a result of screening, the use of hormone replacement therapy and increasing back ground risk.[2, 3]

The cost-effectiveness of the Norwegian screening program and the achievable breast cancer mortality reduction was reported by Norum and Wang et al. in 1999 and 2001 respectively.[4, 5] Norum used an estimated 30% reduction in breast cancer deaths at the cost of £8,561 (12,971 USD at the exchange rate in 2000) per life year saved. Wang calculated several scenarios at different positive predictive values of the program. At a maximum estimated breast cancer mortality reduction of 20%, the costs were 5,622 USD per life year saved, and at a maximum estimated mortality reduction of 40% the costs were 2,813 USD per life year saved.

The use of mass screening programs for breast cancer has been under debate since 2001, when the Cochrane collaboration first published a systematic review on the topic.[6] Kalager investigated the mortality reduction, by comparing historical groups, based on the staggered implementation of the NBCSP. They found a mortality reduction of only 10%. [7, 8] The focus of the debate is on the estimated breast cancer mortality reduction and the estimated overdiagnosis rate. These estimates vary greatly depending on the analysis chosen to correct for lead time and historical bias, the minimal amount of follow up to allow for full dwell time, and the definition of denominator and numerator[9-11]. Historical bias occurs when incidence rates rise, independent of screening, due to increases in background incidence. Recently the Research Council of Norway reviewed the literature and had several analyses conducted on breast cancer mortality reduction. They found estimates between 7 and 30%. They concluded based on the quality of the studies that a mortality reduction of 20-30% is a reasonable estimate.[12]

In 2008, the Research Council of Norway set up a project to evaluate the NBCSP. “The objective of the research-based evaluation was to investigate whether the NBCSP fulfils its intentions and purpose to estimate.”[12] This study was done as a part of this project. The council concluded that “The estimates indicate that the Norwegian program performs on average at the level that could be expected from the majority of previous reviews of the mammography screening trials.” This is in line with the conclusions of the International Agency for Research on Cancer, as published in their handbook.[13]

The aim of the study is to estimate the breast cancer mortality reduction due to screening and to calculate cost-effectiveness in the NBCSP. We established trends in breast cancer mortality, using joinpoint analysis, and simulated the NBCSP using microsimulation to estimate expected mortality reduction as a result of screening, and calculate cost-effectiveness by QALY gained for women invited to screening, using direct and indirect costs of screening and treatment.

Materials and Methods

Joinpoint analysis

Data on breast cancer mortality were obtained from NORDCAN.[14] Breast cancer mortality was given as a crude rate and calculated by year. We evaluated breast cancer mortality trends with joinpoint analysis, with the tool provided on the Surveillance research website of the National Cancer Institute.[15] We analysed breast cancer mortality in women aged 55-80 and 0-100 years in the years 1984-2011, and allowed for a maximal of 5 joinpoints.

Model description

The MIcro-simulation SCreening ANalysis (MISCAN) model simulates a female population by simulating individual life histories from birth to death.[16-18] The age-composition of the study population was determined by calibrating the model with the birth table and life table from Statistics Norway from 2005. Each woman has a probability of an onset of breast cancer, based on incidence rate, which we obtained from the Cancer Registry of Norway. The first transition from disease free to preclinical disease is dependent on the onset. Each preclinical disease stage has two possibilities: the disease can be clinically detected or the disease can have a transition from the first preclinical disease state to the next preclinical disease state. Preclinical ductal carcinoma in situ (DCIS) can also regress back to normal. Progression of breast cancer is modelled in a pseudo Markov transition model (Figure 1). In the model any woman can only develop breast cancer once in her life history. Treatment is implemented in the model based on data from the Dutch screening organisations and the Eindhoven Cancer Registry.[19, 20] Early detection has an improved prognosis and therefore reduced mortality. Breast cancer mortality is stage-dependent and based on the data from the Swedish breast cancer screening trials.[21, 22] Screening is superimposed on the natural history. Data from the Cancer Registry of Norway on coverage and attendance, by age (we used five year age groups), year (1990-2010), and stage for the whole country were used to model screening attendance by age and year.

We performed two runs; one population run, based on the Norwegian composition of the population in 2005 (used to estimate current and future breast cancer mortality reduction in the population), and a cohort run, based on an imaginary cohort of 10,000,000 women all born in 1955, with complete follow-up to 2055. The model assumes all women die at the age of 100 years at the latest. In the cohort run we only included the NBCSP, and not opportunistic screening for the cost-effectiveness analysis. All output used in the cost-effectiveness analysis is from the cohort run.

Additional data

Screening outside the NBCSP was included based on the data published by Lynge et al, which took place between 1983 and 2008.[23] HRT-use was implemented as an additional risk. The frequency of HRT use was estimated using data from the Norwegian Prescription Database by ten year age group from 1987 to 2006, from the Norwegian Institute of Public Health.[24] We used a relative risk of 2.2 to have an onset of breast cancer for HRT-users, the relative risk found in previous studies. [3]

Observed incidence rates were higher than the estimates made by the model based on mammography use and HRT-use alone. To allow for the steep increase in breast cancer incidence in Norway we added an additional risk factor of 1.75 in the years 1997-2010 for all women aged 30-100. The additional risk factor creates more onsets and thereby increases breast cancer incidence. This is

similar to the effect of HRT-use, but stronger on a population level. A detailed description of the model can be found in a previous paper, which is in press. [25]

Breast cancer mortality reduction

We compared the observed breast cancer mortality to the estimated mortality rate in the model (Figure 2). To calculate mortality reduction we compared mortality rate in the situation with screening to the mortality rate without screening. We estimated the expected breast cancer mortality reduction from 2014 to 2034.

The survival rate after treatment was modelled on international sources and the Swedish randomized controlled trials. Details are described in the article of de Gelder et al. [20]

Costs and effects

Direct medical costs including costs of screening, diagnostics and treatment were used in this analysis. The direct non-medical costs of screening are the costs for travel for screening and follow-up examination, and the indirect costs are the costs as a result of productivity loss (societal perspective). All of these costs were obtained from the University of Oslo.[26]

The cost of screening was calculated by multiplying the number of visits with the average screening costs. The average costs per woman attending screening are 812 NOK (83.72 Euro), when only taking direct medical costs into account, or 1,262 NOK (130.11 Euro) when also taking direct non-medical costs and indirect costs (productivity loss) into account. [26] The number of false positives was calculated using the positive predictive value of screening. This is 12.5% in Norway in the years 1996-2005; for every screen detected cancer, 8 women were evaluated after a recall.[27]

To calculate the cost of a diagnosis for a woman who has not been screened we calculated the number of women examined per diagnosis. Positive predictive value of a diagnostic mammography is 59%.

[28] We used the number of false positives as a measure for the number of women undergoing a diagnostic procedure following a diagnostic mammography. The detection rate for symptomatic women is 10.3/1,000 examinations.[29]

The costs for treatment according to stage were provided by the University of Oslo.[30] The costs are shown in Table 1. The initial costs are the costs in the first 6 months since diagnosis. If a woman survives she will have continuous care up to 10.5 years after diagnosis. If she dies of breast cancer she will have six months of terminal costs. If she dies of other causes within 10 years since diagnosis, she will have continuous care up to her death.Treatment costs were given by disease stage: DCIS, TNM I, TNM II, TNM III, and TNM IV; and in three time frames: initial treatment, for the first six months since a diagnosis; continuous care, from the seventh month up to ten years and six months since diagnosis; and terminal care, the last six months prior to death from breast cancer. The probability of receiving a certain treatment was based on data from the Norwegian Cancer Register.

Women who died of breast cancer within six months since their diagnosis were assumed to only have terminal costs. Women who died of breast cancer between 6 months and ten years since their diagnosis were assumed to have initial costs, some continuous care costs, and terminal costs.

Women who died of breast cancer after 10.5 years were assumed to have initial costs, all continuous care costs, and terminal costs.

We assumed that women who died from other causes did not receive terminal breast cancer care. If these women died within the first six months since their diagnosis, we calculated the cost of treatment for the time they were alive since their diagnosis. The treatment costs for a woman who died from other causes after six months since diagnosis was calculated by six months of initial care and continuous care for the time they were alive in the period of continuous care.

Because we had costs per timeframe, we used model output on cause of death, number of deaths in the first six months after diagnosis, between six months and 10.5 years after diagnosis, and after 10.5 years after diagnosis. We also used number of diagnosis per stage, the life years in each timeframe and number of visits.

The effect of screening was estimated by calculating the life years gained (LYG). We calculated quality adjusted life years (QALYs) by adjusting life years with utilities, such as described by Haes et al.[31] We adjusted for the screening, diagnostic phase, therapy, disease free survival, terminal illness and palliative care. Based on the data from the Norwegian Cancer Registry we calculated the probability of a certain event by disease stage, and multiplied the number of life years in every disease stage with the probability and the utility. The summarized utility loss and quality adjustment are in table 2 (Table 2). From left to right the columns list the utility loss based on the publication of Haes, the number of events per 100,000 women years in the situation without screening, and in the situation with screening, the difference between these two situations, the average duration associated with an event, the resulting quality of life adjustment, the total of life years gained in the situation with screening, the total loss of quality of life, and finally the quality of life adjusted life years gained. Costs and effects were calculated for a cohort of 10 million women born in 1955 and followed until death. Both effects and costs were discounted at 3.5% per year to take time preference into account (NICE).[32] The cost-effectiveness ratio (CER), costs per QALY compared to a situation without screening, was calculated.

Results

Joinpoint analysis

Crude breast cancer mortality rate for women aged 55-80 rose steadily from 1981 to 1995. In 1995 a significant difference in the annual percent change was found, when breast cancer mortality rates began to drop, coinciding with the start of breast cancer screening, but five years after opportunistic screening came up. For the age group 0 to 100 breast cancer mortality was already declining from 1984, in 1994 a significant percentage change was seen, and from 1994 breast cancer mortality decreased more rapidly (Figure 2).

Mortality

Based on a population run (i.e. a realistic representation of the population of Norway, gradually exposed to screening) of women aged 55-80 in the years 2014-2034. Because we anticipate that mortality will decrease up to 2022 we chose a long follow-up. 2014 was chosen because the program had been nation-wide from 2004, so in 2014 it had been in place for 10 years, and there was a steady situation. Breast cancer mortality reduction was expected to increase up to the year 2022. The reduction was maximally 30%, compared to a situation without screening. The model underestimates the total mortality reduction (Figure 2).

Cost-effectiveness analysis

Results are given per 100,000 women (Table 3). False positive rate was calculated by multiplying the number of clinically diagnosed cancers with 1.7, and the screen detected cancers with 8. QALY gained was calculated as shown in table 2. Breast cancer mortality reduction was calculated by calculating the difference between breast cancer deaths without screening and with screening, divided by breast cancer deaths without screening. Number needed to screen is the number of breast cancer deaths prevented divided by the number of screening test.

Direct medical costs of screening was calculated by multiplying the number of screening test by 812.[26] Total costs of screening was calculated by multiplying the number of screening test by 1,262.[26]

Costs of diagnosis is derived from the number of diagnosed cancers and false positives multiplied by 2,869, which is the cost of a recall examination.[26]

The calculation for the costs of treatment is explained in the materials and methods section.

Total costs are the added costs of screening, based on direct medical costs of screening, diagnosis and treatment; and total costs of screening, based on total costs of screening, diagnosis and treatment.

The incremental costs are the difference between the total costs with screening and total costs without screening, based on direct medical costs of screening; and the difference between the total costs with screening and total costs without screening, based on total costs of screening.

Cost-effectiveness was calculated using discounted output from the model (discount rate 3.5% per year): Incremental costs based on direct medical costs of screening (284,890,930) divided by QALY

gained (2,540); and incremental costs based on total costs of screening (481,474,780) divided by QALY gained (2,540).

Our model showed a life-time breast cancer mortality reduction of 16% for the entire cohort, with a number needed to screen of 1,470. We estimated 399 breast cancer deaths prevented, with approximately 10 deaths prevented annually in the age group 49-100, with a maximum number of 20 deaths prevented in the year 2027 when the cohort is 72 years. The number of QALYs gained was 6,085 /100,000, the number of life-years gained was 6,390, there was a loss of 5% when calculating QALYs from life-years.

Cost effectiveness was NOK 112,162 for only direct medical costs and NOK 189,557 for all costs.

Discussion

The NBCSP is cost-effective even when taking direct non-medical and indirect costs of screening into account, assuming a threshold for cost-effectiveness of 3 times the gross domestic product (GDP) per capita (WHO guideline).[33] The GDP per capita in Norway was USD 99,636 in 2013 (The World Bank).[34] The exchange rate from USD to NOK on 02/10/2014 was 6.44468. The cost-effectiveness threshold thus is 99,636 x 6.44468 x 3 = 1,926,366 NOK.

The costs of screening in Norway are relatively high compared to other countries; this is probably due to the fact that it is a geographically vast country with a relatively small population. The country has a very high welfare level, which results in a high cost-effectiveness threshold. A recent report in the NEJM advocated the use of a threshold of 100,000 USD (NOK 644,680).[35] Therefore, the NBCSP is also cost-effective when using this threshold. This analysis predicts that breast cancer screening reduces breast cancer mortality at a cost-effective price.

With regards to costs of the program in terms of overdiagnosis, the independent UK review found an estimate of overdiagnosis of 11% acceptable, we found 2-3% overdiagnosis in a separate analysis.[12, 36]

Norum found a lower estimate of cost-effectiveness of NOK 89,325 (calculated from the published £8,561 with the current exchange rate of 10.4339).[4] At the time of their analysis no data on breast cancer mortality reduction was available and they assumed a breast cancer mortality reduction of 30%, accordant with the aim of the Norwegian Mammography Project. The results are difficult to compare, since they discounted by 5% per year and they did not adjust for quality of life.[4]

The cost-effectiveness analysis of Wang estimated much lower costs per life-year gained (NOK 24,167, calculated from the published USD 3,750 with the current exchange rate). These costs did not include treatment costs and did not adjust for quality of life.[5] They discounted with 4.5% per year.[1]

Cost-effectiveness is not the only argument to implement or continue a screening programme. There is a need for public support based on proper information on harms and benefits. We estimated breast cancer mortality reduction of up to 30% and an acceptable overdiagnosis rate.[12]

Crude breast cancer mortality rate of women of all ages had a sharp decline in 1994, which cannot be satisfactorily explained by mammography use. The drop in mortality reduction is too soon after the introduction of mammography outside the NBCSP and too large, given the fact that also opportunistic screening has gradually increased, to be the result of opportunistic screening. This decline is probably the result of adjuvant therapy and improvements in overall survival rates, possibly enhanced by the “re-organization of the breast cancer health care system”.[37] In the second half of the 1980s and the first half of the 1990s combined multi-agent chemotherapy and Tamoxifen were being used more frequently.[38] Treatment effects are included in our model. The fact that breast cancer mortality keeps decreasing despite increases in incidence, indicates that over the years following the sharp decline multiple factors have contributed to this decrease.

We found an estimated maximal mortality reduction in 2022 of 30% increasing breast cancer mortality rate for the Norwegian population, gradually having been exposed to screening. This is in line with the estimated breast cancer mortality reduction of approximately 28% found by Weedon-Fekjaer.[39] In the model we used the estimated effects of screening and treatment to establish

mortality reduction. In reality mortality reduction is even greater. Because we do not know what causes the greater reduction in mortality we used a conservative estimate of mortality reduction based on screen effects and treatment effects.

The analysis is based on the outcomes of the MISCAN model. There are some limitations to the model. First the model assumes an increased background risk for breast cancer, which cannot be fully explained.[2, 3, 12] Second we performed analysis on a cohort run. The benefits of a cohort run is that all women in the model are the same age, and that follow up for the entire population is complete. The drawback of a cohort run is that it may overestimate the effects of a program, because in an actual population not all women are exposed to screening at the same age, and follow up is never complete for all women at the same time.

Another limitation of the study is that the data on utilities is from a period when treatment was different from now. Recent figures are not readily available.

In conclusion, we estimate a breast cancer mortality reduction of 16% in women aged 55-80 years, with a projected maximal reduction in 2022 of 30%. The NBCSP is cost-effective in preventing breast cancer specific mortality.

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Table 1. Estimated costs for treatment by disease stage and period.[30]

Initial costs for first 12 months following diagnosis:

	DCIS	TNM1	TNM2	TNM3	TNM4
Mean:	70,642.63	106,868.50	214,542.19	263,548.04	247,895.15
95% CI:	65,000-77,000	102,000-111,000	205,000-224,000	232,000-294,000	200,000-301,000
SE:	3	2.3	4.8	16	26

Continuous care per two months following the first 12 months after diagnosis:

	DCIS	TNM1	TNM2	TNM3	TNM4
Mean:	1,034.52	1,643.52	3,125.05	4,347.90	9,111.90
95% CI:	837-1,240	1,481-1,814	2,862-3,389	3,022-5,849	6,945-11,539
SE:	102	84	133	721	1.158

Terminal costs (last 6 months before death):

	DCIS	TNM1	TNM2	TNM3	TNM4
Mean:	174,504.20	133,712.30	168,846.80	138,925.30	182,511.20
95% CI:	124,000-234,000	106,000-161,000	153,000-186,000	97,000-181,000	142,000-226,000
SE:	28	14	9	21	21

Table 2. Utilities and quality adjustment. LY: life years, QALY: quality adjusted life year.

Health stage	Utility loss	No screening	Screening	Difference	Duration §	Quality adjustment	LY gained	Quality of life lost	QALY gained
Per 100,000 women aged 50 years in 2005 with complete follow-up:									
Screening	0.01		586,555	586,555	0.0962	67.68			
Diagnostic phase	0.11	14,025	14,157	132	0.0192	1.33			
Initial surgery	0.13	9,913	10,000	87	0.1667	1.92			
Initial radiotherapy	0.20	6,815	6,797	-18	0.1667	-0.60			
Initial chemotherapy	0.28	2,367	2,134	-233	0.5000	-32.93			
Initial hormonal therapy	0.18	4,098	3,760	-338	2.0000	-121.80			
Terminal illness	0.71	6,002	5,611	-391	0.0833	-23.18			
Palliative therapy + chemotherapy	0.47	1,554	1,358	-196	0.3333	-30.70			
Palliative therapy + radiotherapy	0.42	4,156	3,861	-296	0.0833	-10.32			
Palliative therapy + surgical therapy	0.38	5,973	5,582	-391	0.0962	-14.40			
Palliative therapy + hormonal therapy	0.34	2,646	2,346	-300	1.1667	-118.05			
							6,390.00	304.95	6,085.05
In life years:									
Disease free 2m-1y mastectomy	0.16	84	78	-6	0.8333	-0.80			
Disease free 2m-1y breast conserving	0.09	149	139	-10	0.8333	-0.72			
In life years:									
Disease free >1y mastectomy	0.05	49,674	53,309	3,636	1.0000	192.68			
Disease free >1y breast conserving	0.04	90,056	99,927	9,871	1.0000	394.83			

Table 3. Effects, costs and breast cancer mortality reduction per 100,000 women, aged 49 in 2004, with complete follow-up (to 2055), with screening in the NBCSP. QALY: quality adjusted life years. Only the incremental costs/QALY gained are given with a 3.5% annual discount. NOK: Norwegian Krones.

	Without screening	With screening
Screening tests/100,000	-	586,555
Health effects		
Cancer diagnosed	9,968	10,062
Screen detected cancers	-	2,323
False positives	16,945	31,743
Breast cancer deaths	2,425	2,026
QALY gained	-	6,085
Mortality reduction	-	16%
Number needed to screen	-	1,470
Costs (in NOK x1,000)		
Direct medical costs of screening	-	476,283
Total costs of screening	-	740,232
Diagnosis	77,214	119,937
Treatment	2,515,048	2,324,794
Total costs based on direct medical costs of screening	2,592,263	2,921,013
Total costs based on total costs of screening		3,184,963
Incremental costs based on direct medical costs of screening	-	328,750,348
Incremental costs based on total costs of screening		592,700,098
Cost-effectiveness		
Direct medical costs of screening		
Incremental costs/QALY gained, discounted in NOK		112,162
Total costs of screening		
Incremental costs/QALY gained, discounted in NOK		189,557

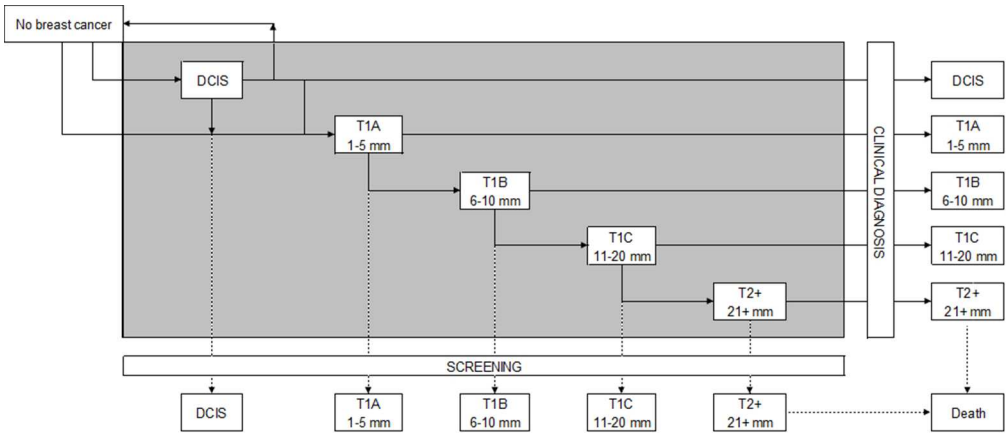

Figure 1. Graphic presentation of the transitions in the MISCAN model. DCIS; ductal carcinoma in situ, T1A; invasive breast cancer with a diameter of 1-5 mm., T1B; invasive breast cancer with a diameter of 6-10 mm.,T1c; invasive breast cancer with a diameter of 11-20mm., T2+; invasive breast cancer with a diameter greater than 21 mm. Every woman has a chance of having an onset of breast cancer. This may be a DCIS or a T1A tumour. From DCIS she may regress back to not having breast cancer, be clinically or screen-detected or progress to T1A. The possibility of regression exists only in the DCIS state.

347x148mm (72 x 72 DPI)

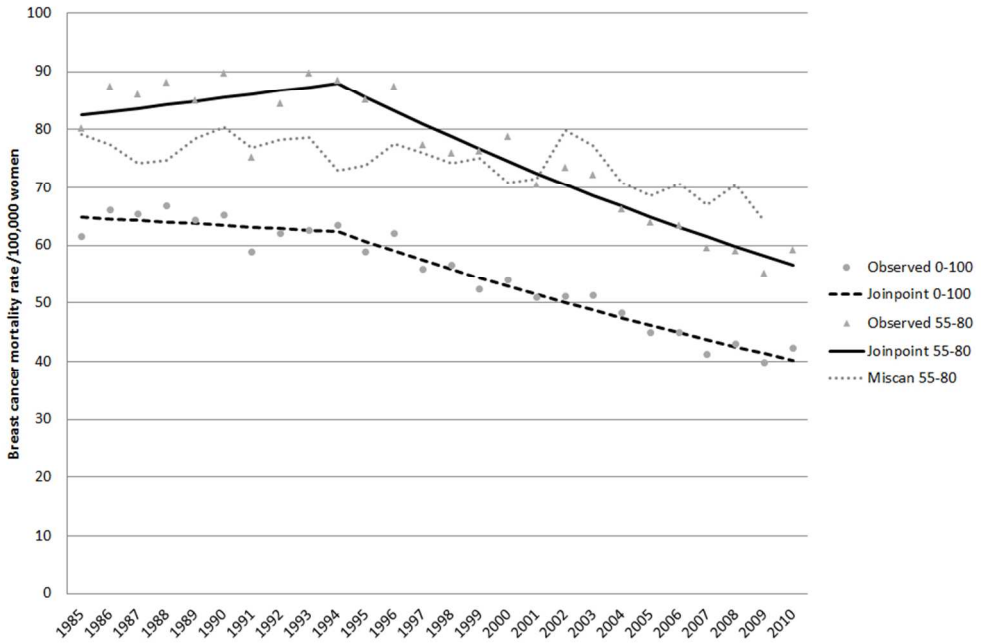

Figure 2. Joinpoint analysis and MISCAN model estimate of breast cancer specific mortality rate per 100,000 women aged 0-100 and 55-80.

344x225mm (72 x 72 DPI)