Chapter 2

Effect of implementation of the mass breast cancer screening programme in older women in the Netherlands

Population-based study

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Abstract

Objective

It remains unclear whether mass breast cancer screening has a beneficial effect in older women. In the Netherlands, the upper age limit of the breast cancer screening program was extended from 69 to 75 years in 1998. If a screening program is effective, it can be expected that the incidence of early stage tumours increases, while the incidence of advanced stage tumours decreases. The aim of this study was to assess the incidence of early stage and advanced stage breast cancer before and after the implementation of mass screening in women aged 70-75 years in the Netherlands.

Design

Prospective nationwide population-based study in the Netherlands between 1995 and 2011.

Setting and participants

National cancer registry. Patients aged 70-75 years who were diagnosed between 1995 and 2011 with invasive or in situ breast cancer were selected from The Netherlands Cancer Registry (n=25,414). Incidence rates were calculated using population data from Statistics Netherlands.

Main outcome measure

Incidence rates of early stage (stage I, II or in situ) and advanced stage (stage III and IV) breast cancer before and after implementation of screening. Hypotheses were formulated before data collection.

Results

The incidence of early stage tumours strongly increased after extension of implementation of screening (248.7 cases per 100,000 women before screening up to 362.9 cases per 100,000 women after implementation of screening, incidence rate ratio (IRR) 1.46 (1.40 to 1.52) $p<0.001$). However, the incidence of advanced stage breast cancers decreased to a far lesser extent (58.6 cases per 100,000 women before screening to 51.8 cases per 100,000 women after implementation of screening, IRR 0.88 (0.81 to 0.97), $p <0.001$).

Conclusions

The extension of the upper age limit to 75 years has only led to a small decrease of advanced stage breast cancer, while the incidence of early stage tumours has strongly increased.

Introduction

Breast cancer is the largest contributor to cancer incidence and cancer mortality in women worldwide[1]. Due to the ageing of Western societies, the proportion of older women with breast cancer will increase in upcoming years[2]. Older breast cancer patients often suffer from comorbidity and functional limitations[3;4], resulting in an increased risk of adverse outcomes and side effects of breast cancer treatment[5-7]. Also, previous studies have shown that breast cancer-specific mortality increases with age[8]. It has been assumed that diagnosis at an earlier stage through screening programs could improve breast cancer prognosis, and may therefore be beneficial for older women[9]. Several current guidelines recommend breast cancer screening with mammography for women aged up to 75 years[10;11], and in the Netherlands, the upper age limit of the mass screening program was extended from 69 to 75 years in 1998[12].

However, there is no strong evidence for beneficial effects of breast cancer screening in older women, as randomized trials on breast cancer screening rarely included women over the age of 69. Although trial data on screening in older women are lacking, there have been some observational studies that hint at a beneficial effect of screening in older women on mortality rates[13-15]. However, several possibly confounding factors might influence outcomes of population-based studies that investigated mortality rates after screening in the older population. For example, it is known that interval-detected tumours are generally more aggressive than screen-detected tumours[16], which can result in bias. Furthermore, comorbidity and poor physical functioning in older women lead to poor attendance to the screening program, and can therefore result in biased outcomes of these observational studies[17].

Another, more appropriate way to investigate the efficacy of a screening program in population-based data, is to investigate the incidence rates of advanced stage cancers after implementation of a screening program[18]. If a screening program is effective, it can be expected that the incidence of advanced stage cancer decreases, while the early stage breast cancer increases[18]. This approach does not suffer from the confounding factors that are often present in observational studies that study the effects of screening on mortality rates[18].

Therefore, the aim of this study was to assess the incidence of early stage and advanced stage breast cancer before and after implementation of the mass screening program in women aged 70-75 years in the Netherlands.

Methods

Study population

All patients aged 70-75 with invasive and in situ breast cancer who were diagnosed between 1995 and 2011 were selected from the Netherlands Cancer Registry. The Netherlands Cancer Registry contains information of all newly diagnosed malignancies in the Netherlands. Patients are detected through the central pathology database. Trained personnel review the charts of all patients with a pathologically confirmed malignancy. In order to compare changes in incidence rates with incidence rates of breast cancer in the Dutch population in general, the incidence of breast cancer in patients aged 76-80 years was additionally assessed, as they did not undergo routine screening and could therefore be used as a reference population.

Since the Netherlands Cancer Registry registers anonymous population data, no written informed consent was required. The research ethics committee of the Netherlands Cancer Registry approved the research protocol.

Tumour stage was described by the Tumour-Node-Metastasis (TNM)-classification at year of diagnosis. Pathological T, N, and M stage were used. If pathological stage was missing, clinical stage was used for the analyses. Early tumour stage was defined as stage I, stage II or in situ disease. Advanced tumour stage was defined as stage III or IV disease.

Statistical analyses

For all analyses, Stata version 10.0 was used. All statistical tests were two-sided and p-values < 0.05 were stated to be statistically significant.

To calculate national incidence rates, population data from Statistics Netherlands were used[19]. Person-years were derived for each year by using the number of women living in the Netherlands. National incidence rates were calculated by dividing the number of incident tumours by the number of female residents of the same age in the Netherlands in the year of diagnosis. Time trends in the incidence of different tumour stages were presented graphically with corresponding 95% Confidence Intervals (CI's).

The screening program was implemented in the Netherlands between 1998 and 2001. In these four years, all eligible women were invited for mammography screening[20]. Hence, the included years were divided into three time-periods: a period before screening (1995-1997), a screening uptake period of five years in order to prevent bias due to a too short definition of this period (1998-2002), and a period after implementation of screening (2003-2011, defined as "active

screening"). We assessed the changes in incidence rates over these three periods by calculating Incidence Rate Ratio's (IRR's) using Poisson regression analyses. Additionally, we assessed the change in incidence rates over time in patients aged 76-80 years, in order to take changes in incidence rates in the general older breast cancer population independent of screening into account. By dividing the IRR of patients aged 70-75 and the IRR in the reference population (76-80 years), we calculated the ratio of these two IRR's with corresponding 95% CI's.

Next, we calculated the ratio between the observed changes in early stage and advanced stage breast cancer in patients aged 70-75 years, in order to estimate the number of "extra" early stage tumours that were found per "prevented" advanced stage tumour.

Sensitivity analyses

We performed several sensitivity analyses. First, we both shortened and lengthened the screening uptake period (1998-2001 and 1998-2003 respectively), in order to assess the impact of our definition of the screening uptake period on the outcomes. Second, we excluded

Table 1 *Characteristics of women diagnosed with breast cancer in the Netherlands during implementation of screening in women aged 70-75 years, presented per age-group.*

	Pre-screening (1995-1997)	**Screening uptake (1998-2002)**	**Implemented screening (2003-2011)**
	N (%)	N (%)	N (%)
70-75 years (n=25,414)			
Stage at diagnosis			
in situ	156 (4.6)	718 (9.1)	1,477 (10.5)
I	986 (28.8)	3,346 (42.3)	6,824 (48.5)
II	1,632 (47.6)	2,994 (37.8)	4,015 (28.5)
III	371 (10.8)	472 (6.0)	1,206 (8.6)
IV	283 (8.3)	381 (4.8)	553 (3.9)
Source population (person-years)	1,115,508	1,842,139	3,394,055
76-80 years (n=13,028)			
Stage at diagnosis			
in situ	121(5.5)	207 (5.0)	436 (6.5)
I	584 (26.6)	1,058 (25.4)	1,851 (27.7)
II	1,038 (47.3)	2,013 (48.4)	2,781 (41.7)
III	243 (11.1)	434 (10.4)	1,041 (15.2)
IV	210 (9.6)	449 (10.8)	589 (8.8)
Source population (person-years)	686,507	1,282,037	2,386,061

all patients with stage II disease from the analyses, in order to assess the impact of different definitions of early stage breast cancer. Finally, we performed the analyses with year of diagnosis as a continuous variable (starting from 1998) instead of using the three periods as described above, in order to make sure that we would not miss small changes in incidence rates due to loss of power due to the use of three time-periods.

Results

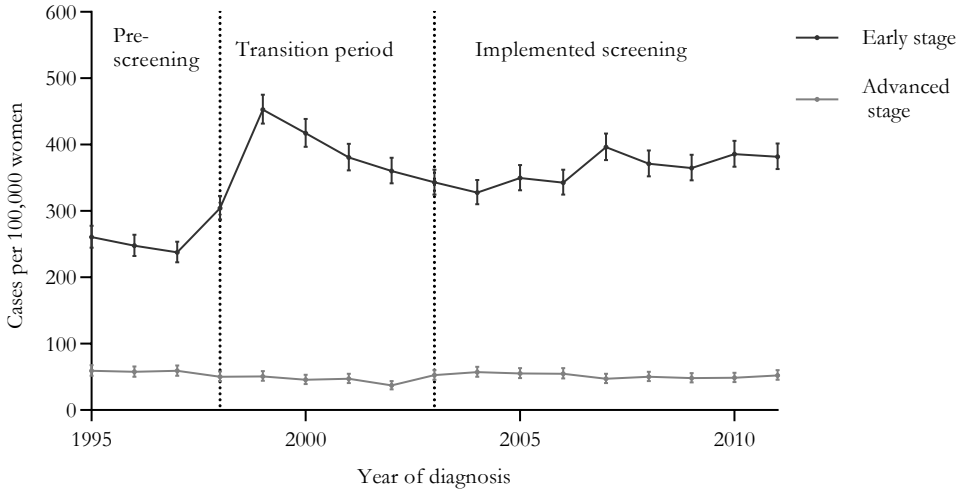
Patient characteristics

Overall, 25,414 patients aged 70-75 and 13,028 patients aged 76-80 were included from the Dutch Cancer Registry (Table 1). The majority of patients were diagnosed with stage I or stage II breast cancer in both age-groups.

Time trends in tumour stages

Figure 1 shows the incidence rates of different tumour stages in patients aged 70-75 before and during active screening. Corresponding Poisson regression analyses are presented in Table 2. The incidence of early stage breast cancer strongly increased after extension of the upper age limit to 75 in 1998 and decreased slightly after 2002, after which the increase of early stage disease again continued (248.7 cases per 100,000 women before screening up to 362.9 cases per 100,000 women during active screening, IRR 1.46, 95% Confidence Interval (CI) 1.40-1.52, p<0.001). This increase was explained by a strong increase in the incidence of

Figure 1 *Breast cancer incidence incidence in patients aged 70-75 years*



DCIS and Stage I tumours; the incidence of DCIS and stage 1 tumours (combined) more than doubled from 107 per 100,000 women in 1995 to 274 per 100,000 women in 2011. The increase in incidence rate was not accompanied by a similar decline in stage 2 tumours, as the incidence of stage 2 tumours declined from 154 per 100,000 women in 1995 to 108 per 100,000 women in 2011.

Although the incidence of advanced stage breast cancers did significantly decrease, the absolute decrease was small (58.6 cases per 100,000 women before screening to 51.8 cases per 100,000 women in the active screening period, IRR 0.88, 95% CI 0.81-0.97, p <0.001).

In women aged 76-80, the incidence of early stage breast cancer slightly decreased (253.9 cases per 100,000 women before 1998 to 212.4 cases per 100,000 women after 2003, IRR 0.84, 95% CI 0.79-0.88, p<0.001). In contrast, the incidence rate of advanced stage breast cancer did not significantly change in the evaluated time frame (66.0 cases per 100,000 women before 1998 to 67.2 cases per 100,000 women after 2003, IRR 1.02, 95% CI 0.92-1.13, p=0.74).

Table 2 *Breast cancer incidence before and after implementation of screening in the Netherlands*

	70-75 years				**76-80 years**				**Relative ratio**	
	Incidence	IRR_{70-75}	95% CI	p-value	Incidence	IRR_{76-80}	95% CI	p-value	IRR_{70-75} / IRR_{76-80}	95% CI
Early stage										
Period										
Pre-screening (1995-1997)	248.7	1.0 (ref)		<0.001	253.9	1.0 (ref)		<0.001	1.0	
Screening uptake (1998-2002)	383.1	1.54	(1.47-1.61)	<0.001	255.7	1.01	(0.95-1.06)	0.81	1.52	(1.41-1.65)
Implemented screening (2003-2011)	362.9	1.46	(1.40-1.52)	<0.001	212.4	0.84	(0.79-0.88)	<0.001	1.73	(1.61-1.87)
Advanced stage										
Period										
Pre-screening (1995-1997)	58.6	1.0 (ref)		<0.001	66.0	1.0 (ref)		0.73	1.0	
Transition (1998-2002)	46.3	0.79	(0.71-0.87)	<0.001	68.9	1.04	(0.94-1.17)	0.46	0.76	(0.66-0.88)
Implemented screening (2003-2011)	51.8	0.88	(0.81-0.97)	0.007	67.2	1.02	(0.92-1.13)	0.74	0.86	(0.76-0.98)

Incidences represent cases per 100,000 women per year; CI=confidence interval

Consequently, the relative ratios of the IRR's in both age-groups were almost similar to the IRR's in patients aged 70-75 years (Table 2).

Ratio between early stage and advanced stage tumours

First, we calculated the ratio between early stage and advanced stage tumours. The incidence rate of early stage tumours increased by 114.2 cases per 100,000 women (362.9-248.7), while the incidence rate of advanced stage tumours decreased by 6.8 cases per 100,000 women (58.6-51.8). Hence, the ratio of advanced and early stage tumours was 114.2/6.8=19.7 cases per 100,000 women per year, which means that for every advanced stage tumour that was prevented by screening, 19.7 "extra" early stage tumours were diagnosed.

Sensitivity analyses

Additional sensitivity analyses are presented in suppl. Table 1. Changing the length of screening uptake period did not alter the results. However, the exclusion of patients with stage II breast cancer resulted in a stronger increase of early stage breast cancer in patients aged 70-75 years (IRR 2.39, 95% CI 2.25-2.54, $p<0.001$ during active screening compared to the pre-screening period). Finally, by analysing the year of diagnosis as a continuous variable, starting from 1998, we observed no change in incidence rates over time (IRR 1.00, 95% CI 1.00-1.00, $p<0.88$ per year for early stage tumours, and IRR 1.00, 95% CI 1.00-1.01, $p=0.37$ per year for advanced stage tumours).

Discussion

The major finding of this study is that the extension of the upper age limit of the mass screening program in breast cancer in the Netherlands to 75 years has not resulted in a strong decrease of advanced breast cancer incidence, while the incidence of early stage breast cancer strongly increased in patients aged 70-75.

The main strength of this study is the detailed and well-registered information of a very large number of unselected older breast cancer patients over a long period of time from a national cancer registry. This made it possible to evaluate time trends of incidence rates of tumour stages after extension of the screening program of the age-limit to 75 years in 1998. Using this methodology, we were able to assess the benefits of screening older women without inducing several forms of bias. Furthermore, we were able to adjust the observed changes in incidence rates for changes in incidence rates in the general population using a cohort of women aged 76-80 years during the same time period. Also, the breast cancer screening program in

the Netherlands is accessible for all citizens, and the attendance rate was as high as 73% in women aged 70-75 years between 1998 to 2007[20]. This study also has its limitations. Possibly, the length of follow-up after implementation of the screening program was not long enough to result in a decrease in incidence of advanced tumours. However, a previous study by Esserman et. al assessed the incidence rates of localized, regional and metastatic breast cancer after implementation of screening in the United States. A (small) decline in metastatic breast cancer occurred around 3 years after implementation of screening[18]. Hence, it is likely that any decline in diagnosis of advanced stage tumours would have occurred after three years, and we extended this so-called screening uptake period to five years to make sure that we did not miss a reduction due to the definition of our screening uptake period. In addition, we lengthened the period to six years in our sensitivity analyses, which did not alter the results. Furthermore, the incidence rate of early stage breast cancer in the age-group 76-80 years was likely to be influenced by breast cancer screening as well, as early stage tumours that were diagnosed in patients aged 75 years were not diagnosed the year these patients turned 76. Finally, it may appear strange that the incidence rates of both early and advanced stage tumours did not significantly change over time when the year of diagnosis was handled as a continuous variable. This can most likely be explained by the fact that the observed changes in incidence rates were not linear as shown in Figure 1.

Current guidelines on breast cancer screening are mostly based on randomized clinical trials that were performed in the seventies and eighties of the twentieth century[9]. However, these trials rarely included patients over the age of 70, and no patients over the age of 74 were included[9]. Therefore, we can only compare our findings with previous observational studies. Although there have been some previous observational studies that investigated the incidence of advanced stage cancer after implementation of a breast cancer screening program[21;22], unfortunately, these studies did not report specific incidence rates in older women. For example, a recent study evaluated three decades of screening mammography in women aged 40 years and older in the United States, and concluded that screening has only marginally reduced the rate at which women present with advanced cancer[21]. In contrast, a recent study assessed the incidence of advanced breast cancer after implementation of mammography screening in the United States using the same data, but with adjustments for prescreening incidence trends[23]. This study did find a decline in advanced breast cancer incidence. However, it must be noted that it is extremely difficult to adjust for changes in breast cancer incidence using data from another time-frame, as many other circumstances may have changed since that time period and it is therefore unclear if this is a reliable method. Therefore, in the current study we chose to use a control group that did not have access to mammography screening in the same timeframe.

Another previous study that investigated the incidence of advanced stage tumours in the South eastern part of the Netherlands in women aged 40-75 years from 1980 to 2009, found no decrease in advanced stage tumours in women aged 50-75 years[22]. In addition, a systematic review from 2011 evaluated the incidence rates of advanced breast cancer after implementation of mass screening in several European countries. Again, this study concluded that in general, incidence rates of advanced breast cancer did not change much despite 7-15 years good participation in mammographic screening[24]. Finally, a recent Norwegian study showed that the incidence of advanced stage breast cancer in women aged 50-69 did not increase after implementation of mass screening[25]. Hence, our findings are mostly in line with these previous studies that included younger women, and may suggest that the capacity for screening to impact the incidence of advanced breast cancer may be limited.

In contrast, several studies that investigated the effects of the breast cancer screening program on survival, concluded that the screening program contributed to an increase in breast cancer survival rates in the Netherlands[26-28]. These contradicting results can be explained by the fact that studying survival rates as an indicator for the effect of screening programs is notoriously difficult due to several forms of bias that are present in such studies[17]. First, due to increased detection of early stage tumours, possible favourable effects of screening on survival are generally overestimated since a large percentage of early stage screening-detected tumours are indolent, and have an excellent prognosis[18]. Consequently, interval-detected tumours are generally more aggressive[16]. By comparing screen-detected tumours with interval-detected tumours, observed survival differences are often attributed to favourable effects of breast cancer screening, while in fact, the observed survival difference can be (partly) explained by differences in tumour biology. This phenomenon is called length-time bias[29]. Second, lead-time bias is usually present: breast cancer diagnosis is confirmed at an earlier stage, which means that patients live longer knowing that they have breast cancer while the actual cancer survival is not higher[29]. And third, women who attend to a screening program are generally healthier[30-32], which leads to a self-selection bias. This was demonstrated in a recent study by Badgwell et. al, which concluded that patients aged 80 years and older with a screen-detected breast cancer had a lower a risk of breast-cancer mortality compared to non-screen detected patients of similar age, but also had a lower risk of mortality due to other causes than breast cancer. This suggests that the results were strongly biased by the fact that healthier women more often attend to the mass screening program[30].

Due to these forms of bias, several studies state that investigating the effects of the screening program on incidence rates of advanced tumours in population-based studies is the most appropriate way to study its benefits[18;21;33]. Esserman et. al proposed three hypothetical

scenarios after implementation of a breast cancer screening program in the overall population, independent of age[18]. In the most ideal scenario, the incidence of early stage tumours increases, while the incidence of advanced stage tumours decreases and the total number of cases remains equal. In the worst case scenario, the incidence of early stage tumours increase without a decrease of advanced stage tumours. The third, intermediate case scenario is between these two scenarios. Comparing the results of our study with these scenarios, it mostly resembles either the intermediate case scenario or even the worst case scenario according to Esserman et al, as the strong decrease in advanced stage breast cancer that should be observed in a successful screening program stayed absent in our data. Since we have shown that each "prevented" advanced stage tumour resulted in 19.7 "extra" and therefore overdiagnosed early stage tumours, this implies that mass screening in women aged 70-75 leads to a considerable proportion of overdiagnosis.

Overdiagnosis and overtreatment could have a great impact on quality of life and physical function of older breast cancer patients, as they are at increased risk of adverse outcomes of breast cancer treatment[5-7]. Consequently, unfavourable effects of screening may outweigh the benefits from a certain age[12]. Moreover, the additional costs of treating overdiagnosed tumours could result in a tremendous increase in health expenditure due to the screening program, while no actual health benefits are being obtained. Interestingly, the NHS Breast Cancer Screening Program in the UK are currently undertaking a large randomized Controlled Trial in patients aged 71-73 years old in which an age extension from 70 to 73 years is randomly phased-in, allowing the investigators to evaluate the effects of screening on breast cancer incidence and mortality[34]. Until results of this trial become available, we propose that routine breast cancer screening in women over the age of 70 should not be performed on a large scale. Instead, the harms and benefits of screening should be weighed on a personalized basis, taking remaining life expectancy, breast cancer risk, functional status and patients' preferences into account[35;36].

In conclusion, the extension of the upper age limit to 75 years has not led to a strong decrease in incidence of advanced stage breast cancer, while the incidence of early stage tumours has strongly increased. This implies that the effect of the screening program in older women is limited and may lead to overdiagnosis. Therefore, we propose that instead of using mass screening, the decision to participate in the screening program should be personalized based on remaining life expectancy, breast cancer risk, functional status and patients' preferences.

Supplemental Table 1 *Sensitivity analyse*

	70-75 years				76-80 years				Relative ratio	
	Inci-dence	IRR $_{70-75}$	95% C.I.	p-value	Inci-dence	IRR $_{76-80}$	95% C.I.	p-value	IRR $_{70-75}$ / IRR $_{76-80}$	95% CI
Shortened transition period										
Early stage										
Period										
Pre-screening (1995-1997)	248.7	1.0 (ref)		<0.001	253.9	1.0 (ref)		<0.001	1.0	
Transition (1998-2001)	323.0	1.56	(1.49-1.64)	<0.001	258.5	1.02	(0.96-1.08)	0.56	1.53	(1.42-1.65)
Implemented screening (2002-2011)	367.9	1.46	(1.40-1.52)	<0.001	215.6	0.85	(0.80-0.90)	<0.001	1.72	(1.60-1.85)
Advanced stage										
Period										
Pre-screening (1995-1997)	58.6	1.0 (ref)		<0.001	66.0	1.0 (ref)		0.85	1.0	
Transition (1998-2001)	48.6	0.83	(0.75-0.92)	0.001	68.3	1.03	(0.92-1.16)	0.57	0.81	(0.69-0.94)
Implemented screening (2002-2011)	50.4	0.86	(0.79-0.94)	0.001	67.6	1.02	(0.92-1.14)	0.65	0.84	(0.74-0.96)
Lengthened transition period										
Early stage										
Period										
Pre-screening (1995-1997)	248.7	1.0 (ref)		<0.001	253.9	1.0 (ref)		<0.001	1.0	
Transition (1998-2003)	376.4	1.51	(1.45-1.58)	<0.001	248.3	0.98	(0.92-1.03)	0.44	1.54	(1.43-1.66)
Implemented screening (2004-2011)	365.3	1.47	(1.41-1.53)	<0.001	212.4	0.84	(0.79-0.88)	<0.001	1.75	(1.62-1.88)
Advanced stage										
Period										
Pre-screening (1995-1997)	58.6	1.0 (ref)		<0.001	66.0	1.0 (ref)		0.85	1.0	
Transition (1998-2003)	47.4	0.81	(0.73-0.89)	<0.001	69.7	1.06	(0.95-1.18)	0.33	0.76	(0.66-0.89)
Implemented screening (2004-2011)	51.7	0.88	(0.81-0.97)	0.007	66.4	1.01	(0.90-1.12)	0.92	0.87	(0.76-1.00)

Early stage defined as stage 0-1, stage 2 breast cancer excluded										
Early stage										
Period										
Pre-screening (1995-1997)	191.5	1.0 (ref)		<0.001	102.7	1.0 (ref)		0.26	1.0	
Transition (1998-2002)	195.3	2.15	(2.02-2.30)	<0.001	98.7	0.96	(0.88-1.05)	0.40	2.24	(2.01-2.59)
Implemented screening (2003-2011)	248.8	2.39	(2.25-2.54)	<0.001	95.8	0.93	(0.86-1.02)	0.11	2.57	(2.33-2.84)
Advanced stage										
Period										
Pre-screening (1995-1997)	58.6	1.0 (ref)		<0.001	66.0	1.0 (ref)		0.73	1.0	
Transition (1998-2002)	46.3	0.79	(0.71-0.87)	<0.001	68.9	1.04	(0.94-1.17)	0.46	0.76	(0.66-0.88)
Implemented screening (2003-2011)	51.8	0.88	(0.81-0.97)	0.007	67.2	1.02	(0.92-1.13)	0.74	0.86	(0.76-0.99)
IRR per year (continuous, starting from 1998)										
Early stage										
Year of diagnosis		1.00	(1.00-1.00)	0.88		1.00	(1.00-1.00)	0.88	1.00	(1.00-1.00)
Advanced stage										
Year of diagnosis		1.00	(1.0-1.01)	0.37		0.99	(0.98-1.00)	0.17	1.01	(1.00-1.02)
Incidences represent cases per 100,000 women per year; CI=confidence interval										

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