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Impressive time-related influence of the Dutch screening programme on breast cancer incidence and mortality, 1975-2006

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The aim of this study was to assess changes in the trends in breast cancer mortality and incidence from 1975 to 2006 among Dutch women, in relation to the implementation of the national breast cancer screening programme. Screening started in 1989 for women aged 50–69 and was extended to women aged 70–75 years in 1998 (attendance rate approximately >80%). A joinpoint Poisson regression analysis was used to identify significant changes in rates over time. Breast cancer mortality rates increased until 1994 (age group 35–84), but thereafter showed a marked decline of 2.3–2.8% per annum for the age groups 55–64 and 65–74 years, respectively. For the age group of 75–84 years, a decrease started in the year 2001. In women aged 45–54, an early decline in breast cancer mortality rates was noted (1971–1980), which is ongoing from 1992. For all ages, breast cancer incidence rates showed an increase between 1989 and 1993, mainly caused by the age group 50–69, and thereafter, a moderate increase caused by age group 70–74 years. This increase can partly be explained by the introduction of screening. The results indicate an impressive decrease in breast cancer mortality in the age group invited for breast cancer screening, starting to show quite soon after implementation.

Key words: breast cancer screening; trends; mortality; incidence

Worldwide, breast cancer is the most common cancer and the leading cause of death among women with cancer. In Europe, the average age-adjusted (European standard population, ESR) incidence and mortality rates were 94 and 26 per 100,000 women, respectively, in 2006.[1] In The Netherlands, these figures were much higher, with an incidence rate of 128 and a mortality rate of 30 per 100,000 women.

The efficacy of mammographic screening in reduction of breast cancer mortality has been shown in randomized controlled trials.[2,3] Screening also improves outcomes for diagnosed cancers, which are detected earlier and probably treated more effectively.[4,5]

If a screening program is indeed effective, breast cancer mortality in population statistics will be declining for the age groups invited for screening probably about 7–10 years after the start of the program.[6] Furthermore, breast cancer incidence rates are highly sensitive to mass screening, resulting in a transient increase in incidence and a stage shift to earlier stages, microinvasive and *in situ* cancers in the steady state situation.[7]

This study was performed to analyze the changes in breast cancer mortality and incidence over the last 3 decades among Dutch women, taking account of the implementation of the Dutch breast cancer screening program for different age groups.

Material and methods

The Dutch screening program

In 1989, a breast cancer screening program was gradually implemented in The Netherlands, inviting all women aged 50–69 years (formally 49–68; women will be invited for the first time in the year that they become 50, but for evaluation, we considered the age they had on January, *i.e.*, 49 years. Thereafter, they will be invited 9 times, biennially). Coverage of the target population, that is, the percentage of eligible women was annually invited; increased from 11% in 1990, to 26% in 1991, 48% in 1992, 69% in 1993, 77% in 1994, 88% in 1995 and to its full population capacity in 1996. In 1997, the upper age limit was extended to 75 years (coverage age extension: 26% in 1998, 86% in 1999, 91% in 2000 and to full capacity in 2001). In 2005, more than one million women received an invitation to participate in the screening program, and ~900,000 were screened (mean overall attendance rate of 82%).[8]

Materials

Breast cancer deaths and population data according to age and calendar year were obtained from Statistics Netherlands[9] from 1950 to 2006. We obtained the incidence rates for invasive breast cancer from 1975 to 1986 from the *Stg. Medische Registratie*. In 1986, a nationwide population-based cancer register was introduced, which was completed in 1989. Because of the incomplete data in the early days of the cancer registry, we did not include incidence rates from 1987 to 1988 in the trend analysis. For the period 1989–2003, we used data on invasive breast cancer from the National Cancer Registry website.[10] The analysis of incidence by age focuses on women aged 35–49 years (not invited to participate in the program), 50–69 (invited to screening from 1989), 70–74 (invited from 1997) and 75–84 (not invited to screening). Because we expected the maximum effect of the screening program on the breast cancer mortality no sooner than 5 years after the starting age of 50 years, we used the 10-year age group 55–64 years and 2 younger and 2 older 10-year age groups for the analysis of mortality. Age-adjusted rates were calculated for women standardized to the ESR.

Statistical methods

The trends in breast cancer mortality and incidence (at the least) from 1975 to 2005 were analyzed by the joinpoint regression method.[11] In this analysis, series of joined straight lines of the age-adjusted rates on a log scale were fitted. For each line segment, the estimated annual per cent change (EAPC) is calculated, which is based on the slope of the line to describe the linear trends by period. The line segments are joined together at so-called joinpoints, denoting a statistically significant change in the slope. The analysis starts with the minimum number of joinpoints (straight line) and tests whether 1 or more joinpoints (maximum 4) is significantly better and must be added to the model. The overall statistical significance was set at $p < 0.05$. In the final model, each joinpoint (if any) represents a significant change in the trend.

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TABLE I – AGE-ADJUSTED (EUROPEAN STANDARD POPULATION) BREAST CANCER MORTALITY AND INCIDENCE RATES PER 100,000 WOMEN AGED 35–85 IN THE NETHERLANDS

Year	Number of breast cancer deaths	Age-adjusted mortality rate	Number of breast cancers		Age-adjusted incidence rate	
			Invasive	Noninvasive[1]	Invasive	Noninvasive
1975	2,256	69.9	5,557		180.1	
1976	2,241	67.8	5,483		176.4	
1977	2,293	68.9	5,963		188.1	
1978	2,271	67.0	5,655		176.2	
1979	2,420	70.5	5,813		178.2	
1980	2,383	67.9	5,833		177.0	
1981	2,523	70.7	6,121		183.1	
1982	2,552	70.3	6,475		189.1	
1983	2,552	69.9	6,272		180.8	
1984	2,579	68.5	6,595		187.3	
1985	2,667	70.3	6,899		192.6	
1986	2,641	69.4	7,216		200.9	
1987	2,771	71.2	5,763		156.1	
1988	2,828	71.5	6,843		181.9	
1989	2,891	71.6	7,279	350	191.9	9.7
1990	2,868	71.0	7,788	350	202.6	9.7
1991	2,953	71.9	8,138	502	210.0	14.0
1992	2,914	70.4	8,798	651	224.9	17.9
1993	2,961	69.8	9,056	702	230.8	19.2
1994	3,003	70.3	9,353	771	233.2	20.8
1995	2,906	67.0	9,005	821	222.6	21.8
1996	3,007	68.4	9,282	794	225.5	21.0
1997	3,031	67.7	9,361	926	225.3	23.8
1998	2,923	64.6	9,607	991	225.8	24.9
1999	3,085	67.1	10,516	1,039	241.4	25.3
2000	2,873	61.4	10,514	1,125	240.7	26.9
2001	2,884	60.3	10,851	1,113	245.2	26.4
2002	2,883	60.4	10,773	1,043	241.2	24.3
2003	2,819	57.8	10,799	1,085	238.5	25.2
2004	2,760	55.5				
2005	2,726	54.0				
2006	2,742	53.9				

[1]1975–1988 number of noninvasive breast cancers is unknown.

Joinpoint regression analysis (a log-linear Poisson regression model using rate) was performed using the public-use statistical software (version 3.0) from the Surveillance Research Program of the U.S. National Cancer Institute for the analyses of trends.[12]

Results

Table I shows the number of breast cancer deaths, the number of women aged 35–84 with breast cancer and age-adjusted (ESR) mortality and incidence rates in The Netherlands. From 1975 to 2003, the absolute number of women with newly diagnosed invasive breast cancer doubled from 5,557 (*i.e.*, 180.1 per 100,000) to 10,799 (238.5 per 100,000). The number of women with a noninvasive breast cancer increased even more (tripled) in the period of 1989–2003. Between 1975 and 2006, the absolute number of women who died from breast cancer increased from 2,256 to 2,742, respectively. In contrast, the age-adjusted mortality rates declined from 69.9 in 1975 to 53.9 in 2006.

As shown in Figure 1, the adjusted mortality rates had a joinpoint in 1994 with a slight upward trend (EAPC 0.22, 95% Confidence Interval −0.01, 0.44) for the period 1976–1994, followed by a statistically significant steep decline in subsequent years (EAPC −2.32, CI −2.70, −1.94). The joinpoint analysis for the incidence rates of invasive breast cancer revealed 3 patterns; a slight increase in 1975–1989 (EAPC 0.55, CI −0.01, 1.12), a steep increase from 1989–1992 (EAPC 5.24, CI −2.76, 13.90) and a significant slight increase from 1992–2003 (EAPC 0.73, CI 0.22, 1.23).

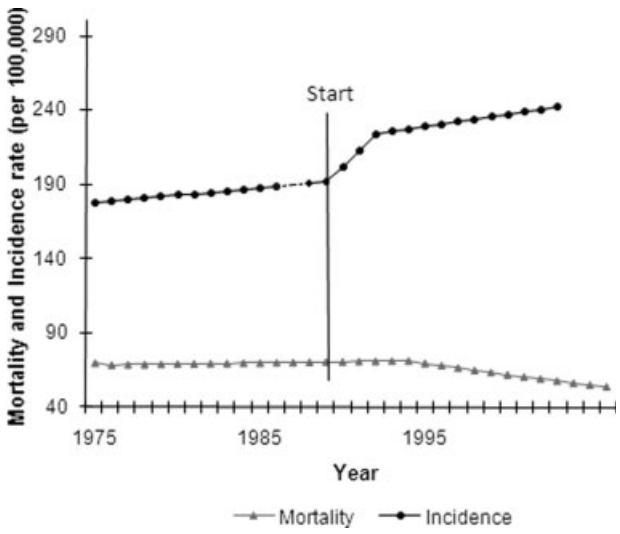

FIGURE 1 – Age-adjusted (European standard population) breast cancer mortality and invasive breast cancer incidence rates per 100,000 women aged 35–84 in The Netherlands. Incidence figures for the period 1987–1988 are incomplete. Start: beginning of the Dutch screening program.

Table II and Figure 2 show the adjusted mortality rates for the different age groups in the joinpoint analysis. Mortality rates for the 35–44-age group were almost steady from 1950 to 1994 and decreased thereafter by 2.7% per year. For the 45–54-age group, after an increase with 1.4% per year from 1950 to 1971, the mortality rates steadily decrease with 1.8 and 1.9% per year for the period 1971–1980 and 1992–2006, respectively. Between these 2 periods, the mortality seems to be stable.

TABLE II – MORTALITY: JOINPOINT REGRESSION ANALYSIS OF AGE-ADJUSTED (EUROPEAN STANDARD POPULATION) BREAST CANCER RATES PER 100,000 FEMALES AGED 35–84 YEARS IN THE NETHERLANDS

Age group	Trend 1 year	EAPC (95% CI)[1]	Trend 2 year	EAPC (95% CI)[1]	Trend 3 year	EAPC (95% CI)[1]	Trend 4 year	EAPC (95% CI)[1]
All (35–84)	1957–72	1.11[2] (0.81, 1.40)	1972–76	−1.83 (−4.76, 1.19)	1976–94	0.22[2] (0.01, 0.44)	1994–2006	−2.32[2] (−2.70, −1.94)
35–44	1950–94	−0.12 (−0.34, 0.10)	1994–2006	−2.65[2] (−4.25, −1.02)				
45–54	1950–71	1.37[2] (1.02, 1.72)	1971–80	−1.81[2] (−3.22, −0.39)	1980–92	0.16 (−0.76, 1.08)	1992–2006	−1.91[2] (−2.59, −1.23)
55–64	1950–55	−1.83 (−4.57, 0.98)	1955–69	1.39[2] (0.74, 2.38)	1969–94	0.18 (−0.06, 0.42)	1994–2006	−2.31[2] (−3.02, −1.60)
65–74	1950–60	−0.86[2] (−1.59, −0.12)	1960–94	0.41[2] (0.29, 0.53)	1994–2006	−2.83[2] (−3.41, −2.25)		
75–84	1950–64	1.52[2] (0.75, 2.30)	1964–2001	0.02 (−0.16, 0.19)	2001–06	−4.81[2] (−8.30, −1.19)		

Joinpoint estimation based on period 1950–2006.
[1]EAPC, estimated annual percent change; CI, confidence interval.–[2]EAPC is statistically significant different from 0 ($P < 0.05$).

The age groups invited for screening (women aged 55–64 and 65–74 years) showed a decrease in mortality rate in 1994 of 2.3 and 2.8%, respectively. In the period up to 1994, mortality rates were slightly increasing for both age groups. For the oldest age group, who were invited for screening in their 70th–74th year of life, a stable mortality rate was seen until 2001 followed by a significant 4.8% decrease in mortality rates per year.

Results of the joinpoint analyses by age group for the incidence of invasive breast cancer are reported in Table III and displayed in Figure 3. One joinpoint was found in the youngest age group 35–49 years. Before 1989, incidence was stable, whereas a significant increase of 1.2% per year was found afterward. The incidence rate for the women aged 50–69 showed 4 line segments. First, there was a nonsignificant increase in the prescreening period between 1975 and 1989. This was followed by the screening period with a significant increase of 7.8% per year from 1989 to 1993, a nonsignificant decrease in 1993–1997 and again a significant increase of 2% per year until 2003. The age group of women aged 70–74 showed 4 trends in incidence rates as well. There was a significant increase of 1.5% per year for the period 1975–1992, followed by a nonsignificant decrease in 1992–1995 in the prescreening period, further a steep significant increase of 16.3% per year in 1996–99 and a significant decrease of 3.7% per year thereafter in the screening period. The age group of 75–84 years showed 1 joinpoint in 1999, with an increase of 1.5% per year before and a decrease of 4.5% per year in the period after this joinpoint.

Discussion

Our study reveals an impressive decline in the breast cancer mortality and a rising incidence in The Netherlands, both in the general age group (35–84) and in the age group invited for screening. These results show the profound impact that the implementation of a screening program can have on mortality and incidence.

Our results support the reduction in the breast cancer mortality in The Netherlands for women aged 55–74 years, reported earlier by Otto *et al*.[13]) and corroborate the striking time relation between implementation of screening and effects on mortality. About 5 years after the introduction of a breast cancer screening program, the mortality rates for the age groups likely to be affected by screening show a much larger decline than the non-screened age groups. The start of the decline appeared even earlier for the older age group invited for screening, probably as the result of a cumulated effect of having undergone screen examinations before and after the age of 70. It seems that the implementation of the Dutch screening program affects the mortality sooner than the 7–10 years stated by Jatoi *et al*.[6]

Besides the effect of screening, mortality reflects the overall effect of diagnostic activity and treatment over the period between symptoms and dying. Improvements in treatment could be responsible for part of the recent downturn in breast cancer mortality.[6,14,15] The effect of a better treatment protocol fits with the mortality data for women not affected by the screening. For the youngest women (35–44 years), the decline could correspond to the search and identification for high-risk families with inheritable breast cancer and the introduction of genetic counseling in the late 1990s. The decline in breast cancer mortality in the 1970s for the age group 45–54 (see Fig. 2) coincides with the introduction of adjuvant chemotherapy and its target group. Adjuvant chemotherapy was introduced in the 1970s for premenopausal axillary lymph node-positive patients. The usage of chemotherapy increases from about 15% (1975–1979) to almost 30% (1980–1984) for women <50 years.[15–17]

However, for the age group invited for screening, the time relation between introduction of a better treatment and the breast cancer mortality is not that clear. In the early 1980s, treatment considerably improved. Adjuvant endocrine therapy (Tamoxifen) was introduced for postmenopausal women with node-positive and estrogen receptor-positive breast cancer. The usage of Tamoxifen

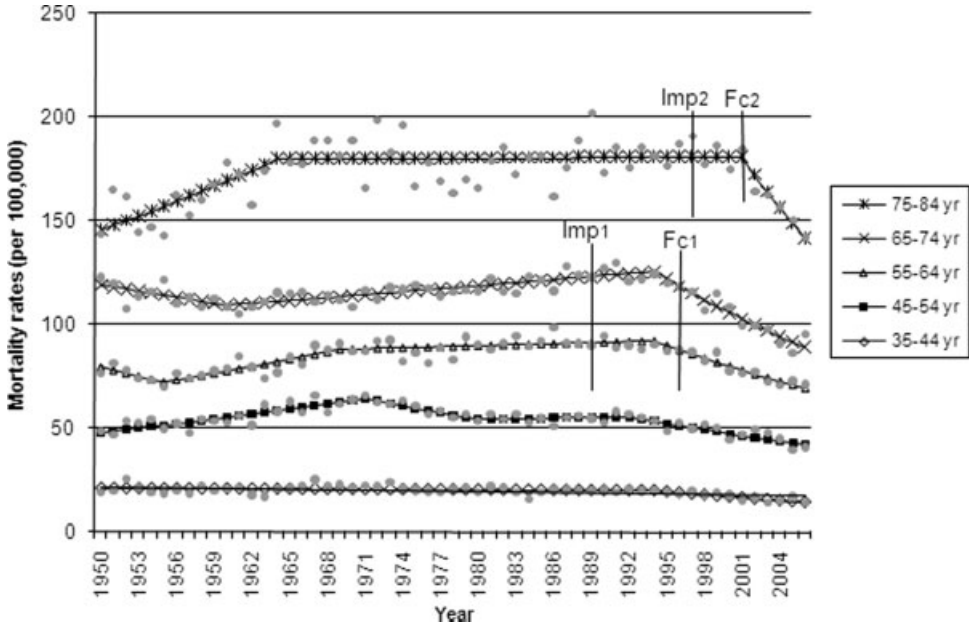

FIGURE 2 – Age-adjusted (European standard population) breast cancer mortality rates per 100,000 women aged 35–84 in The Netherlands. Coverage population 50–69 years: start implementation in 1989 (Imp1); percentage of targeted women annually invited: 11% (1990), 26% (1991), 48% (1992), 69% (1993), 77% (1994), 88% (1995) and full capacity in 1996 (Fc1). Coverage population 70–74 years: start implementation in 1997 (Imp2); percentage of targeted women annually invited: 26% (1998), 86% (1999), 91% (2000) and full capacity in 2001 (Fc2). Grey dots: observed mortality rates.

TABLE III – INCIDENCE: JOINPOINT REGRESSION ANALYSIS OF (INVASIVE) AGE-ADJUSTED (EUROPEAN STANDARD POPULATION) BREAST CANCER RATES PER 100,000 FEMALES AGED 35–84 YEARS IN THE NETHERLANDS

Age group	Trend 1 year	EAPC (95% CI)[1]	Trend 2 year	EAPC (95% CI)[1]	Trend 3 year	EAPC (95% CI)[1]	Trend 4 year	EAPC (95% CI)[1]
All (35–84)	1975–89	0.55 (−0.01, 1.12)	1989–92	5.24 (−2.76, 13.90)	1992–2003	0.73[2] (0.22, 1.23)		
35–49	1975–89	0.08 (−0.40, 0.56)	1989–2003	1.18[2] (0.86, 1.50)				
50–69	1975–89	0.57 (−0.06, 1.20)	1989–93	7.78[2] (3.37, 12.38)	1993–98	−1.51 (−3.94, 0.98)	1998–2003	1.99[2] (0.20, 3.80)
70–74	1975–92	1.48[2] (0.99, 1.97)	1992–96	−4.73 (−10.55, 1.46)	1996–99	16.25[1] (2.55, 31.78)	1999–2003	−3.73[2] (−7.00, −3.50)
75–84	1975–99	1.45[2] (1.18, 1.71)	1999–2003	−4.52[2] (−8.06, −0.84)				

Joinpoint estimation based on period 1975–2003.
[1]EAPC, estimated annual per cent change; CI, confidence interval.–[2]EAPC is statistically significant different from 0 ($P < 0.05$).

increases from less than 10% (1980–1984) to almost 30% (1985–1997) for women aged 50–69 and 50% (1985–1997) for women >70 years.[15–17] Despite this improvement and usage, Figure 2 shows an increase in mortality for the targeted age groups, whereas the mortality rates for the oldest age group seem to be stable. Vervoort *et al.*[15] predicted similar results with a computer-simulation model. For the age group 45–54, mortality reduction was mainly (70%) attributed to adjuvant therapy, whereas the mortality reduction for the age group 55–74 was largely (80%) explained by screening. In 1998, adjuvant systemic therapy was extended to node negative patients (tumor size $\geq$ 2 cm and intermediately/poorly differentiated carcinomas). This therapy extension possibly enlarged the mortality reduction after the start of breast cancer screening, found in our study. New treatments can have a relatively rapid effect on mortality, but this seems to be limited to the younger age groups, that is, 45–54 years.[18–20] Although therapy improvement for Tamoxifen in older women could not be ruled out completely, our data suggest a mortality reduction induced by (the implementation of) screening rather than therapy improvement for women older than 54.

It is difficult to disentangle the effects of screening, treatment improvements and population changes in risk factors. This study is entirely based on descriptive data analysis and therefore should be interpreted with caution for inference on causal relations. Furthermore, a decrease in mortality was also reported for "all ages" group in countries without national screening programmes[21] and, in several countries, before organized screening was introduced.

With regard to incidence, the introduction of the screening program clearly influences the rates in the different age groups. Because of lead time, length-biased sampling and possibly overdiagnosis, the screening programme will detect more cancers.[22] This rise in incidence emanating from screening is interrupted by a slight decrease during implementation of the program, which can be explained by a shift from women invited for their 1st screening (with a higher detection rate) to more women attending for their subsequent screening (with a lower detection rate).

The expected prevalence peak associated with screening is temporary,[23] which is clearly shown for the 2 invited age groups. In the steady state situation, the incidence will decrease, but for the

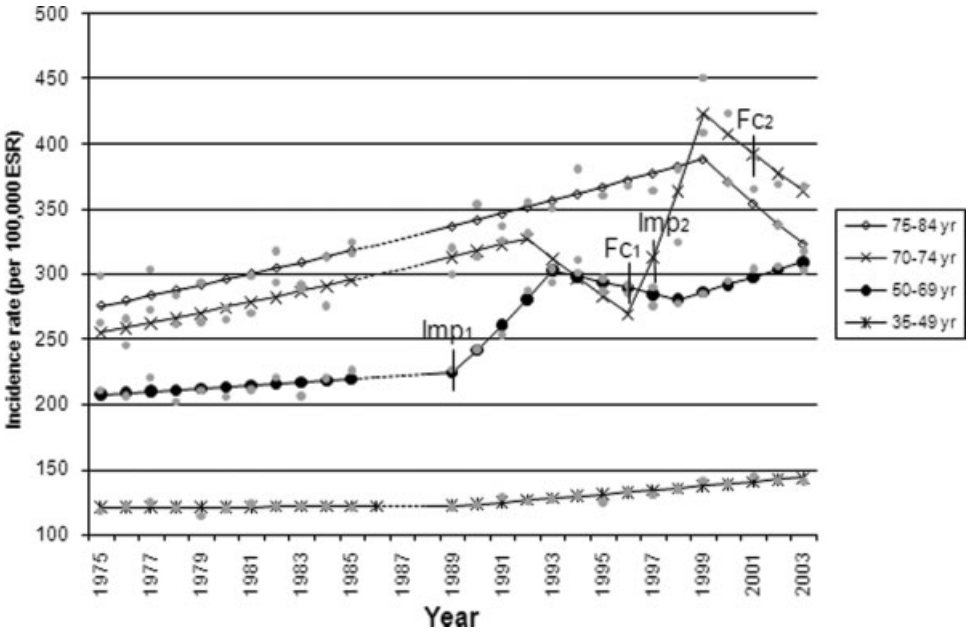

FIGURE 3 – Age-adjusted (European standard population) invasive breast cancer incidence rates per 100,000 women aged 35–84 in The Netherlands. Incidence figures for the period 1987–1988 are incomplete. Coverage population 50–69 years: start implementation in 1989 (Imp1); percentage of targeted women annually invited: 11% (1990), 26% (1991), 48% (1992), 69% (1993), 77% (1994), 88% (1995) and full capacity in 1996 (Fc1). Coverage population 70–74 years: start implementation in 1997 (Imp2); percentage of targeted women annually invited: 26% (1998), 86% (1999), 91% (2000) and full capacity in 2001 (Fc2). Grey dots: observed incidence rates.

invited group remains at a higher level in comparison with no systematic screening, due to the continuing screening in every consecutive year.

One problem of the age distribution used in this study is the contamination of the so-called noninvited and invited to screen groups. Because of the definition of age and the execution of the Dutch screening program, women aged 49 years were also invited for screening from the beginning of the program, whereas women of 69 years old were formally invited for their initial screening examination just from 1998 onward. The contamination with screened women (age 49 years) can explain the increase in incidence in the noninvited screen group since the introduction of the screening programme. In 2003, 16% of all breast cancers in women aged 45–49 years were the result of a screening examination within the program. The postponed screening of women aged 69 years can explain the further increase in incidence for the age group 50–69 years from 1998.

For the latter age group, besides contamination, several other factors can cause the continuing increasing incidence. First, from 1990 onward, the detection rates have increased by 26% in the next 10 years for subsequent screen examinations.[24] Second, the increase could be enlarged due to a change in referral strategy by the screening radiologists since ~1997, that is, higher referral and higher detection rates.

Another specific effect of screening a certain age group is the influence on the incidence in the consecutive group. The decrease before the start of the screening in the age group 70–74 years is the result of the screening in age group 50–69, in which prevalent cancers that normally would have been diagnosed at the age of 70–74 were captured. The same thing happened for the oldest age group 75–84, which caused a decrease in incidence rates in this group.

So, the introduction of mass screening seems to be the most likely explanation for the increase in incidence rates in The Netherlands, as noted in many other European countries over the last 2 decades.[25] It is unlikely that these changes in incidence are caused by substantial changes of the recognized risk factors for breast cancer related to endogenous hormones as stated by MacMahon[26], for example, later age at first birth, nulliparity, use of hormone replacement therapy (HRT) or postmenopausal overweight. For instance, the increased mean age at first birth for the last 3 decades[9] is too early to have an effect on the invited age groups. Furthermore, prescribing of HRT was already low (NL: 9%, US: 38–50%) in The Netherlands and even declined to less than 3% in 2004.[27] Therefore, changes in HRT-use cannot be the reason for an increasing incidence in our study over the last 2 decades.

In conclusion, the results indicate an impressive decline in the breast cancer mortality for the age group invited for breast cancer screening, starting to show quite soon after implementation of the national program. Incidence rates almost meticulously follow the implementation of the breast cancer screening program.

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