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EFFECT ON BREAST CANCER MORTALITY OF BIENNIAL MAMMOGRAPHIC SCREENING OF WOMEN UNDER AGE 50

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The effects on breast cancer mortality seen after 16 years of biennial screening of younger women are assessed in this prospective cohort study. Since 1975 some 13,500 women, aged 35–49 in 1975, were invited to participate in the Nijmegen screening programme comprising a mammographic examination every 2 years. By the end of 1990, 75 women had died of breast cancer out of the 332 cases diagnosed after the start of the screening project. Women from the same birth cohort, living in Arnhem, a neighbouring city with a comparable population and without a screening project, were used as controls. In this city, 74 breast cancer deaths out of 284 cases occurred during the same period. In Nijmegen, after 16 years of follow-up, breast cancer mortality showed a non-significant reduction of 6% (95% confidence interval: 32% reduction, 29% excess). In the relevant period, after a time lag of 10 years from the start of the programme, this reduction rose to 20% (95% confidence interval: 48% reduction, 23% excess). No reduction in breast cancer mortality was observed in the first decade of screening. For a later period, a shift towards a reduction emerges, but the data are as yet inconclusive.

Up until now the benefit of periodic breast cancer screening, with modern mammography, of women under 50 years of age has been controversial (Beral, 1993; Fletcher *et al.,* 1993; Sickles and Kopans, 1993; Jatoi and Baum, 1993; Harris, 1994).

In the oldest trial, the Health Insurance Plan (HIP) study from the early sixties, with 4 annual mammographic examinations combined with physical examination, positive results were only observed after a long follow-up of 8 years (Shapiro *et al.,* 1988). Since the HIP study, the quality of mammography has improved considerably, facilitating the detection of more tumours in an early stage of development before they have reached an incurable stage. Modern mammography therefore might be expected to produce a stronger effect on breast-cancer mortality. However, this expectation is lowered by the fact that in most ongoing trials the screening interval is at least 2 years, instead of 1 year as in the HIP trial. Moreover, mammography is commonly used as the only screening modality, whereas the HIP study also included palpation. In addition, the prognosis of today's breast cancer patients may already have improved to such an extent (*e.g.,* due to early self-detection and a greater cautiousness regarding suspect lesions in the breast), that early detection by population screening might have a lower effect than anticipated.

So far, the results of ongoing trials for women under age 50 have been inconclusive (Andersson *et al.,* 1988; Roberts *et al.,* 1990; Frisell *et al.,* 1991; Miller *et al.,* 1992). There appears to be little evidence of benefit, at least in the first 10 years after the initial screening examination. A recent analysis of the combined Swedish data, a pooling of 5 studies with a screening interval of 1.5 to 2 years, has shown a non-significant benefit of 13% after a follow-up of 7 to 12 years (Nyström *et al.,* 1993). This study suggests that, in this age group, a potential beneficial effect cannot be expected in the first decade after the start of screening.

In our study, breast cancer mortality in the study population of Nijmegen, aged 35 to 49 at the start of the first screening round in 1975 (13,500 women), has been analysed after 16 years of follow-up. The results are compared with those of the neighbouring city of Arnhem.

STUDY POPULATION AND METHODS

In the city of Nijmegen (150,000 inhabitants) a population-based biennial screening programme for breast cancer was set up in 1975 (Peeters *et al.,* 1989*a*). Single-view mammography was carried out as the only screening procedure every 2 years. In the first screening round, all women born in the period 1910–1939 were invited. The present study is restricted to women born in 1925–1939, aged under 50 at January 1, 1975. For the "date of entry" into the study the date of first invitation was taken. In the present analysis, women who moved into the area of Nijmegen were also included. This immigration was approximately 1% yearly. The end of the study period was set as the date of death, the date of moving out of Nijmegen, or the end of 1990. By this time 8 screening rounds had been carried out. The attendance rate was 87% in the first screening round and stabilized at about 65% after the fourth round.

The control group consists of women of the city of Arnhem. This neighbouring city, 15 miles distant from Nijmegen, also has some 150,000 inhabitants. The date of entry into the study for a woman from the control group was considered to be the date midway through the first screening round in Nijmegen, *i.e.* January 1, 1976, or, alternatively, the date when she moved into Arnhem. The follow-up period ended upon death, upon moving out of the city or by the end of 1990. Because no information on an individual level was available, mid-year estimates for woman-years at risk for birth cohort 1925–1939 were calculated from the official census statistics, published yearly by the Dutch Central Bureau of Statistics.

Information about breast cancer deaths subsequent to diagnosis after entry into the study was obtained by a review of the medical files of the deceased patients.

Since 1975, data on all Nijmegen patients diagnosed as having breast cancer in either of the Nijmegen hospitals have been carefully recorded by the local cancer registry of the Departments of Diagnostic Radiology and Pathology, resulting in a number of 332 patients diagnosed with primary breast cancer between entry into the study and the end of 1990. The list of all patients diagnosed up to the end of 1988 was submitted to the local registrar's office for vital status assessment at December 31, 1988. Since the beginning of 1989 the local registrar's office has supplied us weekly with all the dates of migrations and deaths among Nijmegen women born before 1940. All clinical information concerning the dead patients was

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gathered to ascertain the cause of death, *i.e.*, breast cancer or other. Breast cancer was considered to be the underlying cause of death when distant metastases had been reported prior to death and competing causes of death could be ruled out.

For the control population of Arnhem, the Carcinoma Working Group composed a list of 284 patients with primary breast cancer diagnosed since 1976. The same procedure and criteria for assessing the cause of death were applied in both cities.

The breast cancer mortality rate ratio with 95% confidence interval of the Nijmegen *versus* Arnhem study populations was calculated.

RESULTS

From the start of the screening project until the end of 1990, a total of 332 breast cancer patients, including 38 with ductal carcinomas *in situ*, were diagnosed in Nijmegen. Of these cancers, 38% were detected by screening, 36% appeared in the interval between screenings and 25% were found in women who had been invited for screening but had not responded to the last invitation (Table I). By the end of 1990, 29 patients had left Nijmegen and 82 had died. In Arnhem, in the same birth cohort and calendar period, 284 patients, of whom only 4 were known to have intraductal carcinoma, were diagnosed. During the study period 14 patients had moved away from Arnhem and 84 had died. For 3 Arnhem patients (who died in 1977, 1982 and 1986) the cause of death could not be assessed. Breast cancer was considered to be the underlying cause of death of 75 patients in Nijmegen and 74 patients in Arnhem. Three-quarters of the deaths from breast cancer in Nijmegen occurred in women whose tumour had been diagnosed in the interval between screenings or in women who had not responded to the last screening invitation. Nevertheless, as many as one-quarter of the deaths occurred in women whose carcinoma had been detected at screening. Compared with Arnhem, Nijmegen showed a non-significant 6% decrease in the cumulative number of breast cancer deaths (cumulative relative risk = 0.94; 95% confidence interval 0.68–1.29).

Figure 1 shows the cumulative breast-cancer mortality in the 2 cities for patients diagnosed after the start of the screening project in Nijmegen. Previous studies have suggested that no effect of screening can be expected in the first 10 years after initiation of screening; we therefore considered the breast-cancer mortality rate ratio for 3 time intervals (1976–1980, 1981–1985, 1986–1990) specified separately in Table II. After a time lag of 10 years from the start of the programme, a non-significant reduction in breast-cancer mortality of 20% was found (relative risk = 0.80; 95% confidence interval 0.52–1.23).

DISCUSSION

This study addresses the issue of long-term breast-cancer mortality in young women who had the opportunity of mammographic screening once every 2 years.

Due to the non-randomized design of the Nijmegen programme, special attention was given to potential sources of bias. Of major concern was the comparability of the populations in the 2 cities with respect to risk of breast-cancer death. To evaluate comparability, population mortality rates of breast cancer in the pre-screening period in both cities were assessed. In the period 1970–1974, Nijmegen appears to have had a lower mortality in the 35–64 age group (rate ratio = 0.68; 95% confidence interval 0.48–0.96) (Hendriks, 1982). However, this apparently lower risk for breast-cancer death does not persist in the period 1975–1979, the first years of the programme (Peeters *et al.*, 1989*b*). Taking these figures into consideration, no unambiguous conclusion can be drawn regarding the "baseline" differences in breast-cancer mortality in the eighties for cases diagnosed after the start of the screening project. Any difference in breast cancer mortality between the 2 cities in favour of Nijmegen which is not due to intervention diminishes the reduction attributable to screening.

In the whole 16-year period of follow-up (1975–1990, that is from the start of screening to the end of follow-up) an 8% excess of breast-cancer cases was observed in Nijmegen. Higher incidence is to be expected from any screening programme for breast cancer because of the advanced detection through screening and increasing incidence with age (Boer *et al.*, 1994). In younger women the detection of many ductal carcinomas *in situ* (DCIS) may also contribute to an increase in incidence. In the present study 22% (N = 28) of the screen-detected cancers are DCIS. The likelihood of these DCIS progressing to clinical disease in the absence of screening is unknown. In our study, part of the excess may also be ascribed to an under-recording of breast-cancer cases in the first years in Arnhem. The Carcinoma Working Group, Arnhem, has been operative since 1979. In the 3-year period prior to 1979 the breast-cancer incidence rate in the younger age-groups was 23% less than might have been expected on the basis of the incidence rates in the overall Dutch population as obtained from the Central Bureau of Statistics. Between 1979 and 1988 the incidence rate in Arnhem was the same as that in the total

TABLE I – CUMULATIVE BREAST-CANCER INCIDENCE AND MORTALITY RATE IN NIJMEGEN AND ARNHEM AMONG PATIENTS FROM BIRTH COHORT 1925–1939 DIAGNOSED AFTER THE START OF THE SCREENING PROJECT IN NIJMEGEN UNTIL THE END OF 1990

	Nijmegen, after entry	Arnhem, after January 1, 1976
Number of primary breast cancers	332	284
Screen-detected	128 (38%)	
Interval	119 (36%)	
Non-participant	85 (25%)	
Moved away from the city	29	14
Died from causes of all kinds	82	84
Died from breast cancer	75	74
Screen-detected	19 (25%)	
Interval	28 (37%)	
Non-participant	28 (37%)	
Woman-years	166,307	154,103
Breast-cancer mortality rate (per 100,000 woman-years)	45.1	48.0
Rate ratio	0.94	
95% Confidence interval	0.68–1.29	

Dutch population. A random under-reporting of 23% in the first 3 years in Arnhem would have yielded 4 more breast cancer deaths, increasing the cumulative breast cancer mortality reduction from 6% to 11% and, in the post-10-year observation period 1986–1990, from 20% to 21%.

Determination of the underlying cause of death can be subject to a (differential) misclassification. In the breast-cancer patients of this younger age group, however, competin causes of death were involved only in a minor proportion of th deceased patients. In the overview of the Swedish randomize trials the mortality reduction in the whole study populatio was similar, irrespective of the end-point used for evaluatio (*i.e.,* "breast cancer as underlying cause of death" or "breas cancer present at death") (Nyström *et al.,* 1993).

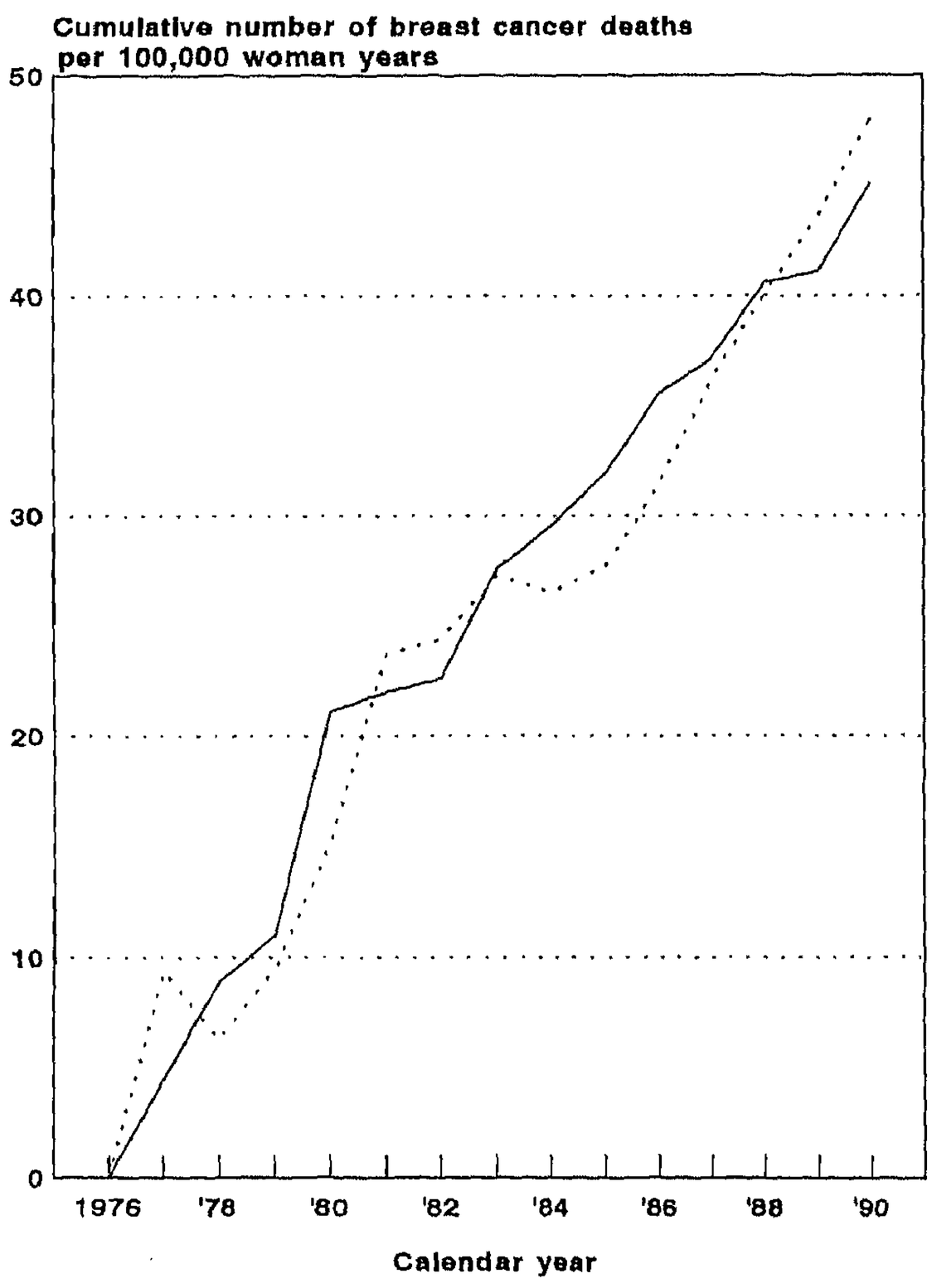

FIGURE 1 – Cumulative breast cancer mortality rate in Nijmegen (——) and Arnhem (------) among patients from birth cohort 1925–1939 diagnosed after the start of the screening project in Nijmegen.

The deaths occurring during the first years of a screening programme will mainly concern patients whose disease was already at an advanced stage at the time of diagnosis. It is thus reasonable to assume that the effect of screening for breast cancer is delayed in any age group. One may expect, however, a longer delay for younger women because of (1) the better relative survival of younger patients with breast cancer (Adami *et al.,* 1986) and (2) an apparently longer lead time of cases of DCIS which are detected more frequently in this age group. In the more relevant observation period, beginning one decade after the start of the programme, *i.e.* the period 1986–1990, our study showed a promising 20%, though still non-significant reduction in mortality. One could advance the idea that this reduction is the effect of the screening of those women who passed the age of 50 during the observation period, but this supposition is not supported by the observations in women of birth cohort 1925–1929 (aged 45 to 49 at the start), among whom no mortality reduction during the period 1986–1990 was observed.

Taking into account all the available information and possible sources of bias, we conclude that biennial mammographic screening of women under the age of 50 in Nijmegen has not resulted in a reduction in breast-cancer mortality during the first decade. For a later period, a shift towards a reduction emerges, but the data are as yet inconclusive.

All women in the 1925–1939 birth cohort have now passed the age of 50 and they will be screened biennially as part of a nation-wide screening programme, which includes Arnhem as well. If longer follow-up reveals that the reduction in breast cancer mortality continues to be present, this could be the effect of screening the younger age group in Nijmegen.

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TABLE II – BREAST CANCER MORTALITY IN NIJMEGEN AND ARNHEM AMONG PATIENTS DIAGNOSED AFTER THE START OF THE SCREENING PROJECT IN NIJMEGEN ACCORDING TO CALENDAR PERIOD AND BIRTH COHORT

Period	Birth cohort	Woman-years		Breast-cancer deaths		Rate ratio
		Nijmegen	Arnhem	Nijmegen	Arnhem	
1976–1980	1935–1939	18,742	16,610	2	0	
	1930–1934	19,062	17,389	4	5	
	1925–1929	18,962	18,811	6	3	
	1925–1939	56,766	52,810	12	8	1.40 (0.57–3.40)
1981–1985	1935–1939	18,720	16,536	8	2	
	1930–1934	18,917	16,987	8	7	
	1925–1929	18,459	18,225	8	12	
	1925–1939	56,096	51,751	24	21	1.05 (0.59–1.89)
1986–1990	1935–1939	17,937	16,120	10	17	
	1930–1934	18,026	16,237	16	16	
	1925–1929	17,482	17,186	13	12	
	1925–1939	53,445	49,542	39	45	0.80 (0.52–1.23)

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