

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/25382>

Please be advised that this information was generated on 2017-12-05 and may be subject to change.

BREAST-CANCER MORTALITY IN A NON-RANDOMIZED TRIAL ON MAMMOGRAPHIC SCREENING IN WOMEN OVER AGE 65

Jos A.A.M. VAN DIJCK^{1,2*}, André L.M. VERBEEK^{1,2}, Louk V.A.M. BEEEX³, Jan H.C.L. HENDRIKS^{1,4}, Roland HOLLAND^{1,5}, Marcel MRAYUNAC⁶, Huub STRAATMAN² and Jan M. WERRE⁷

¹National Expert and Training Centre for Breast Cancer Screening in the Netherlands, Nijmegen, The Netherlands

²Department of Epidemiology, University Hospital and University of Nijmegen, The Netherlands

³Department of Endocrinology, University Hospital and University of Nijmegen, The Netherlands

⁴Department of Radiology, University Hospital and University of Nijmegen, The Netherlands

⁵Department of Pathology, University Hospital and University of Nijmegen, The Netherlands

⁶Department of Pathology, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands

⁷Red Cross Blood Bank, Arnhem, The Netherlands

Recent case-referent studies in the Nijmegen breast-screening programme have shown a reduction in breast-cancer mortality of approximately 50% due to screening of women aged 65 years and older. In this type of study, however, the results may be biased because of self-selection. The purpose of our present study was to compare the breast-cancer mortality rate in a population invited for screening with that of a reference population from an area without a screening programme. In 1977–1978, 6773 women aged 68–83 years were enrolled in the mammographic screening programme in Nijmegen, The Netherlands. The women were followed up until 31 December, 1990. The reference population consisted of women from the same birth cohort from Arnhem, a neighbouring city without mass screening, for whom the entry date was 1 January, 1978. The ratios of the Nijmegen and Arnhem breast-cancer mortality rates with 95% confidence intervals (CI) were calculated. In the study period, 173 patients were diagnosed with primary breast cancer in Nijmegen vs. 183 in Arnhem; 40 Nijmegen patients had died of breast cancer vs. 51 Arnhem patients. The cumulative mortality-rate ratio was 0.80 (95% CI = 0.53–1.22). In the periods 1978–1981, 1982–1985 and 1986–1990, the mortality rate ratios were 1.44 (95% CI = 0.67–3.10), 0.81 (95% CI = 0.37–1.79) and 0.53 (95% CI = 0.27–1.04), respectively. After adjustment for the difference in incidence rate that existed between the Nijmegen and Arnhem populations, mammographic screening of women older than 65 can be expected to yield a 40% reduction in breast-cancer mortality after 10 years. *Int. J. Cancer*, 70:164–168, 1997.

© 1997 Wiley-Liss, Inc.

Unlike most malignancies, the course of breast cancer can be altered by early detection and treatment. In women over the age of 50 years, trials have shown a reduction of breast-cancer mortality of some 25 to 30% in populations that were offered screening vs. unscreened populations (Fletcher *et al.*, 1993; Nyström *et al.*, 1993; De Koning *et al.*, 1995; Kerlikowske *et al.*, 1995). The screening intervals used in these studies ranged from 12 to 33 months and the screening test consisted of 1- or 2-view mammography, sometimes in combination with physical examination.

More recently, a reduction in mortality has been demonstrated in women up to the age of 75 years (Van Dijck *et al.*, 1994, 1996; Chen *et al.*, 1995). The results of the Swedish 2-county study, which was a randomized trial, showed a decrease in breast-cancer mortality due to the screening of women aged 65 to 74 years at entry (Chen *et al.*, 1995). After 14 years of follow-up, a statistically significant 32% reduction in the risk of death from breast cancer was observed in the population invited for screening. In Nijmegen, 2 case-referent studies included women aged 65 years and older at the index invitation (*i.e.*, the most recent invitation to screening just prior to the diagnosis of breast cancer in the case). The estimated reductions in breast-cancer mortality in women screened at the index invitation relative to those unscreened at that time were 42% and 44% after 13 and 18 years of follow-up respectively (Van Dijck *et al.*, 1994, 1996). There has been debate, however, on the validity of case-referent studies as a method of evaluating screening

efficacy, since the results may be biased due to self-selection for screening (Morrison, 1993; Moss *et al.*, 1992). The present study used an external reference population to evaluate whether including elderly women in a screening programme affects breast-cancer mortality.

SUBJECTS AND METHODS

In 1975, a breast-cancer screening programme was started in the city of Nijmegen, The Netherlands (Otten *et al.*, 1996). Initially, women born between 1910 and 1939 (aged 35–66 years) were invited for one-view mammography. Since the second round of screening, 1977–1978, women born before 1910, aged 67 years and older at their first invitation, have also been invited biennially to participate in the screening. The present study included all Nijmegen women born between 1895 and 1909 who had been invited to screening before the end of 1990. In this way, 6773 women entered the screening programme in round 2, while 488 women, who had come to live in Nijmegen after round 2, joined the programme between 1979 and 1990.

Information about invitation and participation of the invited women was stored in a computer file. With the aid of the local authorities, follow-up could be recorded. All patients diagnosed with breast cancer (screen-detected and clinically diagnosed) at either of the 2 Nijmegen hospitals were registered at the Department of Radiology of the University Hospital. Clinical information about deceased patients was obtained from their medical files and reviewed by a panel of physicians who were unaware of the screening history of the patients. The cause of death was ascertained based on the clinical course of the disease and information about any serious co-morbidity. Breast cancer was defined as the cause of death if the disease had progressed to distant sites and if this progression could not be ruled out as the cause of death of the patient.

The reference population consisted of inhabitants of Arnhem, a city located 20 kilometers north of Nijmegen, where mass screening was started in 1989 for women aged 50 to 69 years as part of the national programme in The Netherlands. The Arnhem patients were registered by the "Carcinoma Work Group", which operated until 1991. With the aid of the local authorities, patients who had died or moved away from Arnhem could be identified. The cause of death of deceased patients was established in the same manner as that described above and by the same physicians as in Nijmegen.

For Arnhem, person-years of observation had to be calculated from the official census statistics published annually by the Dutch

*Correspondence to: Department of Epidemiology, University of Nijmegen, P.O. Box 9101, NL-6500 HB Nijmegen, The Netherlands. Fax +31-24-3613505.

Central Bureau of Statistics. These statistics keep track of the number of inhabitants of each sex, by year of birth, on 1 January of each calendar year. Although data for Nijmegen were available on an individual basis, woman-years were also calculated on the basis of the census statistics for the sake of comparability of the information. For each calendar year up to and including 1990, the mid-year population size was calculated as the number of woman-years of observation in that year.

Breast-cancer mortality rates in Nijmegen were based on data from patients in whom breast cancer had been diagnosed after the invitation to the first round of screening in 1977–1978. For 1977 and 1978, a population-time correction was made according to the exact entry dates. The mortality rates in Arnhem were based on data from patients diagnosed from 1 January, 1978, onwards, since this was close to the median date of the first invitation for the Nijmegen population (55% had been invited by then). Patients diagnosed with breast cancer before this date were excluded from the analysis. The ratio of the cumulative breast-cancer mortality rates (*i.e.*, number of breast-cancer deaths in the entire study period divided by the total number of woman-years) was calculated, as well as the ratios of breast-cancer mortality rate over 3 periods. Confidence intervals (CI) were calculated using the method based on the standard deviation of the log-transformed point estimates (Rothman, 1986a).

RESULTS

In Nijmegen, 7261 women born between 1895 and 1909 had been invited for screening in the period 1977 to 1990. A total of 46% had participated in the screening programme at least once, and half of these women had taken part more than once. A marked decrease in the participation rate was observed as the round number and age increased, illustrated in Figure 1 for rounds 2, 5 and 8. In rounds 2 to 8, overall participation rates were 43%, 29%, 22%, 15%, 12%, 10% and 4% respectively.

In Nijmegen, 173 patients were diagnosed as having breast cancer, *vs.* 183 in Arnhem. Breast cancer had been diagnosed in Nijmegen: (1) after a positive screening examination in 57 patients, (2) after a negative screening mammogram (interval cancer) in 21 patients, (3) before the first invitation in 4 patients who had moved to Nijmegen after 1977, and (4) after a refused invitation in 91 non-participant cases.

Table I shows the number of patients who had died from breast cancer, also the woman-years of observation for each calendar year. Two deaths occurred in patients diagnosed before their first invitation who had moved to Nijmegen after 1978. For both populations, the breast-cancer mortality rates (5-year moving average) are displayed in Figure 2. Up to 6 years after the start of screening, the breast-cancer mortality rate in Nijmegen was higher than that in Arnhem. In the subsequent years, the rate in Nijmegen stabilized, but an increase was observed in the late eighties. In Arnhem, the rate reached its maximum after 10 years and continued to decrease afterwards.

Over the entire study period, breast-cancer mortality in Nijmegen was lower than in Arnhem: cumulative mortality-rate ratio = 0.80 (95% CI, 0.53–1.22). Table II shows the ratio of the breast-cancer mortality rates with 95% CI over several periods. In the first period of 4 years, the mortality-rate ratio was 1.44, in the second period of 4 years it was 0.81, whereas in the relevant observation period, 9 to 13 years after the start of screening, it was 0.53 (95% CI, 0.27–1.04).

DISCUSSION

According to the results, the effect of screening manifests itself approximately 7 years after the start of the programme and reaches its maximum after about 10 years. This is what one would expect if analyses include only patients in whom breast cancer was diagnosed after the start of the screening programme. The proportion of

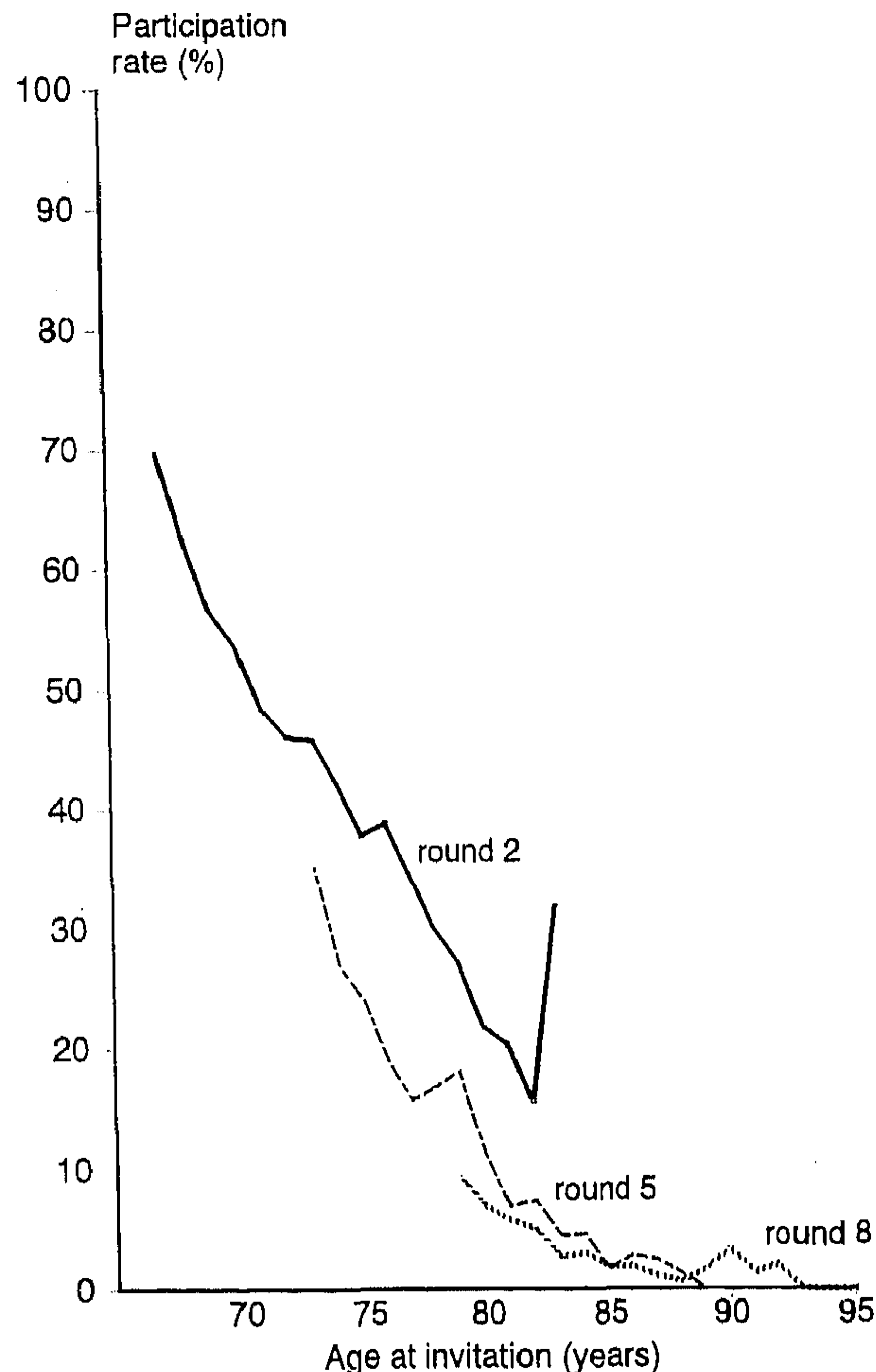


FIGURE 1 – Participation rate according to age at invitation for screening rounds 2, 5 and 8.

TABLE I – NUMBER OF BREAST-CANCER DEATHS AND WOMAN-YEARS OF OBSERVATION BY CALENDAR YEAR AND CITY

Calendar year	Nijmegen		Arnhem	
	Breast-cancer deaths ¹	Woman-years	Breast-cancer deaths ²	Woman-years
1978	1	6823 ³	1	6502
1979	1	6248	3	6222
1980	8 ⁴	5947	1	5961
1981	6 ⁴	5620	6	5725
1982	3	5284	1	5455
1983	4	4967	3	5155
1984	2	4669	6	4836
1985	2	4378	4	4494
1986	1	3988	9	4174
1987	3	3567	6	3863
1988	5 ⁵	3224	6	3526
1989	3 ⁶	2944	5	3156
1990	1	2656	0	2765
1977–1990	40	60313	51	61832

¹Only if diagnosed after first invitation in round 2.–²Only if diagnosed after 31 December 1977.–³Including 1977.–⁴Including 1 death in patient diagnosed before enrollment, but after round 2.–⁵Including 1 death with breast-cancer metastases.–⁶Including 3 deaths with breast-cancer metastases.–Cumulative mortality-rate ratio 0.80 (95% CI, 0.53–1.22).

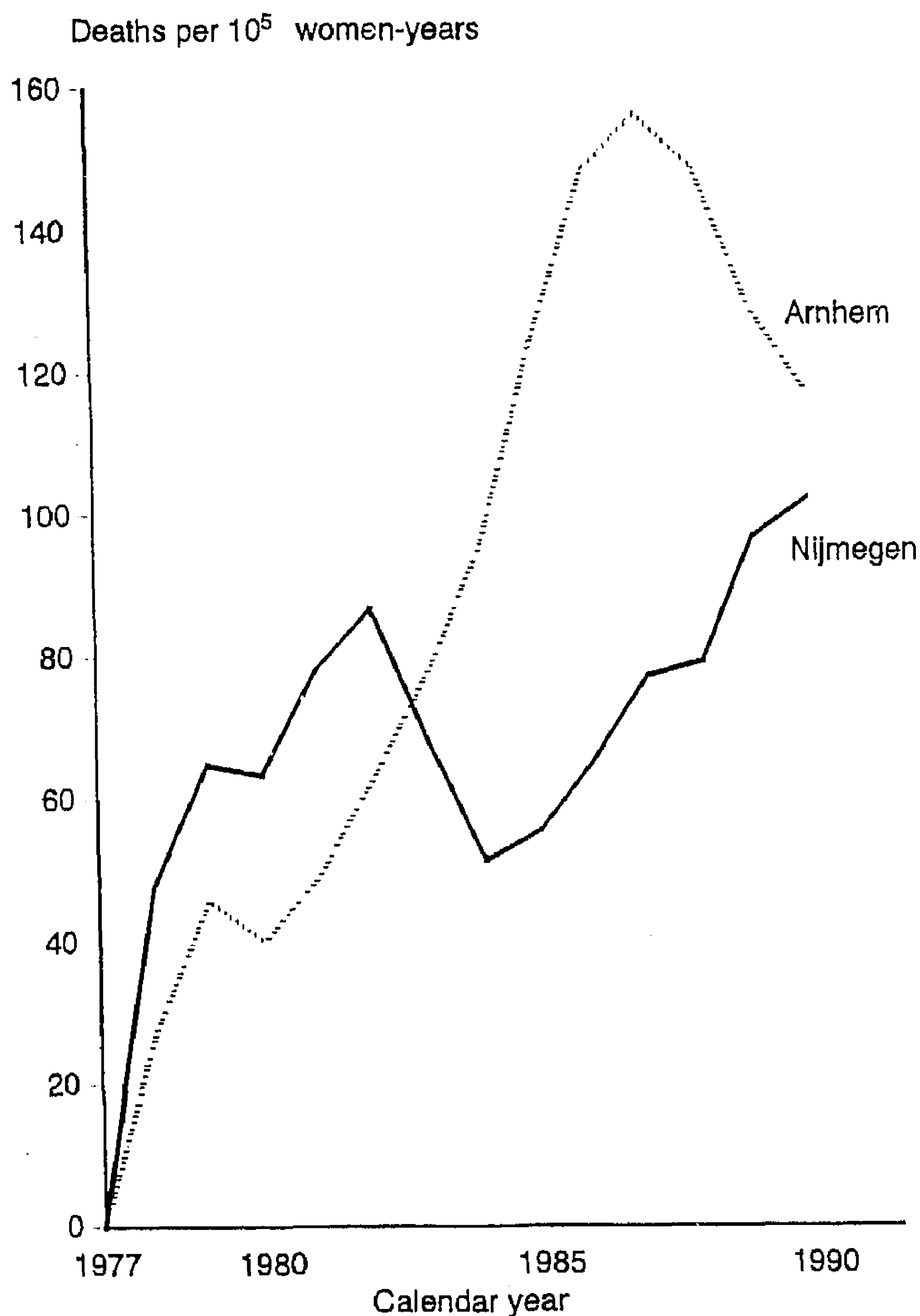


FIGURE 2 – Breast-cancer mortality rates (5-year moving average) in Nijmegen, if diagnosed after first invitation 1977–78, and in Arnhem, if diagnosed from 1978 onwards.

TABLE II – BREAST-CANCER DEATHS AND WOMAN-YEARS IN NIJMEGEN AND ARNHEM IN 3 SPECIFIED PERIODS AND THE MORTALITY-RATE RATIO (95% CI)

Period	Nijmegen		Arnhem		Mortality-rate ratio (95% CI)
	Deaths ¹	Woman-years	Deaths ²	Woman-years	
1978–1990	16 ³	60325	51	61845	0.80 (0.53–1.22)
1978–1981	16	24641	11	24415	1.44 (0.67–3.10)
1982–1985	11	19301	14	19943	0.81 (0.37–1.79)
1986–1990	13 ³	16383	26	17487	0.53 (0.27–1.04)

¹If diagnosed after first invitation. –²If diagnosed from 1-1-1978 onwards. –³Including 4 deaths with breast-cancer metastases.

women who participated in the programme decreased gradually, so the effect of screening on breast-cancer mortality can also be expected to decrease gradually. It is likely that the effect will have diminished 15 to 20 years after the start of screening.

Could the observed mortality reduction be due to screening 46% of the population only, while half of these women had been screened at least twice? In an earlier study, the incidence of breast cancer in Nijmegen and Arnhem was compared in women aged 65 years and older. In the period 1979 to 1988, the incidence rate of breast cancer in Nijmegen (adjusted for age in 5-year categories: 65–69, 70–74, 75–79, 80–84 and 85+) equalled that in Arnhem (RR, 0.97; 95% CI, 0.83–1.14), whereas in the Nijmegen non-

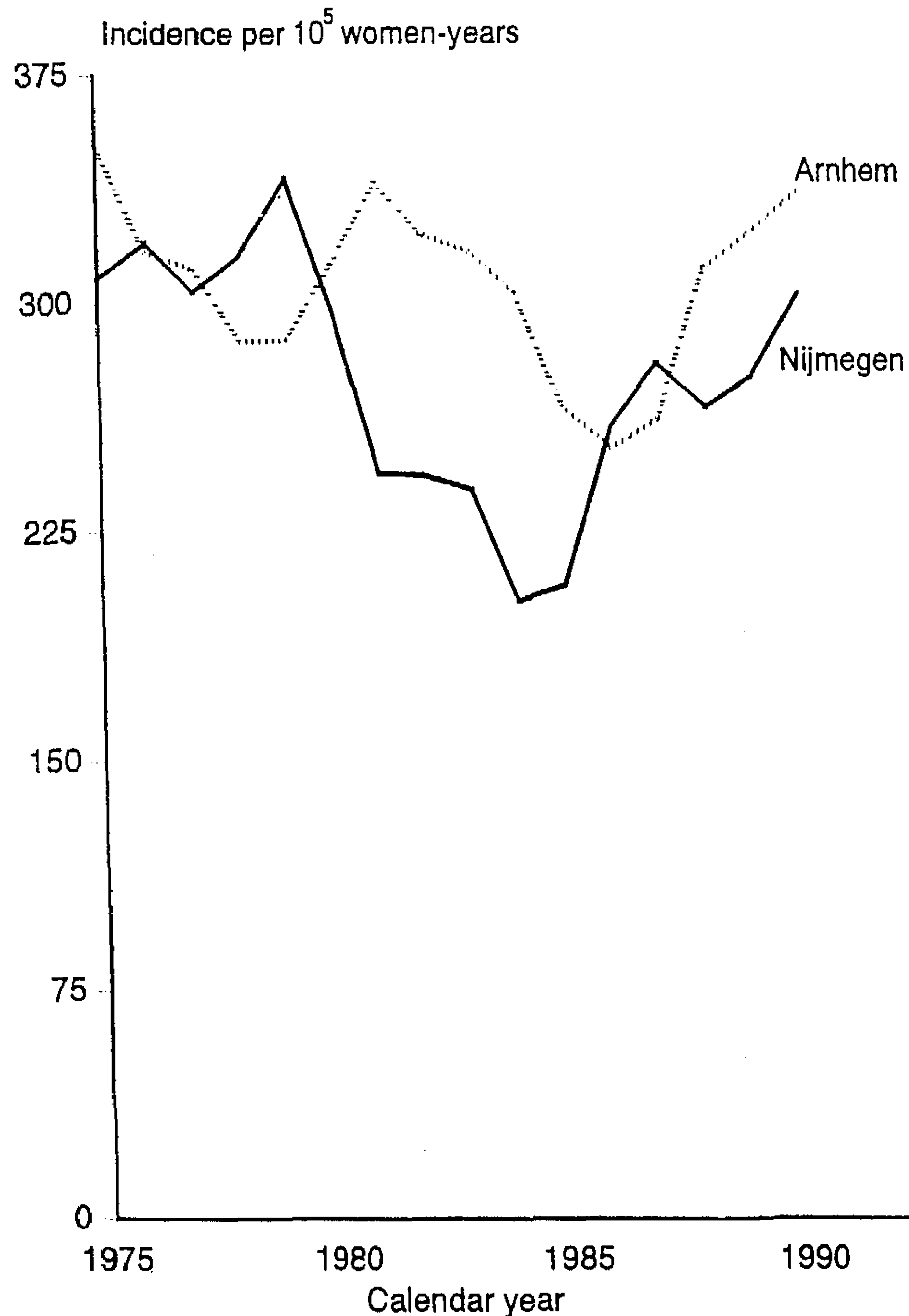


FIGURE 3 – Breast-cancer incidence rates (5-year moving average) in the Nijmegen and Arnhem populations born between 1895 and 1909.

participants, the incidence was much lower than that in Arnhem (RR, 0.72; 95% CI, 0.56–0.93). Therefore the incidence of breast cancer in the participants must have been much higher than in the non-participants (Van Dijck *et al.*, 1996). We concluded that the women who do participate in the screening are at increased risk for breast cancer. As a consequence, actual participation may have a relatively large effect on breast-cancer mortality in the population.

An important question is whether the populations of Nijmegen and Arnhem would have had the same breast-cancer mortality in the absence of screening. This cannot be derived directly, but it can be analyzed using an indirect approach by comparing the incidence of breast cancer. For the period 1975 to 1990, Figure 3 shows the incidence rates of primary breast cancer (5-year moving averages) in Nijmegen and Arnhem in women born between 1895 and 1909. In almost every calendar year, the incidence in Nijmegen was lower than in Arnhem. It was only higher in Nijmegen in 1977 to 1981, when rounds 1 and 2 took place for this birth cohort. In the early eighties, the incidence rate in Nijmegen declined, possibly due to the start of screening in the late seventies. Table III shows the number of diagnosed patients and the woman-years of observation, as well as the incidence-rate ratio for 4 periods. The incidence-rate ratio was 0.90 (95% CI, 0.75–1.07), adjusted for these 4 periods (directly weighted pooled estimate (Rothman, 1986b, 1996c). Correction of the mortality-rate ratio over the relevant observation period 1986 to 1990 gave an estimate of 0.59 (95% CI, 0.30–1.16).

TABLE III - NUMBER OF DIAGNOSED BREAST-CANCER PATIENTS AND WOMAN-YEARS IN NIJMEGEN AND ARNHEM IN 4 SPECIFIED PERIODS AND THE INCIDENCE-RATE RATIO (95% CI)

Period	Nijmegen		Arnhem		Incidence-rate ratio (95% CI)
	Diagnosed patients	Woman-years	Diagnosed patients	Woman-years	
1975-1990	226	81220	257	82891	0.90 ¹ (0.75-1.07)
1975-1976	38	14378	50	14317	0.76 (0.50-1.15)
1977-1980	84	25545	71	25425	1.18 (0.86-1.62)
1981-1985	61	24918	83	25665	0.76 (0.54-1.05)
1986-1990	43	16379	53	17484	0.87 (0.58-1.29)

¹Directly weighted pooled estimate (Rothman, 1986b,c).

Besides incidence, prognosis is also a modifier of breast-cancer mortality. Differences in prognosis could result from differences in treatment between Nijmegen and Arnhem. In Nijmegen, 30% of the patients were diagnosed and treated at the University hospital, while the remainder were patients at the other Nijmegen hospital. At the latter, a "Diagnostic Mamma Team" has been established, comprising radiologists, pathologists and surgeons from the 2 hospitals. Once a week, all the patients are discussed. The goal of these weekly discussions is to reduce the number of invasive diagnostic procedures. Although the patients from the 2 cities were treated according to protocols, the monitoring of diagnostic procedure may have influenced the decision for treatment.

A difference may have existed in the extent of misclassification of the cause of death. The procedures followed and the criteria used to ascertain the cause of death were identical for the Nijmegen and Arnhem patients. However, the physicians who made the classification were not blinded for city. Although unlikely, this may have led to differential misclassification. It is also possible that the information available in Nijmegen was more extensive than in Arnhem, for instance due to the "Diagnostic Mamma Team". An indication that this may have been the case was the fact that the deaths of 4 Nijmegen patients had been classified as "death from other cause with metastases of breast cancer," whereas no Arnhem patients had been classified as such. This category was used only during the last 3 years. Previously, deaths had been classified as either "due to breast cancer" or "due to other causes".

Several case-referent studies have been conducted in Nijmegen. In women aged 67 years or older at entry, breast-cancer mortality after 6 years of follow-up for those screened at least once was 19% lower (RR, 0.81; 95% CI, 0.23-2.75) than in those who had never been screened (Verbeek *et al.*, 1985). In the study reported in 1994, the follow-up period was 12 years (Van Dijck *et al.*, 1994). In women aged 65 years and older who had been invited for screening at least twice, breast-cancer mortality in those who had participated in the most recent screening was 42% lower than in those who had rejected it (RR, 0.58; 95% CI, 0.24-1.41). In those aged 65 to 74, the reduction in breast-cancer mortality was 66% (RR, 0.34; 95%

CI, 0.12-0.97). Our most recent study on women aged 65 years and older after 17 years of follow-up showed that breast-cancer mortality was 44% lower (RR, 0.56; 95% CI, 0.28-1.13) in women who had been screened regularly (*i.e.*, after the 2 most recent invitations) than in women who had not been screened in the past 10 years (Van Dijck *et al.*, 1996). In women aged 65 to 74 years the reduction in 3 case-referent studies, contrast was made between women who were screened and those who were not. The design of the present study was quite different, because contrast was made between the invited Nijmegen population, regardless of their actual screening history, and the uninvited Arnhem population. The most important reason for this design was to avoid bias due to self-selection. However, the price to be paid was a loss of contrast, because less than 50% of the invited population participated in at least one screening round.

The Swedish 2-county trial is the only other project with a long follow-up that included women aged 70 years and older. In that randomized study, the participation rate was 86% in women aged 65 to 69 and 77% in women aged 70 to 74 years. Women of over 74 years were excluded from all the analyses, because of the low participation rate of approximately 50%. After 14 years, the ratio of the cumulative risk (*i.e.*, number of deaths to the number of women enrolled) in the women aged 65 to 74 years at entry was 0.68 (95% CI, 0.51-0.89), which is much larger than in the Nijmegen invited population (cumulative rate ratio, 0.80). However, after the participation rate had been accounted for, the results compared very well.

The results of the present study, although in themselves inconclusive because of the wide confidence intervals, show a reduction in breast cancer mortality in women who were older than 65 years at entry to the screening programme. After 10 years, the reduction in breast cancer mortality may be as large as 40%. In an analysis of the positive and negative effects of screening after the age of 65 years, Boer and colleagues (1995) showed that, under optimistic assumptions, this balance may never become negative. Under pessimistic assumptions the positive effects may outweigh the negative effects until the age of 80 years. When the upper age limit of a screening programme is increased, however, the cost-effectiveness ratio will increase, for 2 reasons: the number of life-years gained will be less and the negative effects and the cost of screening will increase.

ACKNOWLEDGEMENTS

We are grateful to the Dutch "Nationale Ziekenfondsraad" for financial support. We thank Mr. J.D.M. Otten and Mr. E.P. Brummelkamp for gathering and processing the data; Ms. M.E. Eijgenberger for her help with the figures; Mrs. J. Abma-Hill for her linguistic comments; the Carcinoma Work Group Arnhem for gathering the Arnhem data; the Central Bureau of Statistics for the population data, and the local authorities of Nijmegen and Arnhem for providing the follow-up data on the patients.

REFERENCES

- BOER, R., DE KONING, H.J., VAN OORTMARSEN, G.J. and VAN DER MAAS, P.J., In search of the best upper age limit for breast cancer screening. *Eur. J. Cancer*, **31A**, 2040-2043 (1995).
- CHEN, H.-H., TABÁR, L., FAGERBERG, G. and DUFFY, S.W., Effect of breast-cancer screening after age 65. *J. med. Screening*, **2**, 10-14 (1995).
- DE KONING, H.J., BOER, R., WARMERDAM, P.G., BEEMSTERBOER, P.M. and VAN DER MAAS, P.J., Quantitative interpretation of age-specific mortality reductions from the Swedish breast-cancer screening trials. *J. nat. Cancer Inst.*, **87**, 1217-1223 (1995).
- FLETCHER, S.W., BLACK, W., HARRIS, R., RIMER, B.K. and SHAPIRO, S., Report of the International Workshop on screening for breast cancer. *J. nat. Cancer Inst.*, **85**, 1644-1656 (1993).
- KERLIKOWSKA, K., GRADY, D., RUBIN, S.M., SANDROCK, C. and ERNSTER, V.L., Efficacy of screening mammography; a meta-analysis. *J. Amer. med. Ass.*, **273**, 149-154 (1995).
- MORRISON, A.S., Screening for cancer of the breast. *Epidemiol. Rev.*, **15**, 244-255 (1993).
- MOSS, S.M., SUMMERLY, M.E., THOMAS, B.T., ELLMAN, E. and CHAMBERLAIN, J.O., A case-control evaluation of the effect of breast-cancer screening in the United Kingdom trial of early detection of breast cancer. *J. Epidemiol. Community Hlth.*, **46**, 362-364 (1992).
- NYSTRÖM, L., RUTQVIST, L.E., WALL, S., LINDGREN, A., LINQVIST, M., RYDÉN, S., ANDERSSON, I., BJURSTAM, N., FAGERBERG, G., FRISSELL, J., TABÁR, L. and LARSSON, L.-G., Breast-cancer screening with mammography: overview of Swedish randomised trials. *Lancet*, **341**, 973-978 (1993).
- OTTEN, J.D.M., VAN DIJCK, J.A.A.M., PEER, P.G.M., STRAATMAN, H., VERBEEK, A.L.M., MRAYUNAC, M., HENDRIKS, J.H.C.L. and HOLLAND, R.,

- Long-term breast-cancer screening in Nijmegen: the 9 rounds from 1975–1992. *J. Epidemiol. Community Hlth.*, **50**, 353–358 (1996).
- ROTHMAN, K.J., *Modern epidemiology*, pp. 171–172, Little, Brown and Company, Boston, Toronto (1986a).
- ROTHMAN, K.J., *Modern epidemiology*, pp. 177–237, Little, Brown and Company, Boston Toronto (1986b).
- ROTHMAN, K.J., *Modern epidemiology*, p 210, Little, Brown and Company, Boston, Toronto (1986c).
- VAN DIJCK, J.A.A.M., HOLLAND, R., VERBEEK, A.L.M., HENDRIKS, J.H.C.L. and MRVUNAC, M., Efficacy of mammographic screening of the elderly: a case-referent study in the Nijmegen program in the Netherlands. *J. nat. Cancer Inst.*, **86**, 934–938 (1994).
- VAN DIJCK, J.A.A.M., VERBEEK, A.L.M., BEEK, L.V.A.M., HENDRIKS, J.H.C.L., HOLLAND, R., MRVUNAC, M., STRAATMAN, H. and WERRE, J.M., Mammographic screening after the age of 65 years: evidence for a reduction in breast-cancer mortality. *Int. J. Cancer*; **66**, 727–732 (1996).
- VERBEEK, A.L.M., HENDRIKS, J.H.C.L., HOLLAND, R., MRVUNAC, M. and STURMANS, F., Mammographic screening and breast-cancer mortality: age-specific effects in the Nijmegen project, 1975–1982. *Lancet*, **I**, 865–866 (1985).