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Report

Randomized study of mammography screening – preliminary report on mortality in the Stockholm trial

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Summary

In March 1981, 40,318 women in Stockholm, aged 40–64, entered a randomized trial of breast cancer screening by single-view mammography alone versus no intervention in a control group of 20,000 women. The attendance rate during the first screening round was 81 per cent and the cancer detection rate was 4.0 per 1000 women. The detection the rate fell to 3.1 per 1000 in the second round, which was completed in October 1985. During 1986 the controlled design of the study was broken and the control women were invited once to screening which was completed the same year. A total of 428 cases of breast cancer were thus diagnosed in the study group and 439 in the adjusted control group. After a mean follow-up of 7.4 years the number of breast cancer deaths in the study and control groups was 39 and 30 respectively. The relative risk of breast cancer death (screening versus control) was 0.71 (95 per cent confidence interval: 0.4–1.2). Among women older than 50 years at entry the relative risk was 0.57 (95 per cent confidence interval: 0.3–1.1). Cancer deaths among women under 50 were few and perhaps because of this no mortality reduction was seen in this age group. The estimate of mortality reduction lies between the results from two earlier Swedish randomized controlled trials.

Introduction

Evidence from the HIP study of New York strongly supports the hypothesis that an earlier diagnosis could improve the prognosis. The HIP study, which was the first randomized mammographic screening trial, started in 1963 and included patients registered in the Health Insurance Plan of Greater New York. Both physical examination and mammography were used in the screening programme and a reduction in mortality from breast cancer of about 30% was demonstrated in women invited to screening [1].

Two case-control studies in the Netherlands in 1973–74, one in Utrecht with two-view mammography plus a physical examination and the other in Nijmegen with single-view mammography alone, have demonstrated a mortality reduction in women over 50 but not in younger age-groups [2, 3]. In a British study that began in 1979, mammography and/or clinical examination was offered to two groups of women, from Guildford and Edinburgh, while two groups from another two cities were offered training in breast self examination [4]. A small reduction of mortality was demonstrated among women in the group offered mammography but not in the other groups [5, 6].

Two randomized controlled trials in Sweden, the

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two county study (WE-study) and the Malmö trial, have presented mortality results. The WE-study was the larger of the two and at 8 years follow-up a significant 32 per cent decrease in mortality was demonstrated in the total material. The effect seems to be stronger among women over 50, with no significant effect in younger women [7]. The Malmö trial showed no significant effect on mortality in the total study after 8.8 years, but a 20 per cent, non-significant reduction in women over 55 [8].

The Stockholm trial, the third randomized trial in Sweden, started a few years after the other two, but now has 7.4 years of follow-up. The preliminary mortality results for this trial are reported here.

Subjects and screening

The Stockholm study comprised a total of 60,261 women aged 40–64 years at the beginning of the trial, residents in the south-east part of Greater Stockholm. The population of Stockholm is fairly stable, the annual migration rate from the city being about 1.5 to 2 per cent in the participating age groups. The presented cancer cases include all migrants to other parts of Stockholm. Mammography was offered to 40,318 women, the study population (SP), while another 19,343 made up the control population (CP). The screening programme and the first round results have been published earlier, as has the development of advanced cancers after 5 years, which was used to assess an early effect of the screening [9, 10]. Selection was done individually by birth dates; the SP comprised women born on the 1st–10th and the 21st–30th of a month, while the CP women were those born on the 11th–20th of a month. Women born on the 31st were also offered mammography but were excluded from the SP in order to simplify the numerical comparisons. The birth date can be regarded as a sufficient generator of random selection between SP and CP. The number of women summoned for single view mammography and the corresponding number in the control population are given in Table 1. The invitations to the SP women were sent out successively by personal letter by ascending order of birth dates (1st–10th, 21st–30th). The date of entry was defined as the date of invitation to the study. The control women were matched to the screened women, those born on the 11th being matched with SP women born on the 1st and 21st, and so on. The first round began on 9 March 1981 and took 2.5 years to complete; the second round began on 1 September 1983 and took 2.1 years to complete. After 1985 the controlled design of the study was broken and during 1986 the control women were invited once for screening mammography. After 31 December 1986 no more cancer cases were brought into the study. The women in the study were followed up to 31 January 1989, with a mean follow up time of 7.4 years. Participation exceeded 80 percent in both the first and the second screening, with little difference between age-groups (Table 2). At the end of the study, when the control group was invited to mammography, participation was 77 per cent (Table 2). The incidence of recalls for further examination – additional X-rays, fine-needle biopsy, and, if necessary, open surgical biopsy from the first two screening rounds – is given in Table 3.

Table 1. Number of women summoned for single view mammography, and corresponding number of women in the control population

Age (years)	Screening round I (date of birth 1–10)	Control group (date of birth 11–20)	Screening round I (date of birth 21–30)	Control group (date of birth 11–20)
40–44	3805	3712	3902	3873
45–49	3428	3391	3240	3410
50–54	3742	3784	3567	3719
55–59	4246	4361	4233	4170
60–64	4592	4695	4409	4687
	19813	19943	19351	19859

Methods

Mammography

Mammography was performed with a CGR Mammograph (Senograph 500T). A single-view mammogram was obtained in an oblique projection. If malignancy was suspected, the women was recalled for a conventional three-view mammogram. Kodak NMB film was used with Kodak mammography cassettes and Kodak Min-R intensification screens. The film was exposed at 28 kv and developed at 34° C with a total processing time of 2.5 min.

Primary treatment

The primary management of detected breast cancer cases accorded with guidelines published by the Stockholm Breast Cancer Study Group. This implied that the cancer cases were treated according to the same principles in the screening and control groups. The surgical treatment offered to stage I breast cancer patients was generally segmental mastectomy with axillary dissection followed by post operative radiotherapy to the breast (50 Gy/5 weeks), or total mastectomy with axillary dissection. In more advanced cases, total mastectomy with axillary dissection was usually done alone or in combination with adjuvant systemic therapy.

Statistical methods

The mortality rate in the groups is obtained as the ratio between the number of deaths from breast cancer and the number of person-years. The significance analysis and the confidence intervals are based on the reasonable assumption that the observed numbers of deaths are Poisson-distributed and that the uncertainty in the numbers of person-years can be neglected. The relative risk (RR-value) is obtained as the ratio between SP and CP in terms of the above mentioned rate. Confidence intervals of the ratio between the Poisson distributed variables can be estimated with the help of exact confidence limits for binomially distributed variables. Thus, the confidence limits of the rates can be specified.

Assessment at the end of the trial

The end-point in the trial was breast cancer death. In previous studies the definition of breast cancer death has varied. In the HIP- and Malmö studies it was defined as death with breast cancer as the underlying cause according to internationally accepted rules [11]. In the WE-study it was defined as death with breast cancer present at death (locoregional or distant disease). For the purposes of this analysis, breast cancer death was assessed according to the criteria in the WE-study. All detected breast cancer cases in the trial were included in the breast cancer data base of the Stockholm Breast Cancer Study Group. Follow up data in that register is based on continuous reports from the responsible clinicians. The data used in this analysis were retrieved from that data base. To assure completeness of the follow up, all breast cancer cases were also checked against official population registers and a computerised register covering 95 per cent of all inpatient care in the Stockholm region.

Table 2. Attendance rate (per cent) in the Stockholm screening trial. The control group was screened once, in 1986

Age at first screen (year)	Screening I	Screening II	Control I
40–44	81.8	81.1	77.7
45–49	80.4	80.0	77.0
50–54	79.7	79.2	76.6
55–59	80.6	80.0	77.2
60–64	80.8	80.2	79.3

Table 3. Comparative work scheme in the first and second screening rounds

	First screening		Second screening	
No. of participants in screening	32,555	(100.0)	30,765	(100.0)
Complete mammography	1,655	(5.1)	989	(3.2)
Clinical examination, aspiration biopsy	482	(1.5)	246	(0.8)
Surgery	207	(0.6)	122	(0.4)
– Histologic diagnosis of malignancy	128	(0.4)	95	(0.31)
– Histologic diagnosis of benign disease	79	(0.2)	27	(0.09)

Figures in parentheses represent percentage of participants.

Results

A total of 428 cancer cases were found in the SP and 439 in the CP, when it is uprated to match the size of the SP. All cases of cancer in the SP and CP from 1981 to 1986 and the clinical staging are compiled in Table 4. In the SP 173 cases belonged to stages II–IV, while the figure in the CP was 210 cases. Thus, the reduction in the number of advanced tumors after six years of screening was 17.6 per cent (NS; Table 4). The cumulative number of breast carcinomas during the study period 1981–1986 is seen in Fig. 1. When two screening rounds had been completed in December 1985, the number of cancer cases in the SP exceeded the number in the CP by 44 per cent, but following the completion of one screening round in the CP in December 1986, the groups reached the same level. The cumulated number of advanced cases (stages II–IV) in the SP and CP is shown in Fig. 2. During the study 88 patients who were diagnosed as having breast cancer died, 52 in the SP and 36 in the CP. Breast cancer was considered to be the underlying cause of death in 39 patients in the SP and 30 in the CP. The relative risk was 0.71 (95 per cent confidence interval: 0.4–1.2). The reduction of mortality was 29 per cent, not reaching the level of significance (Table 5). The cumulative number of deaths from breast cancer per 40,000 women is shown in relation to years after entry in Fig. 3. Of the women over 50, 23 died from breast cancer in the SP and 22 in the CP. In this age group the relative risk was 0.57 (95 per cent confidence interval: 0.3–1.1) and the reduction of mortality was 43 per cent (NS; Table 5). The cumulative number of deaths from breast cancer in age groups 50–64 and 50–59 years is seen in Figs 4 and 5 respectively. Of the women under 50, 16 died from breast cancer in the SP and 8 in the CP. The relative risk was 1.09 (95 per cent confidence interval: 0.4–3.0) and no reduction in mortality was found (Table 5). The cumulative number of deaths in this age group is seen in Fig. 6. Of the women who died from breast cancer in the study, 85 per cent and 84 per cent in the SP and CP respectively had an advanced disease (stages II–IV) at discovery. Of the 39 breast cancer deaths in the SP, 17 (44 per cent) belonged to the interval group, 14 (36 per cent) to the refusers group, and 8 (20 per cent) to the screened group.

Table 4. Total number of breast carcinomas in the study population (SP) and the control population (CP) with respect to stage distribution. The CP is adjusted in size. The control population was screened in 1986.

Stage at discovery:		CIS	I	II	III–IV	Total
1981	SP	3	20	8	1	32
	CP	0	4	2	1	7
1982	SP	5	46	24	5	80
	CP	0	16	19	1	36
1983	SP	7	56	37	6	106
	CP	10	31	28	7	76
1984	SP	12	39	27	8	86
	CP	8	18	34	4	64
1985	SP	4	36	21	6	67
	CP	0	20	40	14	74
1986	SP	0	27	22	8	57
	CP	28	94	48	12	182
Total	SP	31	224	139	34	428
	CP	46	183	171	39	439

Discussion

A number of steps seem to be of importance when

Table 5. Deaths from breast cancer by age at entry and person years of observation in study population (SP) and in control population (CP)

	Deaths	Population	Person-years	Relative risk; Confidence interval 95%
Age group 40–64:				
SP	39	39,164	270,247	0.71
CP	30	19,943	147,373	CI 95% (0.4–1.2)
Age group 50–64:				
SP	23	24,789	171,092	0.57
CP	22	12,840	92,927	CI 95% (0.3–1.1)
Age group 40–49:				
SP	16	14,375	99,155	1.09
CP	8	7,103	54,446	CI 95% (0.4–3.0)

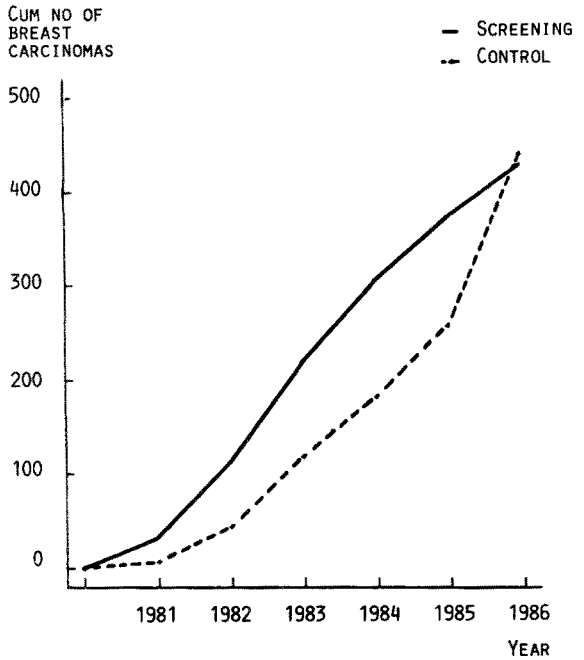

Fig. 1. Cumulative number of breast carcinomas, diagnosed in 1981–1986, in the Stockholm screening project. The control population was screened once in 1986.

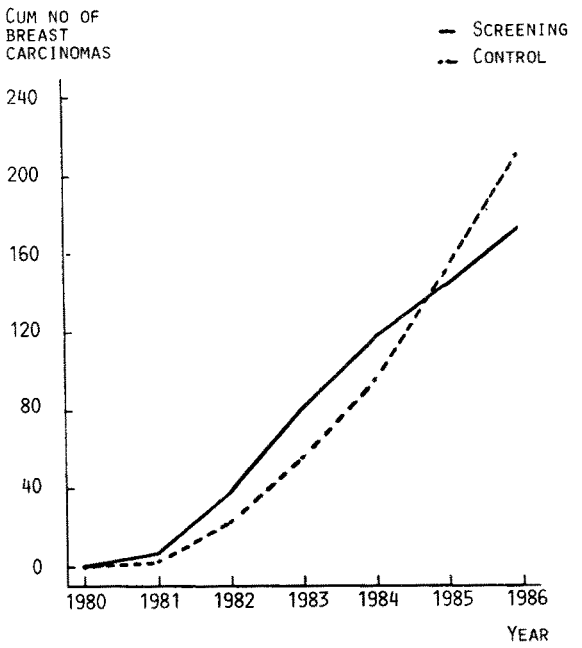

Fig. 2. Cumulative number of advanced breast carcinomas (stage II–IV), diagnosed in 1981–1986 in the Stockholm screening project.

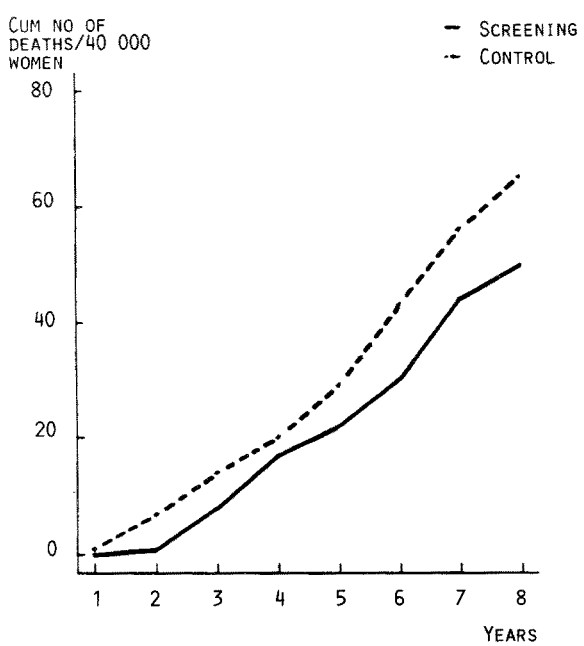

Fig. 3. Cumulative number of deaths per 40,000 women by time since entry in the study, in age group 40–64 years at entry. The control group is adjusted for size.

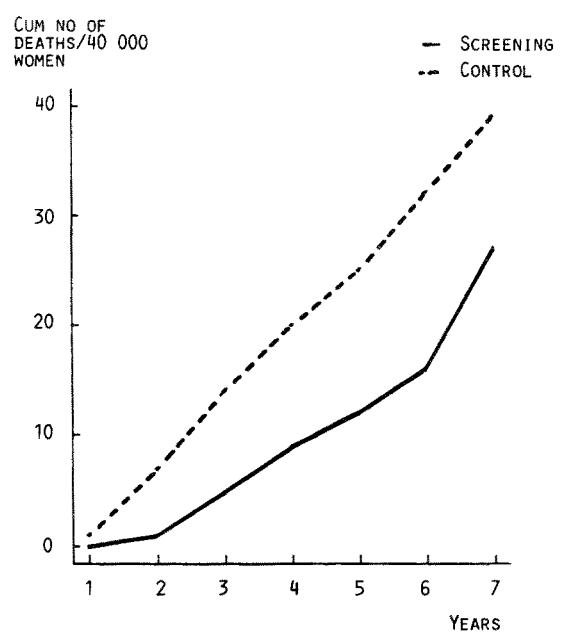

Fig. 4. Cumulative number of deaths per 40,000 women, aged 50–64 years, by time since entry in the study. The control group is adjusted for size.

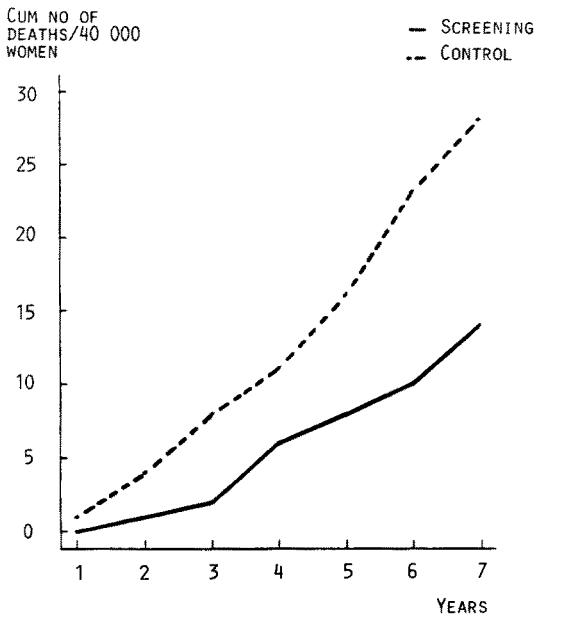

Fig. 5. Cumulative number of deaths per 40,000 women, aged 50–59 years, by time since entry in the study. The control group is adjusted for size.

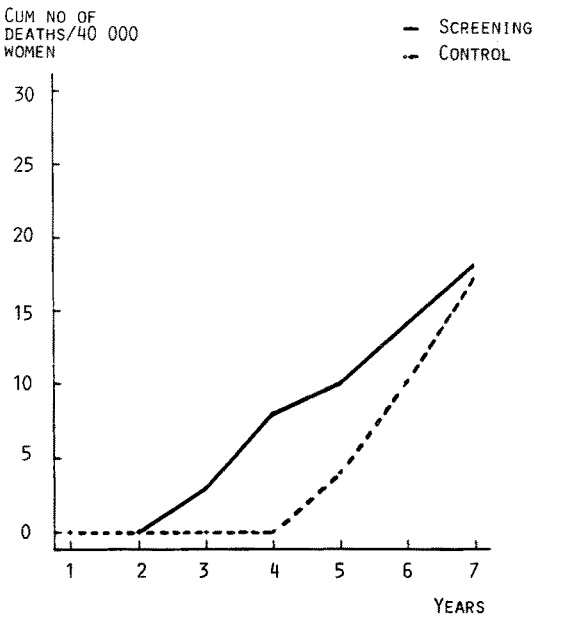

Fig. 6. Cumulative number of deaths per 40,000 women, aged 40–49 years, by time since entry in the study. The control group is adjusted for size.

performing a screening. The attendance rate in the Swedish trials varies from 90 per cent in the WE trial to 70 per cent in the Malmö trial. These figures are relatively high in relation to trials outside Sweden. In the group of non attenders, the number of advanced tumors is high. In the first two screening rounds in the Stockholm trial 45 cases of breast cancer were found clinically among the refusers; 25 (56 per cent) had a breast cancer in stages II–IV and nine of these were primarily inoperable. In the Malmö trial deaths from breast cancer were substantially overrepresented among women who did not attend for screening [8]. Of the women with breast cancer in the group of refusers, 19 (42 per cent) had mammography done in another mammography center outside the trial, and in this group there was a dominance of stage I tumors.

The results of our trial may also have been influenced by the fact that some women in the CP had had mammography. In the Stockholm trial 25 per cent of the invited women had had a mammography during the last three years before the screening start. In the year 1979 8 per cent of all women in Stockholm had had a mammography. These figures are in agreement with those from the Malmö trial [8]. The WE trial on the other hand began earlier than the Stockholm trial (1977) and concerned a predominantly rural population with little access to mammography. The fact that some of the subjects in the control group have undergone mammography probably means that the difference in the mortality outcome between screening and control groups will be underestimated. The size of the study populations varied also in the different trials; 15,748 women participated in the first screening round in the Malmö trial and 32,555 women in the Stockholm trial, while in the largest study, the WE trial, 69,645 women participated in the first screening round [12, 13].

The proportion of interval cancers in relation to the number of cancer cases in the control group is an important measure of the effectiveness of the screening test. In the first year after the first and second screening round in the Stockholm trial, 72 per cent of the cancers were picked up with the screening mammography and in the second year 52 per cent. This means that the proportion of interval cancers was 28 per cent in the first year after the screening round and 48 per cent in the second year, figures that are similar to the WE trial [14]. The proportion of interval cancers was higher among women under 50 years compared to women over 50

in the Stockholm trial, and the experience in the WE trial has been the same [14, 15]. Forty-four per cent of the breast cancer deaths in the SP belonged to the interval group.

The choice of screening method may be of importance. In Sweden mammography is used as the sole screening method; in Malmö and Gothenburg trial a two view technique was used and in the Stockholm and WE trials a single view technique was used. In the HIP study both mammography and clinical examination was used, but this trial started in 1964 with a low sensitivity of the mammography. Also in the Utrecht trial in the Netherlands and in the UK trial the combination of the two screening methods was used.

The number of non-invasive tumors detected in screening programmes is 2–4 times higher compared to an unscreened population [16]. The proportion of early invasive cancers, stage I, is very high among screening-detected cancers. Treatment of these early cancers prevents metastases of breast cancer in most cases [17]. With a natural life cycle of breast cancer, on average 15 years, influence on the death rate in early cancers will not be seen until many years later [18]. Deaths during the first five years after the cancer detection would mainly come from advanced tumors, stages II–IV [19]. In the Malmö and Stockholm trials 89 per cent and 85 per cent respectively of the women who died from breast cancer during the first 6 years of the study had an advanced disease at discovery [8]. Several reports from the WE trial have shown the usefulness of the cumulative incidence of stage II or worse tumors detected during the trial as an early indicator of mortality outcome [20–22]. The experience of the Stockholm trial has been the same, with a reduction in the number of advanced cancer cases in the study group [10]. The absolute reduction in the study group versus the control group was 17.6 per cent in 1986 (Fig. 2).

The mortality reduction from randomized controlled trials with a follow-up of 7–8.8 years has varied from 4 per cent in the Malmö trial up to over 30 per cent in the WE trial. The HIP study in New York and the WE trial in Sweden demonstrated a significant reduction in mortality [1, 7, 23]. The Guildford and the Edinburgh trials in the UK have demonstrated a 20 and 17 per cent reduction of mortality respectively, which was not statistically significant [5, 6]. In this preliminary report from the Stockholm trial the reduction of mortality was 29 per cent. Among women over 50 years the mortality reduction has been higher in all trials, and in the Stockholm trial it was 43 per cent. The number of deaths among younger women seems in this study to be still too small to draw any conclusions after 7.4 years.

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