Mammographic screening and mortality from breast cancer: the Malmö mammographic screening trial

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Abstract

Study objective—To determine whether mortality from breast cancer could be reduced by repeated mammographic screening.

Design—Birth year cohorts of city population separately randomised into study and control groups.

Setting—Screening clinic outside main hospital.

Patients—Women aged over 45; 21 088 invited for screening and 21 195 in control group.

Interventions—Women in the study group were invited to attend for mammographic screening at intervals of 18-24 months. Five rounds of screening were completed. Breast cancer was treated according to stage at diagnosis.

End point—Mortality from breast cancer.

Measurements and main results—All women were followed up and classed at end point as alive without breast cancer, alive with breast cancer, dead from breast cancer, or dead from other causes. Cause of death was taken from national mortality registry and for patients with breast cancer was validated independently. Mean follow up was 8·8 years. Altogether 588 cases of breast cancer were diagnosed in the study group and 447 in the control group; 99 *v* 94 women died of all causes and 63 *v* 66 women died of breast cancer (no significant difference; relative risk 0·96 (95% confidence interval 0·68 to 1·35)). In the study group 29% more women aged <55 died of breast cancer (28 *v* 22; relative risk 1·29 (0·74 to 2·25)). More women in the study group died from breast cancer in the first seven years; after that the trend reversed, especially in women aged ≥55 at entry. Overall, women in the study group aged ≥55 had a 20% reduction in mortality from breast cancer (35 *v* 44; relative risk 0·79 (0·51 to 1·24)).

Other findings—In the study group 100 (17%) cancers appeared in intervals between screenings and 107 (18%) in non-attenders; 51 of these women died from breast cancer. Cancers classed as stages II-IV comprised 33% (190/579) of cancers in the study group and 52% (231/443) in the control group.

Conclusions—Invitation to mammographic screening may lead to reduced mortality from breast cancer, at least in women aged 55 or over.

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Introduction

Many clinical studies have shown that the prognosis of breast cancer is related to the stage of the disease at diagnosis and treatment.[1] Mammography is a sensitive method of detecting breast cancer at an early stage, sometimes even at an in situ stage, and hence mortality from breast cancer should be reduced by mammogaphic screening. Owing to the potential lead time (the amount of time by which diagnosis is advanced through screening) and to length time bias associated with screening (the tendency of screening to pick up slow growing tumours) a randomised trial is necessary to determine whether such a reduction does occur.

The first evidence in favour of mammographic screening came from the study on patients registered with the Health Insurance Plan of Greater New York.[2,3] This study included physical examination as well as mammography and showed a reduction in mortality from breast cancer of about 30% in women invited for screening. Owing to the design of the study the effect of mammography alone could not be assessed. Furthermore, because of differences in mortality from breast cancer between the United States and Sweden and in the use of diagnostic procedures such as mammography the study's results could not be extrapolated to a Swedish population, Substantial technical advances in mammography were made after the American study, and in 1976 a trial was set up in the city of Malmö in southern Sweden to find whether the mortality from breast cancer could be reduced by repeatedly inviting women to attend for mammographic screening. We report the results.

Subjects and methods

All women born in 1908-32 were identified from the population registry of Malmö. Half the women in each birth year cohort were randomly selected as the study groups and invited to mammographic screening. The remaining women were allocated to a control group and were not screened. Each birth year cohort was randomised separately. Invitation was by personal letter, and all 25 birth year cohorts were successively entered into the study, the date of entry being defined as the date of invitation. The screening programme started in October 1976; all 25 birth year cohorts had been through their first round of screening by the end of September 1978. The planned interval between screenings was 18 to 24 months. Women who had moved out of the city were not contacted for subsequent examinations. Women who did not attend a screening examination but were still living in the city were invited to subsequent rounds. The examinations were free of charge. The study was approved by the ethical committee at the University of Lund, Sweden.

Screening was with up to date film screen mammography, improved equipment being used as it became available. In the first two rounds two views (craniocaudal and oblique) were used. In subsequent rounds either both views or only the oblique was taken, depending on the parenchymal pattern: a single oblique view was taken for women whose breasts were mainly fatty on mammography, and both views were taken for women with dense breasts.

Malmö is served by one hospital for somatic diseases, where virtually all patients with breast cancer are diagnosed and treated by a team specialising in breast

diseases. Patients are treated according to the stage of the cancer. The principles of treatment changed somewhat during the study period; in particular, breast preserving surgery was introduced for patients with limited disease. At the beginning of the study period simple mastectomy was the standard treatment for non-invasive breast cancer (stage 0); this was later replaced by subcutaneous mastectomy. The treatment offered for stage I breast cancer from 1979 was breast conservation or mastectomy. For stage II cancer two different randomised clinical trials were started in 1978 to test adjuvant radiotherapy or chemohormonal therapy, or both, and ran consecutively. Treatment for stages III and IV was individualised throughout the study period. As invitation to screening was never used as a stratification variable in the trials of the treatments all patients were treated according to the same principles.

Statistical methods—The predetermined end of the trial was 31 December 1986; no interim analyses were performed. The study was designed to document a 25% reduction in mortality from breast cancer with a power of 0·90 at the 5% level of significance. The effect of screening on mortality from breast cancer was estimated by the relative risk for the study group versus the control group with a test based 95% confidence interval. Women who had been treated for breast cancer previously were included in the analysis only if a new cancer was diagnosed in the other breast during the study. For comparison, analyses were done including and excluding these women.

Assessment at the end of trial—At the end of the trial women in both groups were classified as alive without breast cancer, alive with breast cancer, dead from breast cancer, or dead from other causes. Over 98% of the patients with breast cancer in both groups were registered with and subsequently treated at Malmö General Hospital. The remaining 2% of patients were identified through the national cancer registry. The number of deaths, together with the cause of death, was retrieved from the national mortality registry. Women who had moved out of the country were followed up through the national registry of immigrants and emigrants.

Validation of end points—To achieve an independent evaluation of the cause of death of patients with breast cancer identified in the study an end point committee was formed to reassess the clinical records and findings of postmortem examinations. The committee consisted of one pathologist and one oncologist; they were blinded to the patients to reduce the risk of bias in establishing the underlying cause of death. They separately reviewed the clinical data and findings of postmortem examinations and then independently determined the cause of death. Biopsy material as well as microscopic material from postmortem examination was analysed if necessary. Additional clinical records could be requested if insufficient material for an accurate decision had originally been submitted. When the two committee members did not agree, the case was re-evaluated and determined by a qualified internist. The underlying cause of death was coded according to the eighth revision of the International Classification of Diseases.[4]

TABLE I—*Composition of Malmö mammographic screening trial by birth cohorts and woman years of observation. Women were aged 45-69 at entry*

	Study group			Control group	
Birth cohort	No of women	No of woman years	No (%) attending first screening	No of women	No of woman years
1908-12	4 183	33 550	2 677 (64)	4 169	33 611
1913-7	4 324	38 041	3 113 (72)	4 321	37 779
1918-22	4 600	42 931	3 496 (76)	4 623	42 991
1923-7	4 323	40 723	3 458 (80)	4 313	40 578
1928-32	3 658	31 052	2 890 (79)	3 769	32 057
Total	21 088	186 297	15 604 (74)	21 195	187 016

TABLE II—*Numbers of breast cancers detected in women in study and control groups by age at diagnosis*

	Cancers detected in study group				
Age at diagnosis	At screening	In intervals between screening*	In non-attenders†	Total	Cancers detected in control groups
45-49	16	6		22	14
50-54	60	24	17	101	77
55-59	55	23	16	94	89
60-64	80	16	19	115	93
65-69	97	16	33	146	89
70-74	47	12	16	75	67
75-79	19	3	6	28	18
Total	374	100	107	581‡	447§

*Breast cancer diagnosed in interval between negative screening examination and invitation for next screening.
†Women who did not attend screening examination and in whom breast cancer was diagnosed before invitation for next screening.
‡In addition, seven women in study group had breast cancer diagnosed after moving out of Malmö. Two patients with malignant cystosarcoma phyllodes and one patient with fibrosarcoma were included.
§Includes three patients with malignant cystosarcoma phyllodes and one with fibrosarcoma.

Results

By 31 December 1986 five rounds of screening and most of the sixth round had been completed. The mean duration of follow up in each group was 8·8 years. Table I shows the age distribution of the women in the study. The attendance rate was higher in the first round (74%) than subsequent rounds (70%) and higher among younger than older women.

BREAST CANCERS

A total of 1035 women developed breast cancer, 588 in the study group and 447 controls (table II). The number of breast cancer years was 2835 in the study group and 1869 in the control group. Seventeen per cent of the cancers in the study group appeared in the intervals between screenings and 18% in women who had been invited for screening but did not attend. Thirty six patients in the study group had bilateral carcinoma: in 16 the cancer was diagnosed on both sides within the study period and in 20 it had been diagnosed in one breast before entry into the study. In the control group 32 patients had bilateral carcinoma, the disease being detected on both sides within the study period in nine patients.

The mean age at which breast cancer was diagnosed was 62·4 years for patients whose carcinomas were detected at screening, 59·9 for patients whose carcinomas were detected in the intervals between screening, and 63·5 for non-attenders; it was 61·8 years for patients in the control group.

The median size of invasive carcinomas detected at screening was 1·0 cm, of carcinomas detected in the intervals between screenings 1·9 cm, of carcinomas in non-attenders 2·5 cm, and of carcinomas in the control group 1·9 cm. The size of the actual carcinoma was measured whenever possible; otherwise the size was measured on the mammograms. The largest diameter was used to compute the median tumour size.

Table III shows the distribution of tumours by stage. Bilateral carcinomas were staged according to the most advanced side if synchronous, and according to the first carcinoma if metachronous. Patients who had carcinoma in one breast before the study and in the other breast within the study were staged according to the carcinoma detected in the study period. Most non-invasive carcinomas (stage 0) were ductal (81 (87%) in the study group and 38 (78%) in the control group); the rest were lobular. A large proportion (26%) of non-invasive cancers were discovered in the intervals between screenings. The proportion of advanced cancers was significantly greater in those who did not

attend for screening than it was in the control group (72% *v* 50%; p=0·0001, χ^2 test). On the whole the distribution by stage was more favourable in the study group, which had a smaller proportion of stage II-IV cancers than the control group (tables III and IV).

Table V shows only minor differences in treatment between the study group and the control group with respect to stage 0 disease. As no women with stage 0 cancer died this somewhat skewed distribution of treatment was unimportant.

MORTALITY

Table VI shows the mortality in the population under study. The cause of death was as given in the national mortality registry, which was complete up to the end of 1985 at the time of analysis. Death certificates had been based on findings of postmortem examinations in 58% of cases in the study group and 57% in the control group. There were only minor differences between the groups in the age specific rate of postmortem examinations and no significant difference in overall mortality between the groups. Mortality specific to cause was similar in the two groups.

TABLE III—*Number (percentage) of cases of breast cancer by stage in study and control groups*

Stage*	Cancers detected in study group: At screening (n=374)	In intervals between screening (n=79)	In non-attenders (n=106)	Total† (n=79)	Cancers detected in control group† (n=443)
0	61 (16)	24 (24)	8 (8)	93 (16)	50 (11)
I	241 (64)	33 (33)	22 (21)	296 (51)	162 (37)
II	68 (18)	33 (33)	41 (39)	142 (25)	172 (39)
III	4 (1)	7 (7)	15 (14)	26 (4)	27 (6)
IV	0	2 (2)	20 (19)	22 (4)	32 (7)
II-IV as proportion of:					
All carcinomas				190/579 (33)	231/443 (52)
Invasive carcinomas				190/486 (39)	231/393 (59)

*Staging by Union International Contra le Cancrum's TNM classification.[5]
†Two cases of malignant cystosarcoma phyllodes in study group and three in control group and one case of fibrosarcoma in each group were not staged. Stage was unknown in six cases in study group.

TABLE IV—*Cumulative rate of stage II-IV breast cancers* per 100 000 woman years after entry into study*

Year after entry	Control group	Study group
1	152	196
2	286	287
3	401	398
4	513	500
5	661	584
6	795	654
7	890	749
8	971	831
9	1111	930
10	1210	980

*Staged by Union International Contra le Cancrum's TNM classification.[5]

END POINTS

During the study 193 patients who had been diagnosed as having breast cancer died, 94 in the control group and 99 in the study group (table VII); in both groups 76% underwent postmortem examination. Breast cancer was considered by the independent evaluators to be the underlying cause of death in 66 patients in the control group and 63 in the study group. Most (51) of the deaths from breast cancer in the study group occurred in women who did not attend for screening and in women whose carcinoma was detected in the interval between screenings. In both groups women with breast cancer showed the same pattern of deaths from other causes.

Of the 193 women with breast cancer who died, 41 had at least one other malignancy (19 in the control group and 22 in the study group); it was the cause of death in 14 patients in the control group and in 17 in the study group, according to the independent evaluators. Twenty six of the 41 patients had undergone postmortem examination, and in three the additional cancer was an unexpected finding and was determined to be the cause of death. In another two cases the additional cancer was found to be the cause of death, although clinically the cause of death was attributed to metastases from the breast cancer.

During the analysis we questioned whether all patients with metastases of breast cancer, irrespective of the cause of death, should be included in the assessment of the effect of screening; whether the comparison should be based only on official death certificates; and whether women in whom breast cancer had been diagnosed before the study should be included. Table VIII shows the results of analyses based on these different definitions of end point.

During the first seven calendar years of the screening programme the cumulative number of deaths from breast cancer was higher in the study group than the control group, but at the end of the trial the opposite was the case (figure). The initial trend of a higher number of deaths from breast cancer each year in the study group was reversed six years after the start of the screening programme (table IX). In the seventh and subsequent years the number of deaths from breast cancer was lower in the study group. By the end of 1987 this trend was more pronounced: in 1987, 18 of the patients who died from breast cancer were in the control group compared with six in the study group.

Mortality from breast cancer in the study group was unexpectedly high at first. To investigate this phenomenon further we compared the effect of screening on women younger than age 55 and aged 55 or older at entry into the study (table X, figure). The excess deaths from breast cancer in the study group occurred

TABLE V—*Numbers (percentages) of women with breast cancer given surgical treatment, adjuvant hormone therapy, chemotherapy, and radiotherapy according to stage of disease. Some women were given more than one treatment*

	Stage 0		Stage I		Stage II		Stage III		Stage IV	
	Control group (n=50)*	Study group (n=92)	Control group (n=161)	Study group (n=294)	Control group (n=170)	Study group (n=142)	Control group (n=27)	Study group (n=26)	Control group (n=28)	Study group (n=21)
Breast preserving surgery	9 (18)	31 (33)	54 (34)	95 (32)	15 (9)	7 (5)		2 (8)	2 (7)	2 (10)
Mastectomy	24 (48)	43 (47)	102 (63)	197 (67)	154 (91)	135 (95)	23 (86)	21 (81)	13 (47)	8 (38)
Subcutaneous mastectomy	17 (34)	18 (19)	5 (3)	2 (1)	1 (1)					
Hormone therapy	1 (2)		2 (1)	6 (2)	66 (39)	60 (42)	11 (39)	6 (23)	19 (67)	8 (38)
Chemotherapy	1 (2)				17 (10)	11 (8)	7 (27)	4 (15)	16 (56)	11 (53)
Radiotherapy	1 (2)	6 (7)	64 (40)	123 (42)	119 (70)	106 (74)	22 (81)	22 (85)	3 (11)	3 (16)

*Data on treatment not available for some patients.

TABLE VI—*Cause of death (according to national registry) in study and control groups from date of entry into screening trial until 31 December 1985*

Cause of death (ICD code*)	Study group (n=21 088): No of deaths	% Of all deaths	% Of group	Control group (n=21 195): No of deaths	% Of all deaths	% Of group
Malignant tumours (140-239)	707	39·8	3·35	739	40·8	3·49
Cardiovascular diseases (390-458)	721	40·6	3·42	673	37·2	3·18
Respiratory diseases (460-519)	97	5·5	0·46	111	6·1	0·52
Diseases of gastrointestinal tract (520-577)	47	2·6	0·22	44	2·4	0·21
Diseases of urogenital tract (580-629)	16	0·9	0·08	20	1·1	0·09
Injuries, suicide, and unknown causes of death (800-999)	100	5·6	0·47	120	6·6	0·57
Other	89	5·0	0·42	102	5·6	0·48
Total	1777	100	8·42	1809	100	8·54

*ICD=International Classification of Diseases (eighth revision).[4]

mainly in the younger cohort and during the first six years of the study. In the older cohort the study group had fewer deaths from breast cancer than the control group during the last three years of the study and in 1987. In the younger cohort 29% more women in the study group than the control group died of breast cancer (28 *v* 22; relative risk 1·29, 95% confidence interval 0·74 to 2·25), whereas in the older cohort 21% fewer women in the study group died of breast cancer (35 *v* 44; relative risk 0·79, 95% confidence interval 0·51 to 1·24).

Discussion

Malmö is a city in southern Sweden with roughly 230 000 residents. It has a fairly stable population, the yearly migration rate to and from the city being about 2% in the age groups participating in this study. The number of woman years lost/1000 women/year owing to breast cancer before age 65 equalled the average for Sweden in the five years preceding the screening programme.[6]

The purpose of the study was to assess whether repeated invitation to mammography reduces mortality from breast cancer. By the predetermined end of this study no significant reduction had occurred in the study group, which is at variance with results of a study conducted in the Swedish counties of Kopparberg and Östergötland.[7]

TABLE VII—*Number (percentage) of patients with breast cancer alive, dead from breast cancer, and dead from other causes at end of follow up period 31 December 1986. Cause of death was assessed by an independent committee*

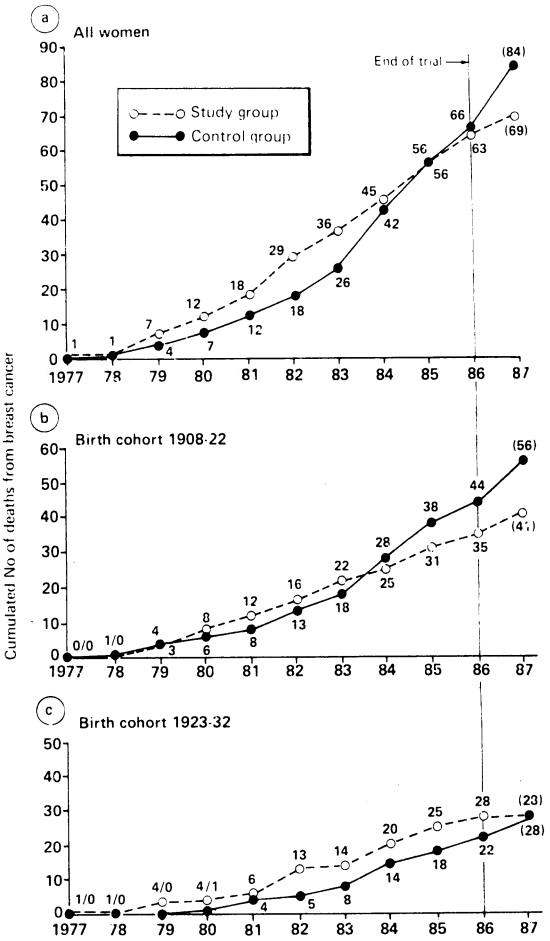
	Cancer detected in study group				Cancer detected in control group*
	At screening	In intervals between screening	In non-attenders	Total*	
		Stage 0			
Alive	60 (16)	24 (24)	7 (7)	91 (16)	48 (11)
Dead from breast cancer	1 (<1)			1 (<1)	1 (<1)
Dead from other causes			1 (1)	1 (<1)	1 (<1)
		Stage I			
Alive	221 (59)	27 (27)	16 (15)	264 (45)	151 (34)
Dead from breast cancer	4 (1)	4 (4)	1 (1)	9 (2)	5 (1)
Dead from other causes	16 (4)	2 (2)	5 (5)	23 (4)	6 (1)
		Stage II			
Alive	58 (16)	22 (22)	32 (30)	112 (19)	130 (29)
Dead from breast cancer	6 (2)	9 (9)	6 (6)	21 (4)	28 (6)
Dead from other causes	4 (1)	2 (2)	3 (3)	9 (2)	14 (3)
		Stage III			
Alive	2 (1)	2 (2)	6 (6)	10 (2)	14 (3)
Dead from breast cancer	1 (<1)	5 (5)	7 (7)	13 (2)	9 (2)
Dead from other causes	1 (<1)		2 (2)	3 (1)	4 (1)
		Stage IV			
Alive			3 (3)	3 (1)	7 (2)
Dead from breast cancer		2 (2)	17 (16)	19 (3)	22 (5)
Dead from other causes					3 (1)
		All stages			
Alive	341 (91)	76 (76)	65 (61)	482* (83)	353† (79)
Dead from breast cancer	12 (3)	20 (20)	31 (29)	63 (11)	66 (15)
Dead from other causes	21 (6)	4 (4)	11 (10)	36 (6)	28 (6)
Total	374 (100)	100 (100)	107 (100)	581 (100)	447 (100)

*In addition seven patients in study group whose breast cancer was diagnosed after they moved out of Malmö were still alive.
†Two cases of malignant cystosarcoma phyllodes in study group and three in control group and one case of fibrosarcoma in each group were not staged. Stage was unknown in six cases in study group.

TABLE VIII—*Deaths from breast cancer until end of December 1985. Potential influence on outcome of using different sources of information and different criteria for establishing end point*

	Study group	Control group
End point assumed by end point committee*	56	56
Excluding patients with breast cancer diagnosed before entry	53	52
Including all patients with breast cancer metastases irrespective of underlying cause of death	58	62
End point based on official statistics*	54	57
Excluding existing breast cancer	50	52

*Death from breast cancer diagnosed during study.



Cumulative number of deaths from breast cancer in study and control groups by calendar year (and preliminary data for 1987). (a) All women. (b) Women ≥55 years at entry into study. (c) Women <55 years at entry

TABLE IX—*Number of deaths from breast cancer and cumulative mortality by year after entry into study*

Years after entry	Control group: No of deaths	Control group: Cumulative mortality (per 100 000 woman years)	Study group: No of deaths	Study group: Cumulative mortality (per 100 000 woman years)
1			1	4·8
2	6	28·7	4	24·0
3	1	33·5	3	38·5
4	3	48·1	7	72·6
5	7	82·5	11	126·9
6	8	122·1	9	171·6
7	13	187·1	9	216·8
8	13	253·0	10	267·6
9	13	329·0	7	308·7
10	2	361·8	2	341·6
Total	66*		63*	

*Relative risk (study group *v* controls)=0·96 (95% confidence interval 0·68 to 1·35, p=0·8085).

The higher case fatality rate of breast cancer in the control group illustrates the lead time and length time bias associated with screening (table VII) and cannot be taken as evidence for the effect of screening on mortality. The slightly higher mean age of patients with carcinoma in the study group compared with the control group is explained by the greater proportion of cancers detected in older women.

There are three main steps in this type of intervention: firstly, to have women attend for screening; secondly, to detect breast cancer; and thirdly, to treat the cancer. Our study differs somewhat in each of these aspects from other studies of the effects of mammographic screening.

The potential benefit associated with screening can

TABLE X—*Deaths from breast cancer and cumulative mortality in women aged ≥55 and <55 at entry into study. Mortality is per 100 000 woman years*

	Women born 1908-22				Women born 1923-32			
	Control group		Study group		Control group		Study group	
Years after entry	No of deaths	Cumulative mortality	No of deaths	Cumulative mortality	No of deaths	Cumulative mortality	No of deaths	Cumulative mortality
1							1	12·6
2	5	38·9	4	31·0	1	12·4		12·6
3	1	46·7		31·0		12·4	3	50·5
4	2	62·6	6	78·6	1	25·0	1	63·2
5	5	102·8	6	126·8	2	50·2	5	126·9
6	5	143·5	4	159·3	3	88·1	5	190·8
7	7	201·2	7	216·9	6	164·3	2	216·5
8	10	285·2	4	250·4	3	202·6	6	294·1
9	8	358·9	2	268·8	5	282·7	5	375·7
10	1	389·2	2	329·2	1	318·5	0	375·7
Total	44*		35*		22†		28†	

*Relative risk (study group *v* controls)=0·79 (95% confidence interval 0·51 to 1·24, p=0·3085).
†Relative risk (study group *v* controls)=1·29 (95% confidence interval 0·74 to 2·25, p=0·3732).

be reduced by a high rate of non-attendance. The attendance rate, especially in the older age group, was lower in our study, than in the Swedish "two county" study[7] but higher than in the Health Insurance Plan trial[2,3] and in a non-controlled breast cancer screening programme in Florence,[8] which showed a reduction in mortality from breast cancer in women invited for screening. The attendance rate in our study was similar to that in the DOM project[9] and Nijmegen projects,[10] both of which were not controlled and showed a reduced mortality from breast cancer. In our study cases of advanced breast cancer and, accordingly, deaths from breast cancer were substantially over-represented among women who did not attend for screening. It is our impression that many of these women already had cancer at an advanced stage at the time of invitation, and attending screening would not have improved the course of their disease. As the control group also contained women with advanced tumours the extent to which the attendance rate affected the results of the study is unclear.

In spite of the lower attendance rate the distribution of breast cancers by stage was similar in our study and the two county study. This may be explained by the shorter interval between examinations in our study and the more extensive use of two views rather than one at screening, which is a more sensitive technique.[11,12] The high sensitivity of our technique is confirmed by the large proportion of non-invasive carcinomas and the small median size of invasive carcinomas among cases detected by screening. Furthermore, the percentage of carcinomas detected in the intervals between screenings was not higher than in most other studies.

The results of our trial may also have been influenced by the fact that some women in the control group had mammography. Mammography was available outside the screening programme throughout the study. A random sample of 500 women in the control group showed that 24% had undergone mammography during the study period, most only once. The rate varied from 13% in women aged 65-69 at entry into the study to 35% in women aged 45-49 at entry. Twenty per cent of the breast cancers in the control group were first detected by mammography. In the two county study 13% of women in the control group had undergone mammography.[6]

In our study free access to mammography implied examinations not only of women in the control group but also of women in the study group between screenings, which accounts for the high proportion of non-invasive carcinomas detected in the intervals between screenings. Furthermore, the availability of mammography was undoubtedly one of the reasons for non-attendance in the screening programme. It is thus difficult to assess the net effect of the mammography done outside the programme.

Though the principles of treatment of breast cancer were not presented in the two county study, there is no reason to believe that they were greatly different from those practised in our trial. Also, there were no important differences in treatment of women with breast cancer in the study and control groups in our study.

The assessment of the vital state of the patients at the end of the trial was important and was performed for all of the population being studied. The validation of the end point (that is, the determination of the underlying cause of death in patients with breast cancer) was crucial. For this purpose a high rate of postmortem examination was important; the rate in this study was exceptionally high. In addition, the records of all patients with breast cancer who died in both groups were reviewed by an independent committee blinded to the identity of the patients to validate the underlying cause of death. The importance of such unbiased assessment is underlined by the fact that in at least 15 of the 193 deaths the underlying cause of death was equivocal, and there was thus the possibility of biased classification. Comparing the number of deaths due to breast cancer given in official statistics with those classified by the independent committee resulted in 10% that were discordant. Furthermore, more than one type of cancer was frequently found in the same patient, which made it hard to assess clinically which had metastasised.

The validity of causes of death other than breast cancer was not confirmed. Because the cause of death of patients with known breast cancer was validated, however, and because it is highly unlikely for undiagnosed breast cancer to cause death there is no reason to believe that unrecognised deaths from breast cancer were concealed among those listed as deaths from other causes.

The most likely effect of screening for breast cancer would be early detection of the disease, thus permitting treatment of non-invasive carcinoma and possibly of early stages of invasive carcinoma, which might prevent metastases of breast cancer. Once a cancer has metastasised local treatment is less likely to influence the course of the disease. The life cycle of breast cancer is long, lasting on average about 15 years.[13,14] Accordingly, intervention at the non-invasive or early invasive stage would not influence the death rate until several years later. The deaths during the first years of the screening programme would have been mainly of patients whose disease was at an advanced stage when it was diagnosed, and thus its course would not have been influenced by detection of the disease. Altogether 89% of the women who died from breast cancer in the study group and all of those who died from breast cancer in the control group during the first six years of the study had been diagnosed as having stage II-IV disease.

It is thus reasonable to assume that the effect of screening for breast cancer is delayed, a point that was recently considered in a review.[15] After a six year delay (counting only the deaths from 1983 to the end of 1986) our study showed a 30% reduction in mortality from breast cancer; when preliminary data from 1987 are included the reduction is 42%.

The effect of mammographic screening seems to be different in young and old women,[3,6] an impression that is supported by our findings. Although there was no overall effect on the mortality from breast cancer, deaths from breast cancer were reduced by 20% in women aged 55 and older at entry into the study, despite a lower participation rate in this group. This seemingly conflicting result could be explained by different tumour biology in old and young women.

Women younger than 55 in the study group had a 29% higher mortality from breast cancer. This higher mortality among younger women was also observed in the two county study.[7] Although this could be a random phenomenon, negative results of a screening examination may have falsely reassured some patients and caused a deleterious delay in diagnosis. Delayed diagnosis may be more dangerous with rapidly growing tumours than with the more slowly growing tumours.

A proportional hazards analysis of patient survival with breast cancer, stratified for stage and adjusted for age at diagnosis, gave a relative risk of 2·3 (p=0·001) for patients whose cancer was detected in the intervals between screenings compared with patients in the control group. This confirms that carcinomas detected in the intervals between screening were more malignant, stage for stage, than those occurring in the control group. It also confirms preliminary results of this study[16] but is at variance with results from the two county study reported by Holmberg *et al.*[17]

Differences in treatment were also considered as a possible explanation for the differential mortality from breast cancer in the beginning of the programme. A study of the chemotherapy and hormonal and x ray treatment of all patients who died during the first six years of the programme showed only minor differences between the study and control groups. There is no reason to believe that induction of cancer through irradiation would be the explanation.[18]

From a public health perspective mammographic screening remains controversial.[19,20] The different outcomes in results of breast cancer screening programmes show that it is difficult to use the results from one study to calculate the expected benefit in another population. The results of our study cannot be used to advocate introduction of mammographic screening in all ages in an urban population. Although firm conclusions cannot be drawn from analyses of subgroups in this study, our data support previous studies showing that invitation to mammographic screening for breast cancer may lead to reduced mortality from breast cancer, at least in women aged 55 and over.

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The course of untreated epilepsy

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Abstract

As little is known about the course of untreated epilepsy the time intervals between untreated tonic-clonic seizures were examined retrospectively in a series of 183 patients presenting to a neurological department having had two to five seizures. After the first seizure a second attack had occurred within one month in 56 patients, within three months in 93, and within one year in 159. The median interval between the first two seizures was 12 weeks (95% confidence interval 10 to 18 weeks), between the second and third eight weeks (four to 12 weeks), between the third and fourth four weeks (two to 20 weeks), and between the fourth and fifth three weeks (one to four weeks). When patients who had had three, four, or five untreated seizures were considered separately a similar pattern of decreasing intervals was seen. Successive intervals between seizures could be compared in 82 patients. In 48 the interval decreased, in 16 it did not change, and in 18 it increased.

These results suggest that in many patients there is an accelerating disease process in the early stages of epilepsy.

Introduction

The prognosis for controlling seizures in epileptic patients has until recently been thought to be generally unsatisfactory. In a comprehensive review Rodin reported that no more than one third of epileptic patients achieve a remission of two years, and he regarded the disorder as chronic in about 80% of patients.[1] This view was based mostly on studies of patients attending hospital clinics and institutions, where patients with chronic epilepsy tend to accumulate. Recent community and hospital based studies of patients with newly diagnosed epilepsy have shown a much more favourable prognosis. In two retrospective community studies about 70% of all patients were found to achieve a four or five year remission.[2,3] In a