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REDUCTION IN MORTALITY FROM BREAST CANCER AFTER MASS SCREENING WITH MAMMOGRAPHY

Randomised Trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare

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Summary A randomised controlled trial to investigate the efficacy of mass screening with single-view mammography in reducing mortality from breast cancer was started in Sweden in 1977. 162 981 women aged 40 years or more and living in the counties of Kopparberg and Östergötland were enrolled in the study and divided at random into 2 groups. Each woman in the study group was offered screening every 2 or 3 years depending on age. Women in the control group were not offered screening. This report is confined to the 134 867 women aged 40–74 years at date of entry. The results to the end of 1984 show a 31% reduction in mortality from breast cancer and a 25% reduction in the rate of stage II or more advanced breast cancers in the group invited to screening. 7 years after the start of the study the excess of stage I cancers in the study group largely outweighs the deficit of advanced cancers.

Introduction

IN 1977, the Swedish National Board of Health and Welfare started a randomised controlled trial in 2 counties to determine to what extent mass screening with single-view mammography could reduce mortality from breast cancer. It started in October, 1977, in Kopparberg and in May, 1978, in Östergötland. We present the first results of the study to the end of 1984.

Methods

A total of 162 981 women aged 40 years or more at randomisation, from Kopparberg and Östergötland counties, entered the study. The randomisation took place at the community level rather than at individual level.[1] For this purpose the combined population of the 2 counties was divided into 19 blocks selected to give relative socioeconomic homogeneity within each block. All women over 40 from a given block entered the study at the same time. The date of entry is taken as the date of randomisation. In Östergötland each block was divided into 2 units of roughly equal size; 1, chosen at random, was allocated to receive screening, and the other was allocated to the control group. In Kopparberg each block was divided into 3 units of roughly equal size, 2 of which were randomly allocated to receive screening and 1 to the control group (table I). In Kopparberg the control group is only half the size of the study group. Women over 74 years of age were invited to screening, but

TABLE I—NUMBER OF WOMEN INCLUDED IN THE STUDY IN THE 2 COUNTIES BY AGE AT ENTRY

Age-group	Study group			Control group		
	Öster-götland	Kopparberg	Total	Öster-götland	Kopparberg	Total
40–49	10 312	9625	19 937	10 625	5053	15 678
50–59	11 918	11 863	23 781	11 416	5632	17 048
60–69	11 646	12 153	23 799	10 920	5674	16 594
70–74	5158	5410	10 568	4975	2487	7462
(≥75	7967	8338	16 305	7997	3812	11 809)*
Total 40–74	39 034	39 051	78 085	37 936	18 846	56 782

*Not included in the present analysis because compliance was poor.

TABLE II—COMPLIANCE RATE WITH THE SCREENING PROGRAMME IN THE COUNTIES COMBINED

Age-group	1st screening			2nd screening		
	Invited	Participated	Attendance rate (%)	Invited	Participated	Attendance rate (%)
40–49	19 937	18 581	93·2	19 475	17 378	89·2
50–59	23 781	21 831	91·8	22 969	20 135	87·7
60–69	23 799	20 920	87·9	22 484	18 187	80·9
70–74	10 568	8313	78·7	9578	6400	66·8
Total	78 085	69 645	89·2	74 506	62 100	83·3

TABLE III—WOMAN-YEARS OF OBSERVATION* IN THE 2 COUNTIES COMBINED BY YEAR OF FOLLOW-UP†

—	Time (mo) since date of entry								
	0–11	12–23	24–35	36–47	48–59	60–71	72–83	84–	Total
Control group	56 782	56 293	55 299	54 495	51 665	39 259	17 275	2948	334 016
Study group	78 085	77 348	76 004	75 075	71 359	54 760	27 960	5681	466 272

*The date of exit from the study is taken as the end of the year of last follow-up.
†Women aged 40–74 at entry.

the compliance rate was less than 50%. This report is confined to the 134 867 women aged 40–74 at randomisation who had not received surgery for breast cancer before randomisation. Women in the study group aged 40–49 at date of entry were invited to screening on average every 24 months, and women aged 50 or more at entry were invited on average every 33 months. Individual letters of invitation were sent out at each screening round to all women in the original cohort still living in the county. The first 2 screening rounds have been completed for all age-groups in both counties. The compliance rate for the 2 counties combined is given in table II. The difference between the number of women invited at the first and second rounds gives the number of women from the original cohort who had died or left the county in the intervening period. All eligible women in the study group have received at least 2 invitations, and some women under 50 years of age have already received 4. The woman-years of observation in the study and control groups are given in table III, by year of follow-up. The average length of follow-up since date of randomisation is 6·0 years.

13% of women in the control group had a mammographic examination as part of routine medical care up to the end of 1984. Most of these examinations were in 1983–84.

The only screening modality used was mammography with the single medio-lateral oblique view.[2] Details of the technique and the organisation of the programme are given elsewhere.[1,3,4] Nationwide cancer registration permits identification of breast-cancer cases even among women who have migrated out of the counties, and all deaths in the cohort were obtainable from the National Bureau of Statistics. The small number of subjects who have left Sweden were the only ones who could not be traced. A death was classified by members of the local project groups as being due to breast cancer only after a full review of the clinical and pathological records. When the cause of death was doubtful the records were reviewed by a combined committee from the 2 counties. The statistical analysis with Mantel-Haenszel techniques was based on individuals. The excess variation resulting from randomisation being at the community rather than the individual level was negligible. Analyses were stratified by county and age. Stratification by county was necessary because the dates on which screening started and the proportion of women allocated to screening were different in the 2 counties.

Results

Compliance at first screening was 89%. The numbers of women in the study and control groups with breast cancer diagnosed between randomisation and Dec 31, 1984, are given in table IV by stage of disease at diagnosis. In the study group there is a highly significant reduction (25%) in the absolute rate of stage II or more advanced cancers ($p<0·001$, table V). This deficit is more than outweighed by the excess in the study group of stage I and in-situ cancers.

Fig 1 shows the evolving cumulative number of stage II or more advanced cancers in the study and control groups (the number of cases in the Kopparberg control group has been doubled to allow for the control-group size). Since the number of cases in the study population is a mixture of prevalent and incident cases, rates related to woman-years at risk were not calculated. The concavity of the curves in the last 3 years of follow-up reflects the falling number of woman-years at risk. The number of deaths from breast cancer in the study and control groups is shown in table VI by county. Overall there is a 31% reduction in mortality in the study group ($p=0·013$, 2-sided test). The cumulative mortality rate in the study and control groups is shown in fig 2. The

TABLE IV—BREAST CANCER CASES DIAGNOSED BETWEEN THE DATE OF RANDOMISATION AND DEC 31, 1984, IN THE STUDY AND CONTROL GROUPS BY AGE AND STAGE OF DISEASE*

—	Invasive cancer				Axillary nodes positive and/or disseminated disease	Ductal in situ
	Total invasive	Stage I	Stage II	Invasive ≤20 mm pNX§		
Study group:						
Ever screened†	951	589	324	38	223	93
Never screened‡	117	27	85	5	61	5
Total study group	1068 (13·7)¶	616 (7·9)	409 (5·2)	43 (0·6)	284 (3·6)	98 (1·3)
Control group	595 (10·5)	209 (3·7)	376 (6·6)	10 (0·3)	253 (4·5)	15 (0·4)

*Women aged 40–74 at entry.
†Includes screen-detected and interval cancers.
‡Includes cancers among non-responders and cancers diagnosed between randomisation and invitation to screening.
§pNX: invasive tumour, size ≤20 mm, axillary nodes not examined histologically.
¶Figures within brackets denote no per 1000 women.

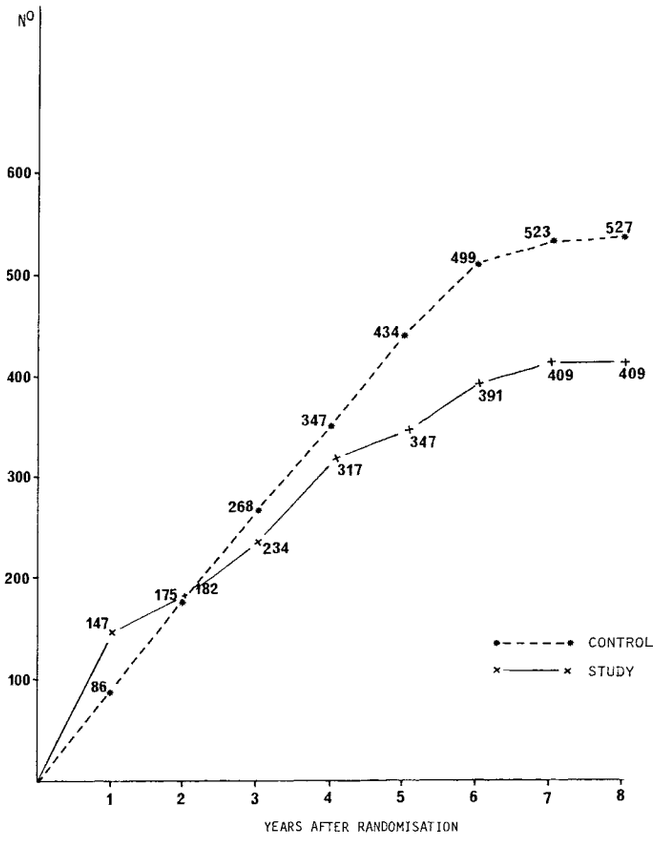

Fig 1— Cumulative number of women with stage II or more advanced breast cancer by time since randomisation, women aged 40–74 at entry.

The figures for the control group are adjusted for the different size of the control group in Kopparberg county.

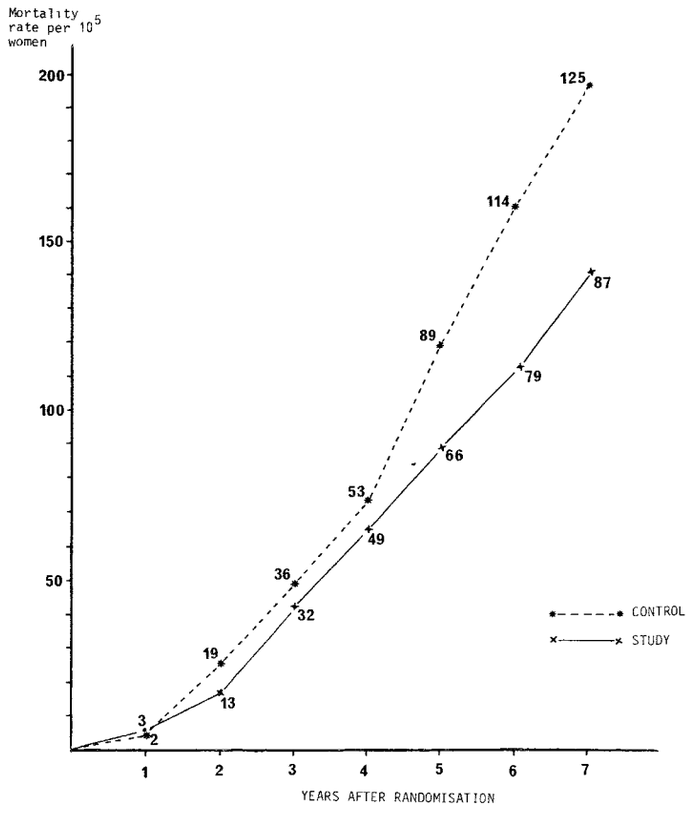

Fig 2—Cumulative mortality rates per 10^5 women by time since randomisation in the study and control groups, women aged 40–74 at entry.

The cumulative number of deaths is shown alongside the curves; the figures for the control group are adjusted for the different size in the control group in Kopparberg.

difference between both groups began to emerge 4 years after the date of randomisation and has steadily widened since. The numbers of deaths are also given in fig 2, with the Kopparberg control numbers doubled, as in fig 1.

Table VII gives the difference in mortality between the study and control groups for the 40–49 and 50–74 age-groups. In the 50–74 age-group, there is an overall reduction in mortality of 40% (p = 0·003). In the 40–49 age-group no reduction has yet been observed, but the confidence interval is wide.

TABLE V—COMPARISON BETWEEN THE STUDY AND CONTROL GROUPS OF THE RATES OF STAGE II AND MORE ADVANCED CANCERS*

—	Kopparberg county		Östergötland county	
	Stage II+	Population	Stage II+	Population
Study group	228	39 051	181	39 034
Control group	151	18 846	225	37 936

$\chi_1^2 = 15·0$ ($p < 0·001$). Relative risk = 0·75.
95% confidence interval (0·65, 0·87).
*Women aged 40–74 at entry.

TABLE VI—DEATHS FROM BREAST CANCER IN STUDY AND CONTROL POPULATIONS*

—	Kopparberg county			Östergötland county		
	Deaths	Population	Relative risk	Deaths	Population	Relative risk
Study group	51	39 051	0·63	36	39 034	0·74
Control group	39	18 846		47	37 936	

Combined χ_1^2 on 1 d f = 6·17, p = 0·013 (2-sided).
Combined estimate of relative risk = 0·69, 95% confidence interval (0·51, 0·92).
*Women aged 40–74 at entry.

Discussion

This is the first randomised trial to show a reduction in mortality from breast cancer after mass screening since the Health Insurance Plan of New York (HIP) study.[5] We used single-view mammography only, whereas complete mammography with physical examination was used in the HIP study. Also, we had a longer interval between

TABLE VII—DEATHS FROM BREAST CANCER BY AGE AT ENTRY

—	Kopparberg county		Östergötland county		—
	Deaths	Population	Deaths	Population	
Age-group 40–49:					
Study	8	9625	8	10 312	Combined χ_1^2 = 0·31
Control	3	5053	7	10 625	Relative risk = 1·26, 95% confidence interval (0·56, 2·84)
Age-group 50–74:					
Study	43	29 426	28	28 722	Combined χ_1^2 = 9·14
Control	36	13 793	40	27 311	p = 0·003 (2-sided) Relative risk = 0·61 95% confidence interval (0·44, 0·84)

consecutive screenings. Even with an interval of nearly 3 years the reduction in mortality in the 50–74 age-group is similar to that in the HIP study for the 50–64 age-group, in which annual screening was used.

2 non-randomised studies,[6,7] one of which used mammography alone but with a shorter interval between screenings,[6] support our results. The reduction in mortality closely parallels the reduction in the number of stage II or more advanced cancers diagnosed in the study population, compared with the control group. In over 90% of patients who have died breast cancer was diagnosed at an advanced stage. The fall in stage II or more advanced cancers has arisen even though a large number of such cases were diagnosed at the first screening round, most of which were in the 60–74 age-group.

The lack of effect on mortality, even with more frequent screening, in the 40–49 age-group may be explained by the small number of deaths seen so far in this group. In formal statistical terms the effect is not different from that in the 50–74 age-group, since the confidence interval for the effect includes the relative-risk estimate for the older age-group. It corresponds, however, with a similar absence of effect in this age-group in the HIP study after 7 years of follow-up. Further follow-up of this group in the HIP study eventually demonstrated a reduction in mortality.[8,9] There is still a 30% excess of invasive cancers diagnosed in the study group, compared with the control group (13·7 per 1000 and 10·5 per 1000, respectively, table IV), whereas in the HIP study the number of these cancers in the 2 groups had equalised 5 years after entry to the study.[8] This difference suggests that cancers are detected at a considerably earlier stage with modern mammography than they were with the detection methods used 15 to 20 years ago, and this may be of considerable importance for the mortality rates in the study group. It is possible that some of the excess cancers might never have surfaced clinically. Consideration of the incidence of interval cancers (ie, those occurring between screenings) should determine whether the deficit of cancers in the years after a negative screening examination corresponds to the numbers detected at screening and will be the subject of a future publication.

The present findings, together with the studies from New York and the Netherlands, show that early detection is effective in reducing breast cancer mortality.

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TREATMENT OF ACTIVE RHEUMATOID ARTHRITIS WITH SLOW INTRAVENOUS INJECTIONS OF THYMOPENTIN

A Double-blind Placebo-controlled Randomised Study

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Summary 41 patients with active rheumatoid arthritis entered a placebo-controlled double-blind randomised study in which 21 received slow intravenous injections (given in fractions over 10 min) of thymopentin (TP-5) 50 mg 3 times a week for 3 consecutive weeks and 20 received placebo in the same way. After 3 weeks of treatment the TP-5 group showed improvement ($p<0·05$ or $p<0·01$) in all but one of the clinical variables tested. There was improvement in the number of joints painful at rest, the number of joints painful on motion, scores for tenderness on pressure and swollen joints, severity of pain on awakening and morning stiffness, and right-hand grip strength; left-hand grip strength remained unchanged. In the placebo group, only morning stiffness improved significantly. The intergroup comparisons showed that thymopentin was significantly better than placebo in reducing tenderness, joint swelling, severity of pain on awakening, and disease activity. 4 weeks after the end of the TP-5 therapy, the improvement was still present although there was a trend towards relapses. No significant modifications occurred in any of the laboratory variables tested and only minor side-effects were experienced by either group.

Introduction

THYMOPOIETIN, first isolated from bovine thymus,[1] has a 49 aminoacid sequence[2] whose residues 32–36 Arg-Lys-Asp-Val-Tyr retain the biological activity of the parent molecule. This pentapeptide has been synthesised and designated thymopentin (TP-5).[3] The molecule influences immunoregulation by several mechanisms. Thymopentin induces the phenotypic differentiation of T cells in vitro[4,5] and in vivo.[6] In addition, functional maturation of suppressor,[7] helper,[8] and cytotoxic T cells[9–11] has been observed after thymopoietin or thymopentin administration to various animal models. In contrast, thymopoietin inhibits B-cell phenotypic differentiation, at least in vitro.[5] Recently TP-5 was reported to modulate the specific antibody response in healthy beings.[12]

Thymopentin has a plasma half-life of only 30 s,[13] being broken down to natural aminoacids by peptidases in human plasma. Despite the brief half-life a single intravenous dose of TP-5 can produce changes in the cellular processes in T lymphocytes persisting for more than 5 days.[14] TP-5 may also modulate immune reactivity, depending upon dose and route of administration.[15–17] Its effect on T and B cells suggests that