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Screening for Breast Cancer: Workshop Report

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THE value of screening for breast cancer, either by mammography alone or by a combination of mammography and physical examination, has been established. Interest now focuses on a range of further questions including the age groups at which screening should be directed, the optimal inter-screening interval, the sensitivity, specificity and predictive value of the screening process, the use of risk factor information to modulate screening policies, costs, and the role of breast self examination in mass screening programmes. Most of the presentations at the conference addressed these issues.

I. THE EFFECT OF BREAST CANCER SCREENING ON BREAST CANCER MORTALITY

Updated results on breast cancer mortality were given from the Swedish 2 county study and the Utrecht programme. Table 1 compares the results to the end of 1986 with those, previously published, to the end of 1984 from the Swedish study. Evidence for a reduction in mortality is considerably strengthened. The Utrecht programme had previously used a case control approach to evaluate the effect on mortality. The case control results were extended but in addition comparisons were made of the overall breast cancer mortality in the age group invited for screening both with the breast cancer mortality in this age group in Utrecht in the years before the programme started, and with the corresponding rates in other urban areas in Holland. Based on the rates for the years 1970–1975 in Utrecht, 128 breast cancer deaths would have been expected in the period 1978–1983. Only 96 deaths were observed. Furthermore, the death rates in women born during 1911–1925 in Utrecht have began to diverge substantially from the rates in other cities in Holland as shown in Fig. 1. There appears to have been a 25% fall in mortality from breast cancer in Utrecht in the years since screening started. Taking account of the proportion of non-responders, misclassification on death certificates and deaths from breast cancer among women diagnosed before screening started, this figure of 25% overall translates into a reduction in risk of some 50% among women screened, well in line with the case control results. Results were given from the case control studies in Utrecht, Nijmegen and Florence on the greater effect on mortality of two screening tests compared to a single test. It was pointed

Table 1. *The Swedish* 2 *county study. Deaths from breast cancer in the study and control group to the end of* 1984 *and to the end of* 1986

	Follow-up to the end of: 31.12.1986 County W		31.12.1986 County E		31.12.1984 County W		31.12.1984 County E	
	Death	R.R.	Death	R.R.	Death	R.R.	Death	R.R.
Study group	77		61		51		36	
		0.64		0.77		0.66		0.77
Control group	58		81		39		47	
	Summary relative risk = 0.68				Summary relative risk = 0.71			
	$P = 0.002$				$P = 0.014$			

*The study population in County W is approximately twice that of the control group.

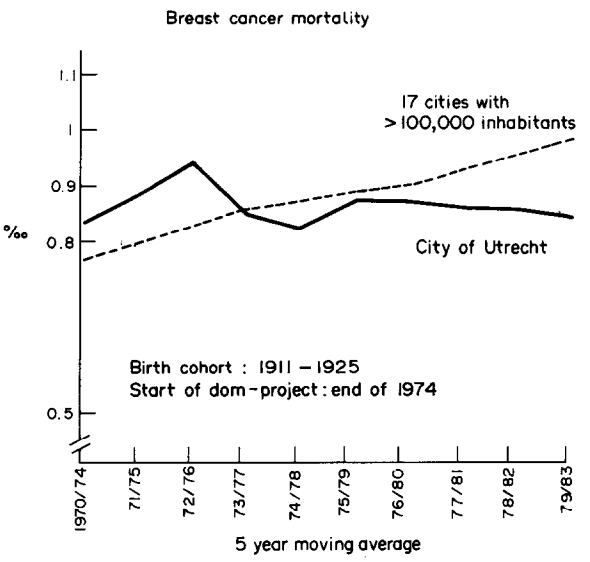
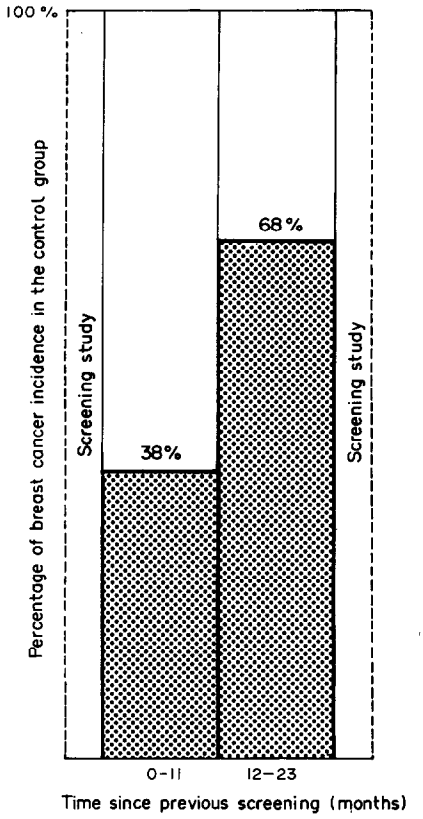


Fig. 1. Comparison of breast cancer mortality between Utrecht and other urban areas in Holland, among women born 1911–1925.

out that this comparison is subject to a certain bias and does not correspond to a comparison that could be made in any randomized trial between groups not selected on post randomization criteria. Further work is required on the use of case control data for evaluating different screening frequencies when mortality is the outcome.

II. AGE AND THE EFFECT OF SCREENING

From the studies which included women under 50 years of age and which have shown overall reductions in mortality, all show a smaller or delayed effect in women under 50 compared to women over 50. In none of these studies, however, have the numbers been large enough to establish that the mortality reduction in the younger group is significantly less than in the older group. In the Nijmegen study, there was an indication that women who refused screening were at lower basic risk for developing breast cancer than women who were screened. If account is taken of this difference, then an apparent 50% reduction in breast cancer mortality emerges amongst women under age 50 at the start of the programme. The standard error of this estimate would appear to be large. Large randomized studies are in progress in Canada and in Sweden (Stockholm and Gothenburg) designed to evaluate the effect of screening in women under age 50. In addition, the Swedish 2 county study has now started screening the control group, nearly 10 years after the start of the study. The results should enable one to evaluate whether delaying the start of screening until age 50 appreciably increases the risk of dying from breast cancer, compared to starting screening at age 40. Further light is cast on the effect of screening premenopausal women by the rate of interval cancers, and the stage of screen



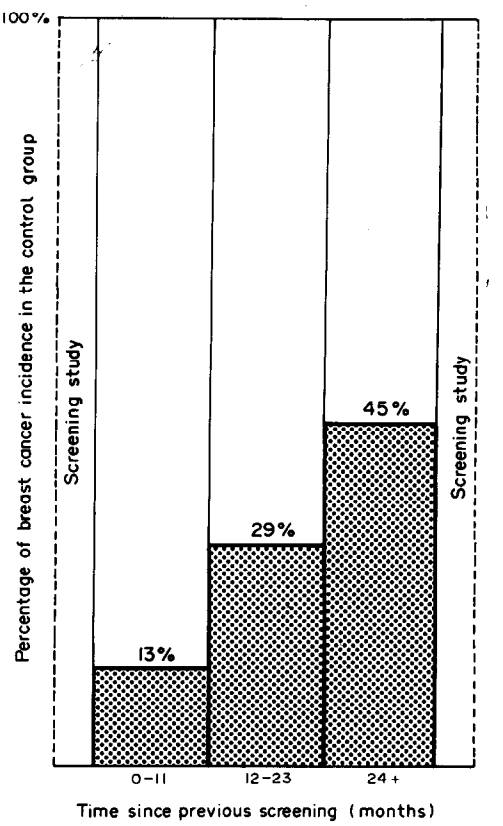


Fig. 2. Breast cancer incidence among screened women in the Swedish 2 *county trial as a percentage of the incidence in comparable unscreened women, in the years following a negative screening test. Top. Women aged* 40–49 *years at entry. Bottom. Women aged* 50–69 *years at entry.*

detected cancers, are discussed in the next paragraph.

III. OPTIMUM SCREENING INTERVAL

No randomized trials have been reported comparing the effectiveness of different screening intervals although the Florence case control study indicated a greater reduction in breast cancer mortality among women screened at intervals of less than 30 months, compared to women screened less frequently. In the absence of such results, use can be made of the rate of interval cancers, and the increase in this rate as time elapses after the last screening test. Results were presented from the Stockholm study, from Nijmegen and from the Swedish 2 county study. For the two latter reports, data were given separately for women under and women over 50 years of age, and it is apparent from these results that the rate of interval cancers returns to the rate in the unscreened more quickly in the younger women. Figure 2 shows the results from the Swedish 2 county study. One can then estimate the proportion of cancers that would be screen detected in a population screened at different frequencies, and such calculations were presented from the Nijmegen data (see Table 2).

Table 2. The expected proportion (%) of cases that will be detected at screening, by age and screening frequency, based on a modelling approach to the Nijmegen study

Age group (in years)	Interval between screens (in years)		
	1	2	3
<50	70	51	40
>50	83	70	61

The age dependency of the sojourn time is reflected in differences by age in the estimated lead times derived from the Nijmegen results. In women over age 50 at the start, average lead time was approximately 2 years, for women under age 50 the corresponding value was about 1 year. Both the Nijmegen and the Swedish 2 county programme used single view mammography as the sole screening modality. Given the results on interval cancer rates, one could not expect screening with single view mammography at intervals of 2 years or more to reduce breast cancer mortality appreciably in women under 50. To be effective, screening would need to be more sensitive (perhaps by adopting 2 view mammography and/or a physical examination) or more frequent, or perhaps both. For women over age 50, among whom clear reductions in breast cancer mortality have been observed, screening by single view mammography every 30 months (as was approximately the frequency in the Swedish 2 county study) should reduce breast cancer mortality by some 50% in screened women. A more elaborate screening modality or more frequent screening might further reduce breast cancer mortality; screening every 3 years would lead to a slightly smaller reduction.

IV. RELATIVE EFFECTIVENESS OF DIFFERENT SCREENING MODALITIES

No randomized studies have reported on the relative benefit of clinical examination and mammography. The Canadian study is designed to assess what extra benefit is provided by mammography in addition to physical examination among women over 50 years of age. In the Edinburgh study, physical examination was performed every year and mammography every second year. Results were presented (see Table 3) clearly indicating the superiority of mammography in detecting early lesions. The implication of these data for determining screening policies requires additional studies.

Table 3. The Edinburgh study. Detection rates of breast cancer per 1000 women in the study and control groups in the first 5 years

	Year of study				
	1*	2†	3*	4†	5*
Study group	4.5	2.3	2.8	1.8	2.2
(screen detected)	5.6	1.7	3.0	0.9	3.2
Control group	1.8	1.9	1.7	2.0	1.8

*Mammography and physical examination.
†Physical examination alone.

V. PREDICTIVE VALUE OF A REFERRAL FOR BIOPSY

The proportion of biopsies which yield a diagnosis of malignancy is a useful indicator of the power of the screening procedure to discriminate a cancer from a non-malignant lesion. In the United States typically only 10–25% of biopsies are malignant. Results were presented from three Swedish studies and from Nijmegen demonstrating a much higher proportion of malignant biopsies. Table 4 gives the results from Gothenburg, underlining the importance of the diagnostic procedures adopted after a non-negative mammogram and before referral for biopsy. Several presentations stressed the value of fine needle aspiration cytology, in particular using the newly developed stereotactic instrument.

VI. BREAST SELF EXAMINATION

Programmes of breast self examination (BSE) education were reported from a number of areas (Nottingham, Huddersfield, Belfast, rural areas near Genoa and in Belgium, and from Canada). No results on mortality were reported but several

Table 4. The Gothenburg study. Referral rates (%) for further diagnostic procedures and for biopsy

Referred for	First round Age group at entry 40–49	50–59	Second round Age group at entry 40–49	50–59
Supplementary mammography	6%	5%	4%	2%
Clinical examination and cytology	1.7	2.2	1.5	0.9
Excision biopsy	0.42	1.0	0.28	0.31
Carcinoma	0.21	0.64	0.13	0.28

studies described a greater proportion of early cancers diagnosed among women practicing BSE. Whether this proportional change reflects an absolute decrease in the rate of advanced cancers has not been documented. The major problem with BSE is poor compliance, reported from most centres. There appear to be major psychological difficulties in persuading the majority of women to attend teaching programmes, and then continuing to perform satisfactory BSE. In Canada the use of calendars had been introduced as a possible means of improving BSE performances, but did not appear to be effective. A randomized study of BSE education is in progress in Leningrad and Moscow.

VII. COSTS AND COST–BENEFIT ANALYSIS

The cost of running a screening programme has been evaluated in a number of countries (Sweden, Holland, U.K., Canada). If mammography alone is used, a total cost of £15 per woman screened can be taken as an average estimate, ignoring any saving due to the reduction of the number of advanced cancers requiring treatment. This latter topic was investigated in detail in Utrecht, in a study of 52 cases of advanced breast cancer. Using the treatment costs given in the Netherlands Sick Fund System, a total of £10,000 extra costs in treating an advanced case was estimated. The effect of this figure on the total cost of a screening programme is not clear, particularly when the differences in cost are discounted over a long time period. An assessment of cost benefit, in terms of cost per person year of life saved, is heavily dependent also on assumptions concerning the long term benefit of screening, and estimates have varied from £600 to £6000. Cost benefit performance might be

Table 5. Current randomized controlled trials of screening for breast cancer

Place	Age group	Interval	Study group	Control group
Gothenburg	40–59	18 months	2-view mammography	Unscreened
Stockholm	40–69	2 years	Single-view mammography	Unscreened
Malmo	45–69	2 years	2-view mammography	Unscreened
Edinburgh	45–64	1 year	Physical examination +2 view mammography in year 1 + single-view mammography in years 3, 5 and 7	Unscreened
Canada (1)	50–59	1 year	Physical examination + 2-view mammography + BSE education	Physical examination + BSE education
Canada (2)	40–49	1 year	Physical examination + 2-view mammography + BSE education	1 Physical examination + BSE education at entry
U.S.S.R.	?	—	Invitation to class in BSE	No intervention
Swedish 2 county study	See study and control groups column	Approximately 2 years	Single-view mammography starting at age 40	Single-view mammography starting at age 50

improved by the use of breast cancer risk factors. Apart from age, no combination of risk factors is at present sufficiently powerful in identifying those liable to develop the disease to be of use in defining sub groups on which screening might be concentrated. It is possible, however, that use of risk factor information could be used to good effect in determining the frequency of screening, an approach illustrated by data from the Edinburgh study.

VII. CURRENT TRIALS

Randomized trials of breast cancer screening currently underway are summarized in Table 5.