SPECIAL REVIEW

SCREENING FOR BREAST CANCER

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It is 100 years since William Stewart Halsted described his radical operation for breast cancer by which the entire breast, the underlying pectoral muscles and the lymphatic contents of the axilla were resected in continuity (1). By designing the operation on anatomical principles, Halsted hoped to improve on the unacceptably high local recurrence rates which then followed surgery for breast cancer, many cases of which presented at an advanced stage. Erroneously he also came to believe that 'If three years had passed without detecting either local recurrence or symptoms of internal disease, one could feel sure that cure had been achieved'. By convention the period after treatment at which cure was assumed was extended to 5 years, and later to 10 years, but it is now clear from long term follow-up studies of patients treated only by radical local surgery and radiotherapy that these time-intervals are still too short and that an excess mortality from metastatic breast cancer remains for 30 or 40 years after treatment (*Figure 1*) (2-4). Not that 'personal cures' do not occur; about one quarter of women do not experience detectable metastases during their life-time; but a proportion of these will have died from other causes. Statistical cure of breast cancer, by which a cohort of women with the disease can expect a similar survival rate to that of age-matched women in the normal population has not been demonstrated.

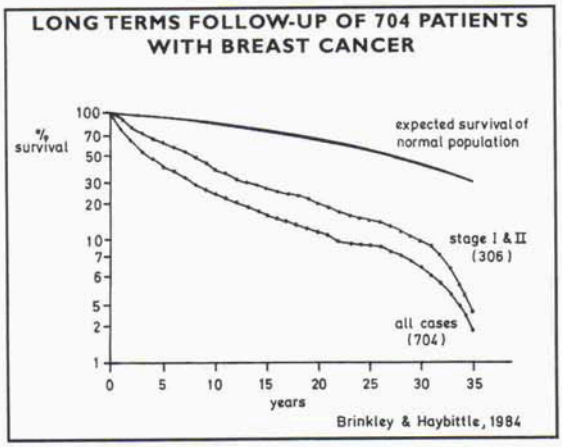

Figure 1: *The classic study of Brinkley and Haybittle which indicated that following the local treatment of breast cancer excess mortality persisted for 35 years (from Brinkley and Haybittle. Lancet, 1984; 1: 1118 with permission).*

Natural History

Halsted subscribed to the view, based on the post-mortem studies of Sampson Handley, that breast cancer spread from its primary site by a process of centrifugal permeation of the lymphatics by a column of cancer cells which advanced to reach the regional lymph nodes (5). There they were believed to remain dormant until such time as the defences of the nodes were breached when 'secondary spread' to bones, viscera and other systemic sites occurred. Embolic spread along lymphatic vessels was regarded as unimportant, such cells being 'filtered' out by the nodes. The potential threat of venous embolisation was disregarded. The natural history of 'early' symptomatic breast cancer was firmly established as that of a loco-regional disease, for which radical removal of the breast and its regional nodes offered the only hope of cure. When it became realised that local recurrent disease also was not prevented, the scope of radical surgery was extended by removing lymph nodes in the neck and from within the chest and postoperative radical radiotherapy was prescribed to destroy residual cancer cells, but, to no avail. The concept that breast cancer was a disease which disseminated late is now no longer tenable.

Breast cancer starts by malignant transformation of the epithelial cells of the terminal ductules within the breast lobules which through a series of genetic changes acquire the properties of unrestrained growth and division (6,7). At this stage the cells do not invade normal tissues but are confined within the basement membrane which maintains the integrity of the epithelial layer. They proliferate only within the lumen of the duct forming an in-situ cancer. The acquisition of invasive properties requires a further series of genetic changes which lead to the expression of proteins by the cancer cell which 'unstick' it from its neighbours, degrade the extracellular matrix and promote migration (8-10). Once this stage is reached the cells penetrate normal tissue barriers, gain access to lymphatic and venous channels, where they are transported to regional lymph nodes and distant sites. In these new sites these processes are reversed. Only a few of the millions of cells liberated from the primary tumour

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withstand the stresses within the vascular system and resist normal host defences, but these will target a capillary in a new site. Having established themselves they migrate through the capillary wall, invade the host tissues, acquire a new blood supply, proliferate a: ' grow under the influence of factors elaborated by them and by normal host cells. At this stage these deposits of surviving cells are but 'micro-metastases' which may or may not survive, or presumably may remain dormant for many years. But potentially they are the forerunners of gross metastatic disease and death. Breast cancer is a chronic progressive disease which disseminates early but recurs late .

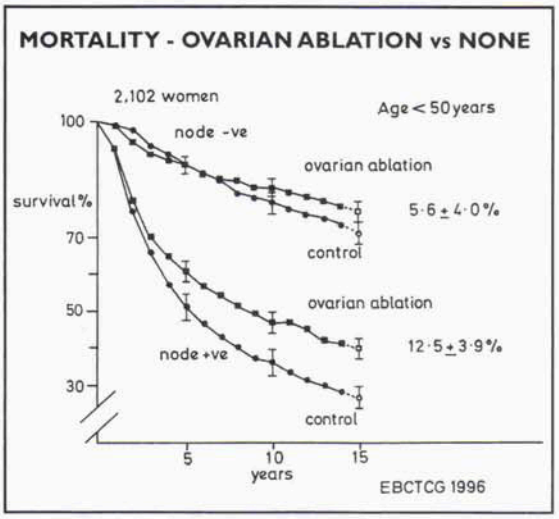

Figure 2: *The outcome of trials of ovarian ablation as adjuvant systematic therapy in early breast cancer in women with node-negative and node-positive disease. (redrawn from Early Breast Cancer Triallists Collaborative Group. Lancet, 1996; 348: 1189-96 with permission).*

Evidence to support the concept that the behaviour of these micrometastases determines the outcome of treatment has come from the effect of systemic treatment by antioestrogens and chemotherapy given as an adjuvant to local therapy. A large overview analysis of worldwide randomised trials which include over 75,000 women has proved that the annual odds of recurrence or death are reduced by 25% following ablation of ovarian function in women less than 50 years of age and by the anti-oestrogen tamoxifen and multiple-agent chemotherapy at all ages *(Figure* 2) (11,12). An absolute reduction in mortality is apparent in women both with involved and non-involved axillary lymph nodes, which at 10 years approximates 10% in node-positive and 5% in node-negative patients. Although this reduction may appear modest, it is equivalent to a reduction or delay of 100,000 deaths for every million women with breast cancer. The recent dramatic improvement in mortality from breast cancer observed in UK is believed largely to be due to the increasing use of systemic therapy as part of initial treatment (13).

A Threshold

An essential principle of screening for any disease is that the test detects the disease at an earlier stage at which treatment confers greater benefit than when delayed until it has become 'symptomatic' (14). For breast cancer this crucial early stage is that before it has disseminated with the formation of micro metastases. Non-invasive cancer is clearly at such a stage, but the potential long time-span of its course may prevent its early detection having an early beneficial effect on mortality. The success of screening for breast cancer depends on whether there is a detectable early stage of invasive cancer before micrometastic disease has been established.

Micrometastatic involvement of the axillary lymph nodes provides clear proof that the disease has disseminated. Its incidence is directly related to the size of the primary tumour. The smaller an invasive breast cancer the less likely is it to have metastasised to the axillary lymph nodes and the better the outcome of local treatment. A recent analysis of 24,740 women with breast cancer included in the Surveillance, Epidemiology and End Results (SEER) programme of the National Cancer Institute has confirmed these relationships (15). For 1,335 women within this series who had tumours less than 1 cm in diameter 5-year survival averaged over 95%. Involvement of the axillary lymph nodes is only one indicator of micro-metastatic disease. Another is the development of clinical evidence of metastases. This was the index used in a French study of 2,648 women in which the size of the tumour measured at the time of primary local treatment was found to be linearly related to the subsequent development of clinical metastatic disease over a follow-up period of 25 years (16). When the diameter of the tumour was 1 cm or less the likelihood of dissemination was less than 20%. Within each size of tumour there was great variation in the likelihood of dissemination, confirming the importance of other biological factors in determining the outcome of treatment. That some of these characteristics may also be time-dependent is suggested by findings that screen-detected invasive cancers may be of less aggressive histological type (17).

A tumour of 1 cm in diameter contains 1 million cells. As with estimated doubling times of between 2-5 months it would take 5-15 years of exponential growth for a cancer to replicate from a single cell, there may be a long period of time during which breast cancer is present in a subclinical phase (8). Contained within this phase is a period (the sojourn

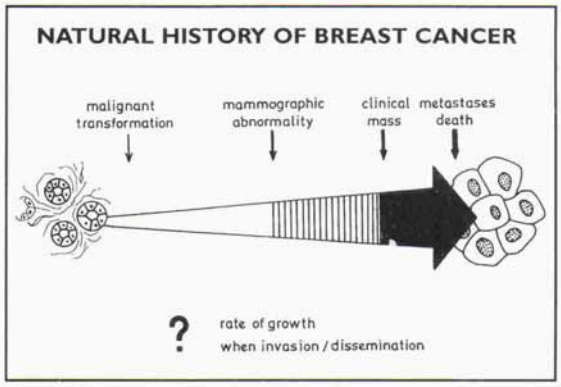

Figure 3: *The natural history of breast cancer to indicate objective of screening (from Forrest. Breast Cancer: the decision to screen. Nuffield Provincial Hospital Trust, 1990 with permission).*

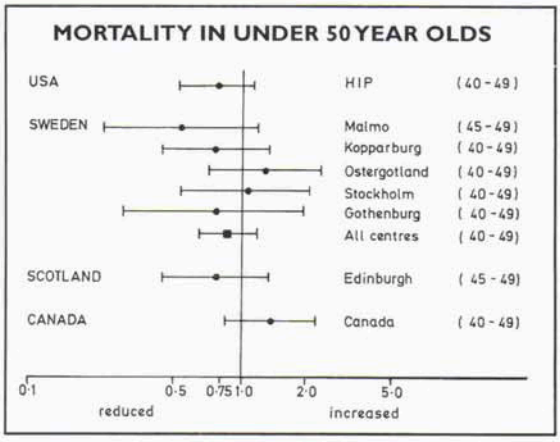

Figure 4: *7-12 years mortality in all randomised trials of population screening by mammography. (from Dixon and Sainsbury. Handbook of Diseases of the Breast. Churchill-Livingstone, 1993 with permission).*

time) when the tumour is detectable by mammography. Detection during this phase is the objective of mammographic screening (*Figure 3*).

Trials Of Mammographic Screening

It has long been recognised that clinically occult breast cancer could be visualised radiologically, but it was only with the technical developments in film-screen mammography during the late 1950s, that mammography was proposed as a potential screening test (18,19). In 1963 the first randomised trial of population screening by mammography was initiated by the Health Insurance Plan in New York, to be followed by the Two-county trial in Sweden and two case-control studies in The Netherlands (20-23). All were reported to show benefit. Six other randomised trials have been conducted in Sweden, Edinburgh (Scotland) and Canada which together with these earlier trials include over half a million women (24-31). Evidence from individual trials, from meta-analyses of reported results and from an independent overview of the four Swedish trials has established that in women of 40-74 years of age, mortality from breast cancer is significantly reduced (32-34) (*Figure 4*). In the six trials with an unscreened control group (excluding the Canadian trial) this reduction averaged 22% *(Table 1)* (32). However it was only significant in women over 50 years of age in whom the mortality reduction was 24% (equivalent to 31% reduction in women who attended for screening). In younger women the mean reduction was an insignificant 15%. Similar mortality reductions have been observed in a large UK comparative trial using geographical controls, in two case-control studies in women invited for screening in Holland and Italy, and in the large Breast Cancer Detection Demonstration Project in USA (35-41). There is also now clear evidence that

Trial	Women aged 40-74 years		Women aged 50-74 years	
	number intended to be screened	relative risk of death	number intended to be screened	relative risk of death
Health insurance plan	31,000	0.71 (0.55-0.91)	15,000	0.69 (0.49-0.97)
Edinburgh	23,000	0.85 (0.65-1.12)	17,000	0.85 (0.63-1.13)
Swedish Trials				
Two counties	77,000	0.78 (0.65-0.93)	57,000	0.72 (0.59-0.88)
Malmo	21,000	0.81 (0.62-1.07)	13,000	0.86 (0.64-1.16)
Stockholm	39,000	0.76 (0.50-1.14)	25,000	0.65 (0.40-1.08)
Gothenberg	21,000	0.81 (0.50-1.29)	11,000	0.91 (0.53-1.55)
[Overview of Swedish trials]		[0.77 (0.67-0.88)]		[0.75(0.65-0.87)]
All trials	212,000	0.78 (0.70-0.87)	138,000	0.76 (0.67-0.87)

Table 1: *Meta analyses of published data on 5-10 years mortality in women over 50 years of age included in randomised trials of population screening by mammography in which control group has no form of intervention. (Wald et al. The Breast, 1993; 2: 209-216 with permission.)*

screen-detected breast cancer is more likely to be non-invasive, or if invasive to be of smaller size with a reduced incidence of lymph-node involvement compared to that presenting in unscreened women (*Figure 5*) (42-44).

UK Screening Programme

In 1987 the UK Government accepted the proposals of a Working Group and initiated a breast cancer screening service as part of the National Health Service (45, 46). At that time the only results were from two randomised trials (Health Insurance Plan, New York,

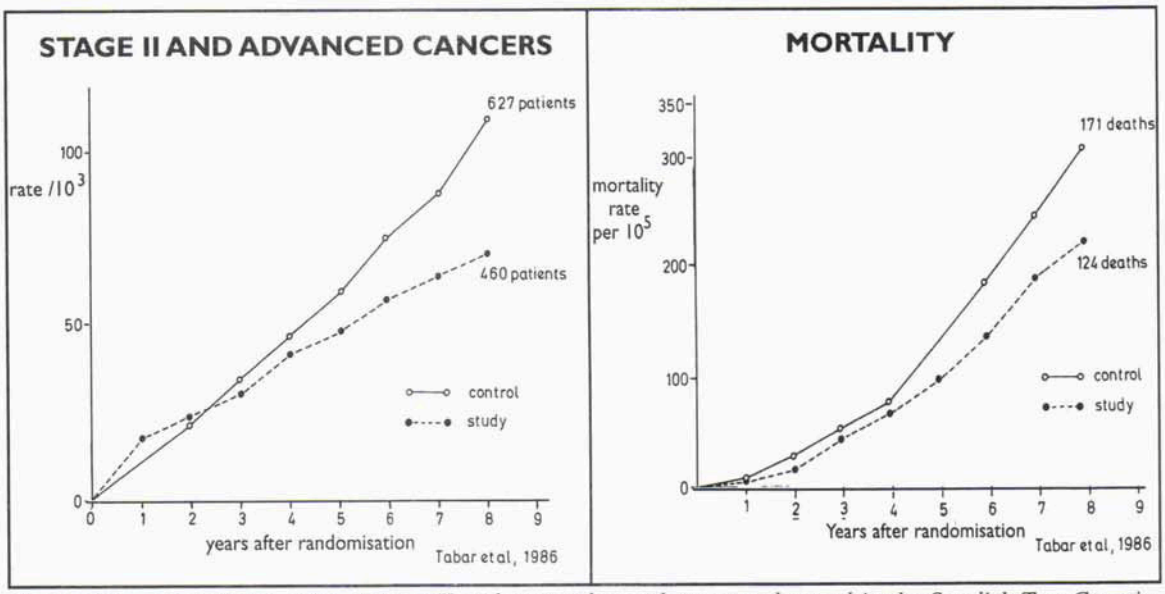

Figure 5: *Cumulative rates of stage II and more advanced cancers observed in the Swedish Two-Counties Trial. (redrawn from Tabar et al. Br J Cancer, 1987; 55: 547-541 with permission).*

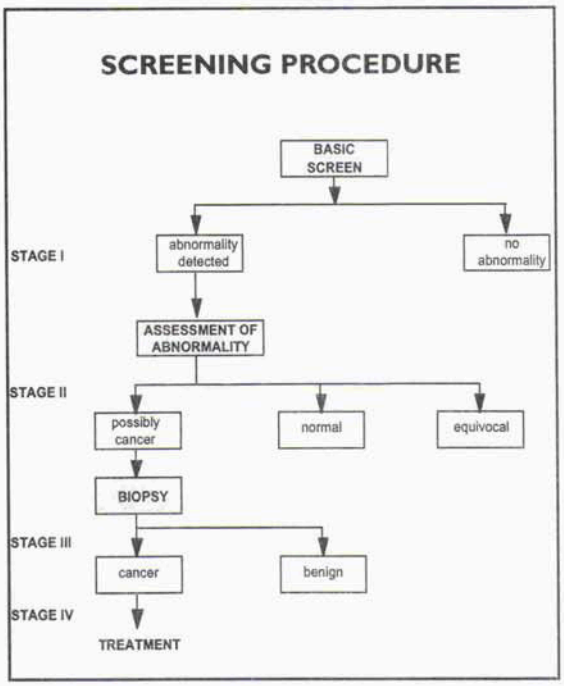

Figure 6: *The Screening Process. (redrawn from Report to Health Ministers of England, Wales, Scotland and Northern Ireland. HMSO, 1987 with permission).*

and Two- Counties, Sweden) and two case-control studies (Nijmegen and Utrecht, Holland) all of which had indicated significant mortality reductions in women over 50 years of age (20-23). In the Swedish two-county trial and Nijmegen case-control study, the screening method used was single medio-lateral oblique mammography; in Sweden, women over 50 years had been invited for repeat screens each 33 months, information which led the Working Group to recommend that the UK programme be restricted to a target group of women of 50-64 years of age who were to be invited for single oblique-view mammography each 3 years. National programmes of mammographic screening were also being set up in Finland, Sweden, Iceland and Norway and since then in Australia, New Zealand, and Canada.

In their Report, the Working Group described four stages in a screening service - the basic mammographic screen, the assessment of mammographic abnormalities, the performance of a biopsy and the treatment of the screen-detected cancer (*Figure 6*). Recognising the problems which might arise were screening to be introduced in an uncontrolled way, they recommended that the screening service should be comprehensive. Steps would be taken not only to provide the neces-

sary mammographic facilities for the 5 million women in the target population, but also the facilities for the evaluation, by diagnostic tests, of those abnormalities detected on the initial screening mammogram, for the biopsy of those lesions suspicious of cancer and for their treatment. This required the institution of a completely new organisation with appropriate management and quality assurance. The UK Government responded by agreeing to support the screening service by 'all necessary back up facilities ... assessment ...diagnostic ... (and) treatment facilities, counselling and after care, and training for key groups of staff' (46).

The Basic Mammographic Screen

It was recommended that the basic mammographic screen should be performed either in urban purpose-built clinics or rural mobile screening vans, equipped with dedicated mammography units. Each unit would perform 12,000 mammograms each year, allowing the screening of 10,000 women in the target population, a small number of older self-referred women and repeat mammograms for those whose initial films were unsatisfactory. With a response rate of 70%, each mammography unit would cater for the needs of 14,000 women in the target population each year, equivalent to a total population of half a million. To cover the whole of UK, 120 units were required. In Scotland, with its population of 5.5 million, 7 static screening clinics were built in the main cities which maintain the servicing of 6 mobile units which travel out into the surrounding country. All films are processed in the main urban units. When it is considered that in Britain there were only 183 diagnostic mammography units in operation in 1985, 128 of which were obsolete, the development of mammographic screening had major implications (45).

Assessment

A basic mammographic screen is not a diagnostic test. It only can separate out those women whose mammogram is normal, is abnormal or of insufficient quality for interpretation. Abnormalities indicating a positive screening test are microcalcifications, discrete opacities (mass lesions), disturbances of architecture and asymmetry. In the British screening service women with abnormalities are recalled to their nearest urban screening clinic which have also been designated as 'assessment centres'; they are not referred either to their general practitioner or directly to the hospital service. These clinics have facilities for clinical examination, sophisticated imaging, fine-needle aspiration and fine needle-aspiration cytology or core needle biopsy which are performed by an expert team including radiologist, clinic doctor, surgeon, histopathologist and cytologist, most of whom also work provide a service to the main urban teaching hospital.

The first step in the investigation of a mammographic abnormality is clinical examination of the breasts, which is facilitated by the examiner (most often a clinic doctor) knowing from the mammogram the location of the suspected abnormality in the breast. If the lesion can be felt, fine- needle aspiration (to determine if cystic or solid) and should it be solid fine needle aspiration cytology are performed leading to a definitive diagnosis in most women. When the lesion is not palpable greater discrimination is required. The tests then used depend on the nature of the lesion.

If a small circumscribed opacity is visible on the mammogram, ultrasonic visualisation will determine whether it is cystic or solid. If cystic, it can readily be aspirated through a needle passed alongside the ultrasonic probe. Should it be solid, magnification mammography is the next step to allow assessment of the border of the lesion. Should this be spiculated an invasive cancer is suspected. Magnification views are also essential for the further definition of micro-calcifications, so that their distribution in relation to ducts and other tissues, can be defined, and also for distortions of architecture, when the 'tenting' of the parenchyma caused by a small invasive cancer may become visible. Additional projections will be required to resolve the reason for asymmetry of the breast parenchyma, which may be due to overlapping densities.

As in palpable breast disease, it is desirable to obtain fine needle aspiration cytology or a core needle biopsy from all suspicious lesions. Radiological localisation using stereotaxic equipment is required to guide the needle to the centre of the lesion. Cytology is particularly helpful in the mass lesion, but of little help for the diagnosis of the cause of calcifications, for which many radiologists now prefer core biopsy. Dedicated units for localisation and core biopsy and even laser treatment of small lesions have now been developed on which the patient is recumbent, but these are expensive and most UK centres rely on simpler 'add-on' equipment used with standard mammography units (47).

As has already been indicated, assessment is best carried out by a dedicated multidisciplinary team. As they all will be present at assessment sessions, decisions can be made without the need for cross-referral between different specialists. Performance can be monitored at regular review sessions which stimulates the development of experience and expertise. The nurse counsellor has become an important member of this team, for women recalled for assessment are anxious and require support.

Biopsy

As a result of the availability of these diagnostic methods and the expertise of the multidisciplinary team, open surgical procedures to obtain tissue for diagno-

sis are now rarely required. This is not the case when assessment is carried out by individual practitioners, when biopsy rates are many times higher. In UK, all biopsies of non-palpable lesions are performed by the 'screening team', with surgeon, radiologist and pathologist working together to ensure that the suspect lesion has been removed and is precisely diagnosed. Pre-operative radiological localisation, usually by the insertion of one or more hooked wires, guides the surgeon to the lesion. Immediate radiology of the specimen is mandatory, and it is now accepted that the radiologist is responsible for confirming that the mammographic lesion has been removed before the surgeon closes the wound.

Treatment

Although the screening service has a responsibility to ensure that cancers detected in the screening programme are treated correctly, treatment is normally carried out in an NHS hospital. The specialist breast surgeon associated with the screening service, although also responsible for the care of symptomatic patients, does not necessarily treat all patients in whom cancer is detected through the screening programme. Those with palpable disease may prefer referral to their local hospital, or occasionally to one in the private sector. However, increasingly women are demanding that the multidisciplinary approach which they have experienced in the screening service should also be available for their treatment and future care. Radiotherapist and medical oncologist then become necessary members of the specialist therapeutic team.

Quality

The Working Group emphasised that the quality of each step in the screening process had to be with the highest quality and recommended that a quality assurance programme be established as part of the screening service. Professional bodies including the Royal Colleges of Radiologists, Pathologists and Surgeons established working groups to develop guidelines for each discipline and laid down the initial standards which should be met in an efficient programme. Particular emphasis was initially placed on its radiological aspects; for example it was recommended that to be competent a screening radiologist should read the films from 6,000 women each year, that recall rates in screened women for further tests should not exceed 10%, that cancer detection rates should not be less than 5 per 1,000 screened women (with 1.5 per 1000 with invasive cancers less than 1 cm in size), and that the benign to malignant ratio on open biopsy should not exceed 3:1 (48). These targets, which were defined in 1992, have since been revised to more stringent levels.

Similar performance objectives have been established for all steps in the screening programme, from the initial definition and invitation of women in the target population to the follow-up of those with screen-detected cancer, and the determination of interval cancer rates (49). Performance is monitored locally by the holding of regular review meetings by screening staff, regionally by the establishment of Quality Assurance Managers with Quality Assurance Reference Centres supported by working groups in each specially, and nationally by the appointment of National Coordinators and coordinating committees in each specially with representatives of each of the 14 health service region of England, and Scotland, Wales and North Ireland. As stated in the 1993 NHS Review of the screening service 'quality assurance is at the heart of the programme' (50). So also is training. Four training centres have been established within the programme.

	number	(%/ratio)
Total screened	1,260,609	
Recalled for assessment	67,475	(5.4%)
FNA cytology	13,466	(1.1%)
Surgical biopsy	6,543	(0.52%)
Cancers detected	6,656	(5.3:1000 screened)
In-situ cancers	1,308	(1.0:1000 screened)
Invasive cancers <15mm	2,655	(2.1:1000 screened

Table 2 *National Health Service review for years 1994-5. Total Screening activity (from NHS Screening Programme Review 1996)*

	target	achieved
Acceptance rate	>70	74.9%
Recall rate	<7	7.2%
Biopsy rate	<1.0	0.69%
Benign biopsy rate	-	0.28%
Cancer detection rate	>5.5/1000	5.9
In-situ cancer	10-20%	19%
Invasive cancers <15mm	>50%	52.8%

Table 3 *Meeting of Targets in National Health Service Programme - Prevalent Screen (from NHS Screening Programme Review 1996)*

The NHS Breast Screening Programme was considered by the National Audit Office in 1992, which in their report, regarded the emphasis on specialisation and rigorous quality assurance as being a great strength (51). In 1995 the House of Commons Health Select Committee reported that 'The NHS Breast Screening Programme is a model service' (52).

Results of Screening

Each screening clinic maintains computerised records which are rigorously checked locally and regionally before being transmitted to the Cancer Screening Evaluation Unit in the Institute of Cancer Research in Surrey, England. Results from the programme are published annually (52-54). Some results for the years 1994-1995 are given in *Tables 2 & 3*.

Not surprisingly, acceptance rates in the invited population (50-64 years) were higher for the second and subsequent (incident) screens (89.2%) that for the first (prevalent) screen (74.9%). So also, as one would expect, were rates of recall for assessment of a mammographic abnormality less (3.4% v 7.2%) as were cancer detection rates (4.3 v 5.9 per 1,000 women screened). For the prevalent round 18.6% of the 6,500 cancers detected were non-invasive and 53% were invasive and less than 15 mm in size. In previous reports 10 mm was taken as the 'threshold' for a minimal invasive cancer. During 1993-1994 24% of cancers were in this category.

It is notable that not only is the surgical biopsy rate low (0.7% for the prevalent and 0.36% for the incident screen) but the ratio of malignant to benign histology on open biopsy is now well above unity. Open biopsies for benign disease (0.28% in the prevalent round) are now uncommon. There are variations between Scotland, Wales, N. Ireland and the 14 regions of England are moderate. For the prevalent screen during 1994-5 uptake rates have varied from 64.3% to 84.7%, recall ratio from 5.4% to 9.7%, biopsy rates from 0.56% to 1.19% and cancer detection rates from 5.0% to 8.4% per 1,000 women screened. Whether these reflect differences in screening practice or in the incidence of the disease is not known.

The target set for the detection of small invasive cancers was greater than 1.5 per 1,000 woman screened, and this would appear to have been met only in 30% of clinics (54). Interval cancer rates have now been reported from two regions of England, and these are higher than those experienced in the Swedish two-county trial, although similar to those in other studies (56-58). There is concern that the sensitivity of mammography and the frequency of screening may be less than desirable, matters which have been subject to research.

Research

The Working Group recognised that their recommendations were preliminary, and emphasised the need for research to determine optimum strategies. Following implementation of the programme, the UK Coordinating Committee for Cancer Research set up a Breast Screening Research Subcommittee which proposed that randomised trials be initiated to determine the best screening test (one or two-view mammography), the optimum frequency of mammography, the effect of screening women under 50 years of age and the management of non-invasive ductal cancer.

Mammographic Technique

The decision to initially recommend single-view mammography as the basic screening test was based on experience in Sweden and The Netherlands. In the event radiologists increasingly asked for a two-view screen (oblique plus cranio-caudal) for the prevalent round, as was standard for symptomatic cases. The results of several retrospective studies and of a UK randomised trial has justified this approach (14,59).

The UK trial was to include 150,000 women attending 9 English screening clinics who were to be allocated randomly to have a single or two-view view mammogram. The design of the trial allowed comparison of one versus two views in both different women and also the same woman, which gave maximum statistical strength. As a result of this design significant findings emerged after an analysis of 40,163 women and the trial was closed.

These findings indicated a clear-cut advantage to two views. There was a significant fall in recall rates (8.16 to 6.97 per 1,000 in different women), and rise in cancer detection rates (5.52 to 6.84 per 1,000 in the same women - an increase of 24%). Two views also reduced the need for further assessment films on recall, and a lower benign biopsy rate despite similar proportions of in-situ and small invasive tumours. Screening by two views cost more than by one view, but the increase was offset by the reduction in cost of further investigations and the higher cancer detection rate. Two-view mammography is now recommended for the prevalent screen in the UK programme.

In the majority of screening clinics the films are still interpreted by a single radiologist, although in Scotland double reading is now routine. Three studies have shown that double reading by two radiologists increases cancer detection rates by from 9 to 15% (for refs see 60). That most recently reported has also shown that it is better to recall on the consensus opinion of two radiologists (if necessary seeking a third opinion) than on acting on a combination of each radiologist's opinion. Compared to single reading, with a recall rate of 6.9% and a cancer detection rate of 7.1 per 1,000, double reading by consensus gave a recall rate of 4.2%, and a cancer detection rate of 8.0. When recall rates were based on the independent opinions of both radiologists the recall rate increased to 9.2% with only a minimal increase in cancer detection (8.1 per 1,000, The lower recall rates associated with consensus

double reading resulted in a savings in overall screening costs.

An alternative to double reading is currently being explored. This employs high resolution digital scanning of mammographic films from which feature detection algorithms for common mammographic abnormalities have been constructed. Prompting systems to alert radiologists to the site of an abnormality are underdeveloped and will shortly be introduced on a trial basis into a number of UK screening clinics (61). The key question to be answered is whether one radiologist, assisted by computer prompting, can reach the performance achieved by double reading by consensus. On-line direct digitisation of mammographic images is also under study (62).

Frequency of Screening

The recommendation for a 3-year interval for screening was based on the Swedish Two- counties trial. Concern with the high interval cancer rates reported during the third year revised Swedish practice, and in that country, as in Holland, 2 years is now accepted as the routine interval for women over 50 years. A UK trial is in progress to compare screening at an interval of 1 year with that of 3 years to which 130,000 women are to be revisited. No results are available.

Age of Target Population

The age at which women are first invited to be screened is causing great controversy (14,63-65). The American Cancer Society, the American College of Radiologists and the American College of Obstetricians and Gynaecologists still advocate that regular mammographic screening should start at age 40 but European national programmes, other than that in Sweden, restrict entry to women of 50 years or more. The National Cancer Institute (NCI), while accepting evidence on the benefit of screening in those over the age of 50 years to be conclusive, have indicated that the findings in women of ages 40-49 who have been included in randomised trials provide insufficient evidence on which to base an informed opinion (*Figure 7*). It advises that younger women wishing to be screened consult their health professionals to decide whether benefit justifies risks and cost. Although it is suggested that in some trials mortality reductions in young women start to emerge 8 years following the introduction of screening, most agree with the NCI view.

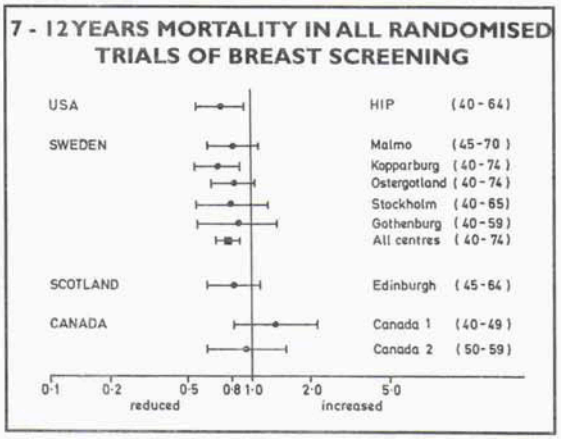

Figure 7: 7-12 year mortality in women of less than 50 years of age in randomised trials of population screening by mammography.

Information on the effects of screening women less than 50 in randomised trials are based on retrospective subgroup analyses (*Figure 7*). Overviews are confounded also by variations in the method of randomisation, attendance rates, quality and frequency of screening. For a valid answer of the effect of screening younger women, a new generation of trials, such as that now being conducted in UK, are required. In the UK trial 150,000 women aged 40-41 years are being randomised either to be screened annually for 7 years or to await entry to the national programme at age 50. The first analysis of mortality will not be available until 2003, but interim analyses using surrogate indices of benefit, such as tumour size and node status will be performed. In considering the results of screening young women, it is vital that the age at diagnosis of cancer as well as the age at first screen is taken into account. Re-analysis of the overview of Swedish trials using computer modelling has suggested that the greater proportion of the 13% mortality reduction in women of 40-49 years which was observed was due to the diagnosis of a cancer at a later age (63).

The recommendation that the upper age for an invitation to be screened should be 65 years was based on the known reduced uptake in older women. In view of their relatively limited life-span, the benefits which can be expected, in terms of years of life saved, is also less than that in younger women. However, a case-referent study from Nijmegen reported that a mortality reduction from screening persist up to the age of 75 (67). In UK, women over the age of 65 years are encouraged to refer themselves to screening clinics for mammography which is carried out as part of the screening service.

Treatment

Screening programmes uncover large numbers of non-invasive cancers, the significance of which is still uncertain. Non-invasive lobular cancer (lobular carcinoma-in-situ (LCIS)) is regarded only as a marker of increased risk of cancer and only requires regular follow-up mammography. Ductal carcinoma-in-situ

(DCIS) is a frankly malignant lesion which carries a 30% risk of invasive cancer within 10 years, a risk which is greater when it is histologically of comedo type or is of aggressive cytological grade. Some surgeons still advocate mastectomy as the treatment of choice, but in Europe wide local excision is preferred unless the disease is extensive. Only one randomised trial has considered the need for routine radiotherapy following local excision this reporting that recurrence rates following local extension alone were excessive (67). A current UK trial is designed to determine whether the administration of tamoxifen will alter this need. Following local excision of in-situ disease, women are allocated for radical radiotherapy alone, for tamoxifen alone or for both. Over 1,200 women have now been recruited to this trial, the results of which will not become available for several years. It is currently considered that DCIS cannot be considered as a single disease and prognostic factors such as size, the extent of necrosis and cytological grade should be taken into account when planning treatment and must be considered when reporting the results of trials (68).

Invasive breast cancers detected by screening are smaller than those presenting symptomatically, and are more likely to be suitable for treatment with conservation of the breast. The results of several controlled trials suggest that even in small predominantly node negative tumours, radical radiotherapy is a necessary part of conservation treatment (for refs see 71). In a Scottish trial this proved to be the case even when tamoxifen or chemotherapy was routinely given (71). In a randomised trial, conducted by the British Association of Surgical Oncology, patients with small (< 2 cm) and well differentiated (grade 1) cancers are being allocated for radiotherapy and for tamoxifen as in the UK trial of non-invasive ductal cancer.

Prevention

Mammographic screening will not prevent breast cancer. For true prevention the cause of the disease must first be known. This is not the case breast cancer. It has long been recognised that functioning ovaries are a necessary prerequisite to the development of the disease, acting as a reversible promoting factor. Reduction in the period of cyclical ovarian function, for example by an early or artificial menopause, reduces life-time risk, while its prolongation by an early menarche or late menopause increases this. Early and multiple pregnancies are also protective, but whether pregnancy acts through suppression of ovarian function or as a result of differentiation of breast epithetial stem cells is unclear. In the belief that ovarian oestrogen is the hormonal cause of this effect, preventative strategies to reduce the availability of biologically active oestrogens are actively being explored. These include administration of the antioestrogen tamoxifen, reduction in dietary fat and increase in the intake of vegetable products (for refs see 71).

Recognition that maximal proliferative activity of the breast epithelium occurs during the luteal phase of the cycle has led to the suggestion that oestrogen by itself does not stimulate proliferation of breast epithelium, but that progesterone also is required (72). In a young woman the secretion of both oestrogen and progesterone can be abolished by the administration of gonadotrophin releasing analogues, which cause a chemical castration. It is suggested that when the secretion of both hormones are inhibited, it is safe to give small amounts of oestrogen alone to reverse adverse effects. In these circumstances, not only would the incidence of breast and ovarian cancer be reduced, but effective contraception would be provided without the risks of the pill. To prevent an increased risk of endometrial cancer by small intermittent courses of progesterone are given. The feasibility of this approach is under study (72).

The sequencing of the BRCAI and BRCA2 genes with the detection of mutations in those with a dominant family history of breast cancer has raised hope that markers for these genes might allow definition of those also at risk from sporadic disease (73,74). This does not appear to be the case. The carrier state for the mutated genes only defines risk for those with family history of inherited type. In a woman carrying the mutated gene prophylactic surgery can remove risk. But professional counselling on the implications of a family history of breast cancer and genetic testing must first be available to all women.

Breast Cancer In Malaysia

From data collected by the Cancer Registries in Singapore and Penang, it would appear that the incidence of breast cancer in Malaysia is still only about one half of that in the western world. Incidence rates are reported to be lower in Malays than in Indians or Chinese (75,76). At the present time a nationally funded programme of population screening by mammography, such as that in UK, is not likely to be cost effective. As many Malaysians present with the disease at a late stage, public education to increase awareness of the benefits of early diagnosis and treatment should have priority.

However, it is apparent that throughout the cast the incidence of breast cancer is rising and there is a case, as during the 1960-70s in UK, to consider setting up a pilot study of mammographic screening, such as that now being undertaken in Singapore. This

would allow experience to be gained on likely compliance, the sensitivity and specificity of screening mammography in Malaysian women, and also study of the nature of screen-detected cancers. It also could explore the needs for organisation of a population screening service were this later to be desired.

A valuable lesson from the UK NHS screening programme has been widespread realisation of the benefits which a multidisciplinary approach has brought to the management of breast disease. At the time the screening programme was initiated, only a few medical centres had designated breast clinics which practised a multidisciplinary approach the management of symptomatic women. This situation is rapidly changing, and guidelines for the management of symptomatic breast disease within the NHS have been formulated by professional bodies. The availability of such guidelines has great relevance to a country such as Malaysia, which relies to such a great extent on the provision of medical services by practitioners who, working in the private sector, have difficulty in accommodating to a team approach.

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