Eur J Cancer, Vol. 28A, No. 4/5, pp. 911–916, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00
Pergamon Press Ltd

The Early Diagnosis of Breast Cancer — A Twenty-Year Experience at The Royal Marsden Hospital

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Over 30 000 women with minimal symptoms were examined between 1968 and 1987 for the detection of early stage breast cancer. Subsequent follow-up screening was selected for women at higher risk because of family history, previous significant benign breast change (e.g. epitheliosis) and hormone replacement therapy. 552 cases of cancer were diagnosed and the current prevalent detection rate is 8.5 per 1000 women examined. Incident cancer (screen-detected and interval) occurred in 6.2 per 1000 women-years at risk. Of the prevalent cancers, 47% were in early T stages of development (TIS, T0 and T1) and this proportion rose to 70% in the screened group. Survival is stage-dependent but the group has not reached its median survival at 15 years. Actuarial estimates of the percentages surviving at 10 years are 73% in the prevalent group and 80% in the incident group.
Eur J Cancer, Vol. 28A, No. 4/5, pp. 911–916, 1992.

INTRODUCTION

In 1987 the National Health Service in the UK adopted the recommendations of the Forrest Committee for breast cancer screening by mammography in women aged 50–64 [1]. In 1968 a clinic devoted to the early detection of breast cancer in women without symptoms or with minimal symptoms began work at the Royal Marsden Hospital. This clinic was originally called the Early Diagnostic Unit, and more recently became the Breast Diagnostic Unit. Over 30 000 new subjects have been examined clinically and this examination has been complemented by imaging techniques which have included: X-ray mammography with xerox and film techniques, thermography and, recently, ultrasound. Tissue diagnosis has been achieved by fine-needle aspiration cytology and confirmed, when necessary, by histological examination following biopsy.

Diagnosis has been achieved with a multidisciplinary team approach; the importance of regular review meetings and of the assessment clinic has been stressed. The methods used to avoid excessive benign biopsy are described below.

Women were referred by their general practitioners to the clinic when a diagnosis of cancer was considered unlikely or uncertain. Patients with clinically apparent breast cancer were referred direct to surgical teams. Referring general practitioners were encouraged also to send women with a family history of breast cancer, particularly in the maternal line; women with a history of a benign biopsy revealing premalignant features (epitheliosis with or without atypia, intraduct papillomatosis, etc.) and women with breasts difficult to assess by clinical examination. These latter women had symptomatic nodular breasts, with and without cystic change.

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This paper was presented at the EORTC Breast Cancer Working Conference, 3–6 September 1991, Leuven, Belgium.
Received and accepted 13 Dec. 1991.

SUBJECTS AND METHODS

In the first screening period (1968–1981) the population of women attending the unit was heterogeneous: most came to the clinic with symptoms of breast disease whilst others came for screening (usually because of a close family history). An initial history relating to breast symptoms, previous breast disease, menstrual status and pregnancy experience was recorded. General health (or illness) and medication were noted and all women had a clinical breast examination. Nursing Sisters have played an important role in the clinical examinations made at screening visits. Also, they taught women self-examination and "breast awareness". They have run breast screening courses on clinical examination for nurse specialists.

At the outset, the unit had a major interest in thermography as a screening tool and all women were examined at 19°C, after 10 min cooling, unclothed from the waist up. The results of thermographic examination of women with breast disease from this unit have been reported [2].

Between 1968 and 1971, selected X-ray mammography was carried out using a tungsten target source and the mammographic film then available. Between 1971 and 1986 all mammograms were performed using the xero-mammographic technique; in general lateral xero-mammograms were taken in the negative mode and the cranio-caudal view in the positive mode. Since 1986 xero-mammography has been abandoned in favour of film screen mammography.

Fine-needle aspiration cytology has been a standard diagnostic test since 1975 in those women considered for biopsy; it has been used extensively by doctors and nurses to support a benign diagnosis and avoid biopsy, or to raise the degree of suspicion such that histological biopsy became necessary. All investigations were reported with knowledge of clinical findings and therefore the sensitivity and specificity of individual tests was not known.

Table 1. Distribution of cancer patients according to early (1968–1981) and late (1982–1987) cohorts and within prevalent, screening and interval groups

	Cancer population		
Presentation type	1968–1981	1982–1987	Total
Prevalent	157	75	232
Screening	115	92	207
Interval	59	54	113
Total	331	221	552

Table 3. Distribution of symptoms in patients with cancer diagnosis in early and late cohorts

	% with symptoms at cancer diagnosis	
	1968–1981	1982–1987
None (%)	35	38
Lump (%)	34	32
Lump and pain (%)	11	8
Pain (%)	7	11
Other (%)	13	11
Total (*n*)	(331)	(221)

Weekly review meetings with radiologists and pathologists were held and followed by a weekly assessment clinic with a surgeon, so that decisions about diagnosis and the need for biopsy could be determined. Too many benign biopsies are an unnecessary cost in any screening programme, but they are a part of the necessary service in a symptomatic breast clinic. Throughout the period of this work regular and continued attempts were made to reduce the benign to malignant biopsy ratio.

Histological biopsy of the benign breast under local anaesthetic to obtain a core by drill biopsy or by Tru-cut needle has never been easily accepted by surgeons or patients in this clinic, although both methods can be very satisfactory in tumour diagnosis. Benign biopsies, therefore, have been excisional, often carried out under general anaesthetic and have involved a stay in hospital (as many of the patients do not live nearby). Women with benign disease were discharged or returned to the unit's screening programme. Women with a diagnosis of cancer were transferred to a cancer treatment unit and many, but not all, were treated at the Royal Marsden Hospital.

The acceptability and compliance during this period was such that approximately 60% of the women returned regularly for screening and the population attending grew uncontrollably. This led to a management decision to limit and refine the practice.

Women attending the clinic during 1982–1987 were assessed and diagnosed; they were then discharged from regular follow-up screening unless they had a "high risk" qualification which included one factor of: a first-line maternal family history, a previous benign biopsy showing premalignant activity (epitheliosis, especially with atypia) and concurrent administration of hormone replacement therapy (HRT). These latter women came mainly from the Menopause Clinic at the Chelsea Hospital for Women in an adjacent building.

During this time we reduced the number of women screened aged less than 50 because we were aware of the lack of benefit of screening in the under-50s [3].

These women at higher risk entered a prospective screening interval study; random allocations were made to screening with intervals of 12, 18 and 24 months. At each visit, thermography and a clinical examination were performed. Alternate visits were supplemented with mammography unless some abnormality was found by clinical examination or thermography, in which case an "interval" mammogram was performed.

The following definitions have been used to describe the different screening groups: prevalent = cancers detected at first attendance; incident = cancers detected at screening (routine follow-up) or interval (presenting between scheduled visits). The UICC (1978) method of staging breast cancer was used throughout [4]. It was not possible to calculate the numbers of screens prior to cancer detection, because the data were only fully computerised in 1985.

Statistical methods

Data were collected and entered onto the Royal Marsden Hospital Clinical Research System (CRS), a computerised system for clinical data management and analysis. Tabulated data were analysed using the χ^2, Mann–Whitney (for trend) and the Spearman rank tests. When the three screening categories were being compared, the prevalent group was assumed to be intermediate between the screening and the interval group when performing tests for trend; two-sided tests for trend were used. Analysis of survival data was undertaken using the logrank test [5]. Kaplan–Meier [6] product-limit survival curves were employed.

Table 2. Age distribution of patients with a cancer diagnosis in early and late cohorts

	% of patients below 50 years of age	
	1968–1981	1982–1987
Prevalent (%)	39	47
Screening (%)	41	30
Interval (%)	48	52
Total (*n*)	(331)	(221)
	N.S.	$P < 0.01$

Table 4. Frequency of symptoms at presentation according to T stage of cancer (1968–1987)

	% symptomatic	*n* = 552
TIS	43	80
T0	41	34
T1	67	207
T2	69	170
T3	80	20
T4	100	12
TX	—	29
	$P < 0.001$ (trend)	

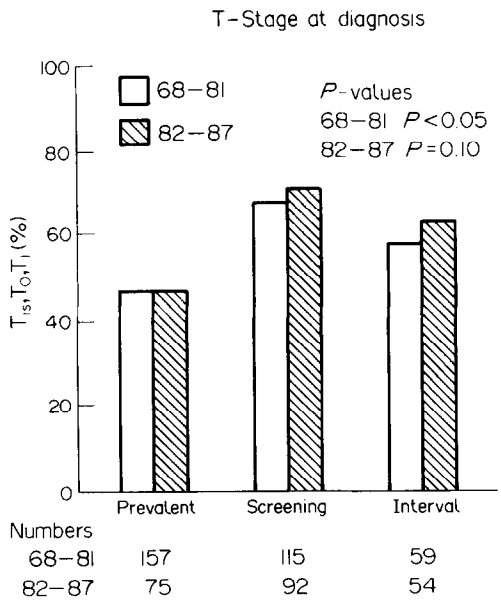

Fig. 1. Early T stage distribution of cancer in three groups of early and late cohorts (*P*-value for overall trend $P = 0.01$). The *P*-values shown are *P*-values for trend, testing the order: screening–prevalent–interval.

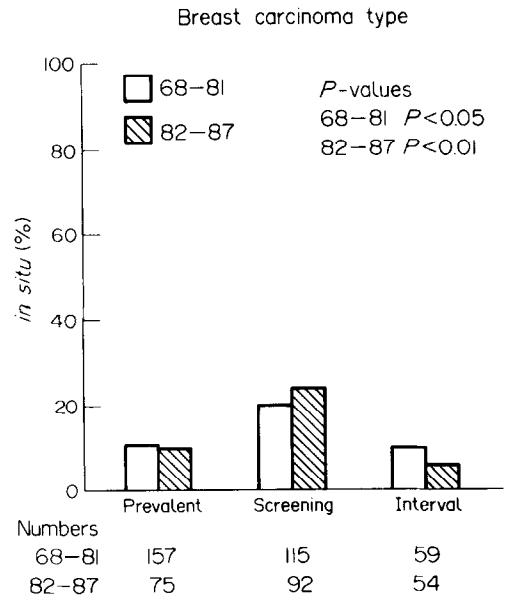

Fig. 2. Early T stage distribution of cancer in three groups of early and late cohorts (*P*-value for overall trend $P = 0.001$).

RESULTS

Cancer population and methods of detection

Between 1968 and 1987, 552 cases of cancer were diagnosed. Table 1 shows their distribution within the prevalent and incident groups for 1968–1981 and 1982–1987.

Table 2 describes their distribution according to age showing the percentage less than 50 years old. In 1982–1987 30% of the screen-detected cancers were in women under 50. 48% of screen-detected cancers were in women with a family history of the disease which, in the general population, applied to less than 15% of women with breast cancer [7]. Over a third of these women had no symptoms at the time of diagnosis and the symptoms of the remainder are described in Table 3. It is of interest that pain was a feature in nearly 20% of the cases and it was the only presenting symptom in nearly 10%. Symptoms are related to the extent of disease in the breast and the rising frequency of symptoms in association with T stage are reported in Table 4. Figure 1 shows the increased detection of early stage disease (TIS, T0 and T1) in the screened population. Figure 2 shows the detection of *in-situ* disease alone in relation to screening. There is a highly significant trend with more *in-situ* disease in the screened group and with least in the interval cancer group. The prevalent group shows an intermediate value. This trend is described in Table 5. Table 6 shows that a similar trend exists with respect to clinical nodal status.

In the first cohort of women examined between 1968 and 1981, 72% of the prevalent cancers had an abnormal thermogram but only 57% were positive in the interval group and 52% in the screening group. In the years 1982–1987, 56% of the prevalent cancers were thermographically positive but only 39% of the screening cancers were thermographically positive. The use of thermography has been discontinued [8].

75% of the mammograms from the prevalent group were abnormal, and 60% suspicious or abnormal in the screened group. The mammographic detection of cancer increased with the extent of disease in the breast. Table 7 shows that 74 cancers were not palpable as a lump, the clinical features in these cases

Table 5. Distribution of in situ *and invasive tumours by presentation type* (1968–1987)

	In situ (%)	Invasive (%)
Prevalent	12	88
Screening	22	78
Interval	8	92
	$P < 0.001$	

$n = 522$.

Table 6. Distribution of nodal status by presentation type (1968–1987)

	N0	N1A	N1B	N2	N3	NX
Prevalent%	56	20	18	3	2	1
Screening%	71	15	8	1	0	5
Interval%	48	21	15	1	1	14

$P < 0.001$; test for trend.
$n = 552$.

Table 7. Value of mammography with increase in extent of tumour (1968–1987)

	Mammograms suspicious or malignant	
	%	(no.)
No lump or skin change	66	(74)
Lump alone	58	(333)
Lump and skin change	83	(116)

$P < 0.001$; this value is a test of heterogeneity.
$n = 522$.

Table 8. Results of fine needle aspiration cytology from cancers in early and late cohorts

	% abnormal cytology	
	1968–1981	1982–1987
Prevalent	82	75
Screening	65	55
Interval	77	77
	$P < 0.05$	N.S.

included diffuse nodularity, local tenderness and nipple change; 66% of the mammograms were positive. In the 446 women with clinically palpable lumps less than 60% were positive when the lump was the only clinical finding but, when there were skin changes such as a crease or dimpling, then the abnormal mammography rate rose to 83%.

In those patients examined with fine-needle aspiration cytology there was a higher positive rate in women with prevalent and interval cancers than in the screening group (Table 8). This may be explained partly by tumour size and by the sampling difficulties associated with the fine-needle aspiration of small lesions [9].

After 1982 the clinical activity was refined, as described above, in an effort to concentrate on women at higher risk of malignancy and to reduce unnecessary biopsies, which were performed at a rate of 6:1 benign to malignant in 1968–1981.

In 1982–1987 the prevalence of cancer detection per 1000 women examined per annum was 8 per 1000 and this had risen to 10.5 per 1000 in 1987. The prevalent biopsy rate overall was 4 benign to 1 cancer, but in 1986 it was 2.6:1 and in 1987 it was 1.5:1.

The incidence of cancer per 1000 women-years at risk from 1982 to 1987 was 4.3 and this rose to 5.7 in 1986 and 6.2 in 1987. The incidence of breast cancer in the South Thames Cancer Registry in the age-cohort of women examined is approximately 1.7 per 1000 women-years [10]. The benign-to-malignant biopsy ratio for this incident cancer detection was 3.5:1 in that 6-year period and 2:1 in 1987.

The results of the screening interval study carried out between 1982 and 1987 are described in Table 9. When women had a 12-monthly screening interval—with a mammogram every second year—73% of the cancers were detected at screening and 27% in the interval between screens. When the clinical screening interval was 24 months and mammography was carried out only every fourth year, 50% of the cancers were detected at screening and 50% appeared as interval cancers ($P = 0.06$).

Instruction in self-examination may have facilitated presentation of these interval cancers but many women avoided regular self-examination preferring to rely on their regular clinic examination.

Table 9. Detection in women randomly screened at 12, 18 or 24 months

Interval (months)	Total*	Screening†	(%)	Interval‡	(%)
12	33	24	(73)	9	(27)
18	28	18	(64)	10	(36)
24	36	18	(50)	18	(50)

* $n = 97$, † $n = 60$, ‡ $n = 37$, $P = 0.06$.

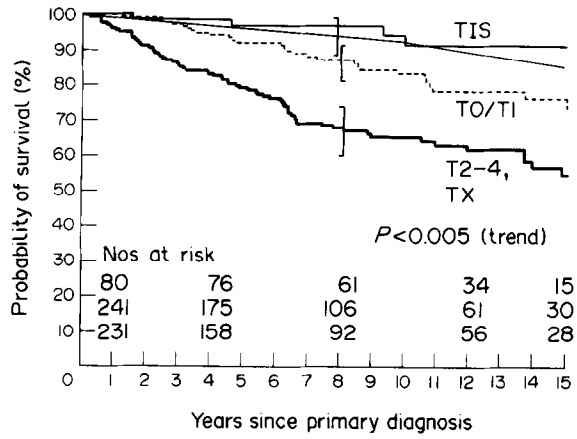

Fig. 3. Survival of 552 cancers according to T stage of tumour.

Cancer detection and survival

Treatment. There has been no single treatment programme prescribed for the women with cancer detected in this clinic, and most did not participate in controlled clinical trials of primary treatment. The majority were treated as individuals according to best available treatments but there was an increasing trend to avoid mastectomy, where possible, over time. Overall, 41% of these women were treated by mastectomy and 18% of those had post-operative radiotherapy; 58% had breast conserving surgery and 50% of that group had postoperative radiotherapy. 12% of the whole group had some form of systemic adjuvant therapy.

The survival is reported according to T stage distribution in Fig. 3. The thin continuous line at the top of the graph overlying the *in situ* population is the expected survival of a normal population of similar age. The confidence limits at 8 years are plotted for the 3 groups: *in situ* cancer (TIS); small or impalpable tumours (T0/T1) and locally advanced disease (T2–4 and TX). At 15 years none of these groups has reached their median survival and this still applies in Figs 4 and 5 where the T stage survival is divided by age 50 and over or aged 49 and under.

Because of the lack of uniform treatment policy and the fact that not all women were treated in our hospital, nodal stage has only been pathologically assessed in 60% of cases. In the

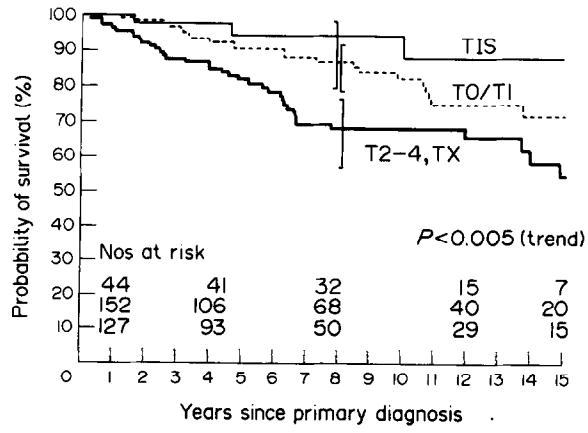

Fig. 4. Survival by T stage in women aged 50 and over.

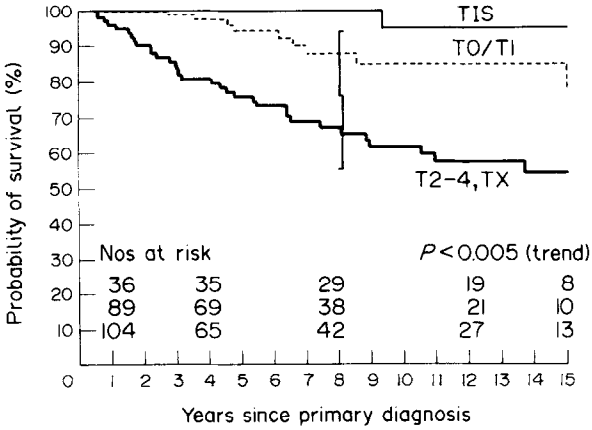

Fig. 5. Survival by T stage in women aged 49 and under.

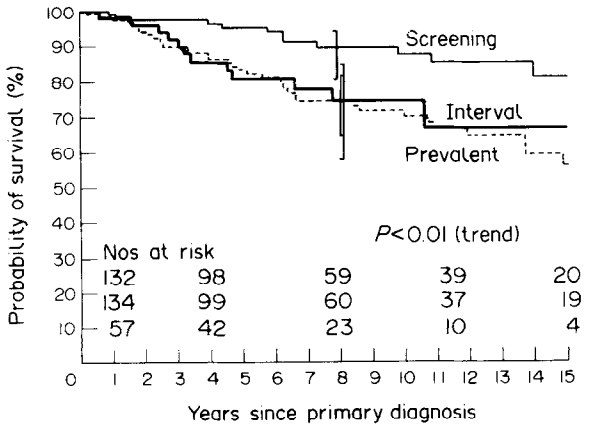

Fig. 6. Survival by presentation type aged 50 and under.

earlier years 1968–1981 some of the women went elsewhere for treatment and because the tumours were small axillary surgery was often thought inappropriate and unnecessary.

When survival by presentation type is examined in Figs 6 and 7, the long-term fate of women with cancer detected by screening is not any different under 49 than it is over 50. The outcome of cancers in these 2 age cohorts is also similar in the interval groups. At 8 years there was also little difference in the survival

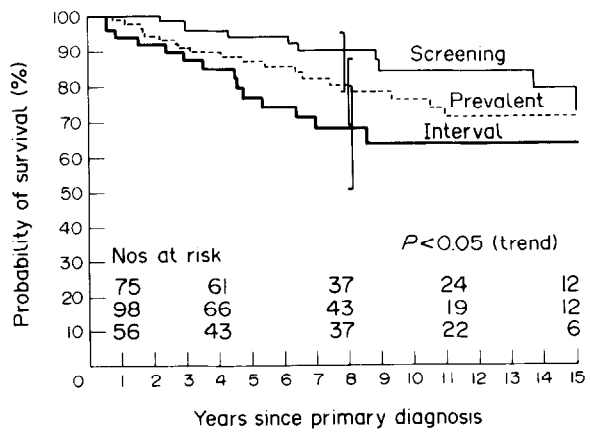

Fig. 7. Survival by presentation type aged 49 and under.

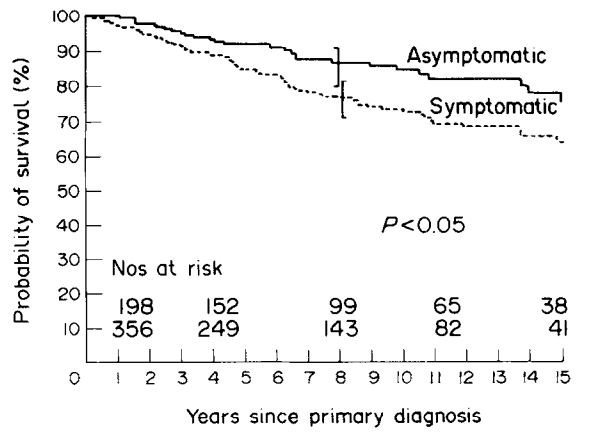

Fig. 8. Survival of 552 cancers according to symptoms at diagnosis.

in the 2 prevalent groups. When overall survival is compared in relation to symptoms (Fig. 8) there is a clear advantage to those women treated for asymptomatic cancer.

DISCUSSION

In the 1960s the HIP study in breast cancer screening was under way [11] and Philip Strax, the enthusiastic radiologist in that programme, was one of a number of proponents of the virtues of the earlier diagnosis of breast cancer by mammography—so that lives could be saved and breast cancer could be cured. It was already clear that mammography could demonstrate cancer (but it might not): it could examine both breasts (screen) and it would provide new information which might be impalpable. In 1968 Peter Greening began this clinic with the aim of selecting a group of women at higher than normal risk for the development of breast cancer. The heterogeneous growth of the population of women attending between 1968 and 1981 threatened to make the clinic unmanageable and unnecessarily expensive when financial constraints within the National Health Service were increasing. Pressure for national screening as a result of the HIP study [3] and of later studies from Sweden and Holland [12, 13] led to the UK National Screening Trials, but it was clear that their results would not be available at least until 1987 [14]. The population of women attending this unit was refined with particular attention to family history and significant earlier benign breast disease. The value of this refinement was confirmed in the increasing prevalence and incidence rates of cancer detection as compared with a normal female population. Approximately 48% (100 out of 207) of the cancers detected at screening were in women with a significant family history. Thus it was shown that regular selective screening of "high-risk" women yielded a higher incidence of early stage disease.

The screening interval study demonstrated that bi-annual mammography (similar to that practised in Edinburgh and Guildford) led to 60% of the cancers being detected at a screening examination. The Forrest Report suggested that mammography alone every third year would detect 75% of incident cancers [15], but if 17% of clinically obvious cancers are missed by (xero) mammography that might be an optimistic assessment. Nevertheless our own results show that clinical examination every 24 months with mammography at 48 months led to 50% of the cancers being in the interval group.

In 1968, Brinkley and Haybittle reported the long-term survival of 704 women treated in East Anglia for breast cancer between the years 1947 and 1950 [16]. That survival was

described according to clinical stage and in relation to the expected survival of a normal population of women of the same age distribution. The authors acknowledged that there would have been some cases treated by surgery alone who did not reach the radiotherapy centre. Nevertheless the median survival of those women was less than 5 years for all cases and approximately 7 years for stages I and II. This unit's group of 552 women has not yet reached median survival, although approximately 17 years has been estimated as a median survival of the stage II cases (T2 and over). It is also possible that survival in this study has been overestimated because of undernotification of deaths, since some patients may have been lost to follow-up because they have died and the hospital has not been informed. When undertaking survival analysis, censoring should be independent of the event (in this case death) of interest. This problem is to be remedied by flagging outstanding patients with the Office of Population Census and Survey (UK).

In this selected group a very favourable survival has been achieved which was clearly stage-dependent and in which lead time bias was not measured. In the HIP study, the survival advantages in the screened group applied more over the age of 50 than under it. That has not been confirmed in this unrandomised and uncontrolled series.

Within the population of women described above, families with a clustering of breast cancer and those which have true familial breast cancer have provided a valuable nucleus of women who were at established higher than normal risk for study in the tamoxifen prevention programme [17].

Early stage breast cancer is detected by screening: the selective use of screening in higher risk women permitted the detection of earlier stage disease with a good long-term prognosis, an important lead-time and possibly with an increased likelihood of cure. However, the continuing downward trend in the survival curves over 35 years reported by Brinkley and Haybittle [18] acts as a salutary caution to any premature ("early") conclusion about cure.

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Acknowledgements—We thank the Board of Governors of the Royal Marsden Hospital and the Department of Health for continuing support; Peter Greening for the idea and his early efforts; our colleagues in the Departments of Pathology and Radiology and the numerous sessional doctors involved in clinical examination. Early computing work was supported by the Eranda Trust. The attending patients have provided endless cheerful help, encouragement and financial support for diagnostic equipment.