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**Evaluation of a surveillance programme for women with a family history of breast cancer.**

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**Abstract:**

**Purpose.** To establish health-related costs and benefits of clinical services for women at increased familial risk of breast cancer.

**Design.** Analysis of costs and outcomes for one UK regional service, supplemented with data from a multi-national collaborative study.

Main outcome measures were aggregate costs for regular clinical examination, mammographic screening and further investigations; breast cancer incidence; proportion of cancers detected at “early” or “late” stage, compared with corresponding data for unscreened women of comparable age; survival in relation to stage at diagnosis; itemised and aggregate costs of management for “early” and “late” stage breast cancer; hence direct health care costs per quality adjusted life year (QALY) gained.

**Results.** The surveillance programme costs £1500 per woman (over 15 years). Breast cancer incidence is close to 6 per thousand examinations; 75% of tumours are detected through screening and 77% are “early” (path stage 1 or 2). Corresponding figures for unscreened women (including relatives of those attending the breast cancer family clinic) indicate that surveillance achieves a beneficial “stage shift”, with reduction in treatment costs and improvement in survival, in about 22% of cases.

**Conclusions.** The current clinical service for women at familial risk of breast cancer costs about £4800 per QALY gained. That figure is sensitive to the rate of detection of breast cancer and the degree of beneficial stage shift achieved. Within the realistic range of estimates for these two parameters, the cost per QALY may be as high as £14000 or as low as £1000.

**Key words:** Breast cancer; familial; surveillance; evaluation.

## **Introduction:**

A family history of the disease is recognised as a strong risk factor for breast cancer<sup>1</sup>. Published guidelines recommend that women with multiple affected close relatives, or with one first degree relative affected under age 40, should be offered annual screening by mammography, with or without clinical examination, from around age 35 to age 50 or 55<sup>2,3</sup>. New referrals to centres offering such services are accruing at the rate of around 200 per million population per year<sup>4</sup>. The original guidelines had only a limited evidence base but in the light of experience it is now possible to evaluate the cost-effectiveness of surveillance. This report is based principally on findings from a single clinic, centred on Dundee, in Tayside, Scotland.

Factors determining cost effectiveness of a service for women with a family history of breast cancer are the number and cost (both financial and psychological) of investigations carried out, number of breast cancers detected, pathological stages of these cancers, cumulative costs of treatment and outcomes (recurrence rate and overall survival). The most valid comparison would be with corresponding costs and outcomes for prospectively ascertained women with comparable family histories who had not been enrolled in any surveillance programme. However, for ethical and practical reasons it is not possible to randomise such women in a controlled trial. Therefore comparisons are based on published data for Scottish and other populations and on retrospective analysis, first of a series of Tayside

women diagnosed with breast cancer before age 50 and second, of young relatives of our index cases who had themselves suffered from breast cancer. Neither group had been enrolled in any screening programme before age 50.

### **Patients and methods:**

Ethical approval for elements of the study which involved collection of patient-specific data was obtained from the Tayside Medical Research Ethics committee.

Over 11 years from January 1995, 46 breast cancers were diagnosed among 42 women enrolled in the Tayside breast cancer family clinic surveillance program. Seven of these occurred in women carrying a germ-line mutation in BRCA1 or BRCA2. Mean age at diagnosis was 48 years. For comparison we identified a consecutive series of 40 women diagnosed with breast cancer under the age of 50, in the same hospital, since 1995 (allowing a minimum of five years follow-up). Pathological stage at presentation and five year recurrence rates were recorded for both groups (Table 1). In addition, from the families of 32 affected patients (excluding BRCA mutation-bearing families) we identified 37 relatives who had been diagnosed with breast cancer under the age of 55 and who had either never had access to pre-symptomatic screening or had been diagnosed at the first (prevalent) round of the UK National Breast Screening Program (NBSP), which offers mammography at 3 year intervals from age 50. In most instances, the relative's diagnosis had been recorded at first clinic attendance of our patient, confirmed in the course

of family risk assessment and updated at subsequent annual clinic visits. Data on outcome were documented for the majority.

Our local findings were compared with the much larger dataset (442 recorded cancers) compiled from several collaborating European Cancer Family centres, including our own<sup>5-7</sup> to confirm that data generated from the limited Tayside series were not unrepresentative.

All procedures carried out in the Breast Cancer Family clinic were tabulated over a 30 month period to obtain accurate figures for surveillance costs<sup>8</sup>. For each clinic patient in whom breast cancer was diagnosed, subsequent investigations, surgical and radiotherapeutic procedures, hospital in-patient periods, out-patient clinic visits and drugs used were recorded and detailed unit costs were derived by reference to published UK data<sup>9</sup>, updated and supplemented where necessary by information from the Scottish Health Statistics on Breast Cancer (ISD Scotland “blue book”). Additional cost details were provided by senior staff of the Finance Department, Ninewells Hospital and Medical School, Dundee and from the Division of Financial Performance Management for NHS Tayside.

Our analysis involves the following assumptions, all consistent with the observed data presented below, with recent reviews of clinical aspects of breast cancer<sup>10,11</sup> and with published findings from breast cancer family services elsewhere in the UK and beyond<sup>5-7,12-14</sup>.

1. Within a “family history” surveillance programme, breast cancers arise at a rate of six per thousand annual examinations and 75% are detected at screening.
2. Seventy-seven percent of these cancers are “early stage” (Path T1/2) and node-negative at diagnosis.
3. Fifty-five percent of breast cancers arising in women under age 50 who have **not** participated in any screening programme are “early stage” and node-negative.
4. Path stage T1-2 node-negative breast cancers have a 70% probability of complete eradication (“cure”) by primary surgery, radiotherapy and, where appropriate, adjuvant chemotherapy.
5. “Late” (node positive) breast cancers have only a 30% probability of “cure” by primary surgery, radiotherapy and adjuvant chemotherapy.
6. Those not “cured” by their primary treatment (30% of “early” and 70% of “late” cases) will require additional treatment and investigations, often involving expensive drugs and are likely ultimately to require palliative care.
7. The quality of life for “cured” breast cancer patients is good<sup>15-17</sup> and, for women diagnosed at around 50 years of age, “cure” of breast cancer provides a further 25 years of life (25 QALYs).



## **Results:**

In the 11 year study period, the Tayside “family history” surveillance programme carried out 8000 annual screens, comprising clinical examination of the breasts and two-view mammography. The yield of 46 breast cancers therefore represents a rate of 5.8 per thousand examinations. As shown in table 1a, 34 (74%) were detected at screening and 36 (78.5%) were “early” stage (Path T1-T2, N<sup>0</sup>). Five year disease-free survival has been 100% for the 29 cases with this length of follow-up. By contrast, for the 40 women (unselected for family history) diagnosed under age 50, who had never been enrolled in a screening programme, only 55% presented at a similarly early stage and five year disease-free survival was 82.5%. For the 37 affected relatives of our index cases who had never had access to regular screening, 11 had died from breast cancer within 5 years of diagnosis, 6 more within ten years and only 11 were known to be alive 5 or more years from diagnosis (Table 1b).

Table 2 records resource use, with unit and cumulative costs, calculated for “typical” pre-menopausal women diagnosed with “early” or “late” stage breast cancer. These calculations take account of the different proportions of “early” and “late” breast cancers expected to be “cured” by primary treatment and hence the varying requirement for “second line” drugs, palliative care and other components of management for advanced breast cancer. They demonstrate that the mean cost for an “early” cancer is £17456, and for a

“late” cancer £45328, a difference of £27872 per patient. Within the “early stage” category, 15% are assumed to be DCIS since detection at this “pre-cancerous” stage will prevent later development of invasive cancer, which is an important purpose of the screening programme<sup>5</sup>. Inclusion of DCIS cases, however, does not materially affect estimates of benefit from screening in this population since ten year survival for invasive breast cancer in women without BRCA1/2 mutations, diagnosed at stage 1 or 2, exceeds 85%<sup>7</sup>.

Using these cost figures as a base, we applied the finding that surveillance increases the proportion of “early stage” breast cancers diagnosed in young women from 55% to 77% (Table 1, adjusted slightly downwards by reference to the larger European dataset<sup>7</sup>). Thus, for every hundred breast cancers arising in women enrolled in the programme, 22 are “transferred” from the “poor” to the “good” prognosis category hence, in cost terms, from the left to the right hand column of Table 2, with a total saving in direct health care costs of £613184 (22 x £27872).

The Tayside “breast cancer family history” service currently undertakes 1000 screens per year so, from the above figures, the shift to earlier stage at diagnosis of breast cancer would apply to 1.32 women per year (22% of 6 cancers). The saving would then be £36791 (1.32 x £27872), against a cost of around £100,000 (@ £100 per screen). Hence the net annual cost of the Tayside programme is £63209 (£100,000 minus the saving of £36791). Now if each woman shifted from “late” to “early” stage diagnosis improves her prospects of “cure” by 40% (from 30% to 70%) and “cure” adds 25 years of

good quality life (QALYs), the gain is 13.2 QALYs per year ( $25 \times 0.4 \times 1.32$ ) at a cost of £4789 per QALY ( $£63209 \div 13.2$ ).

This ignores the fact that many of these women are in productive employment and/or undertaking important family responsibilities which have an economic value. The true cost is therefore likely to be much lower than £4789.

Our calculations are particularly sensitive to variations in two parameters, namely the rate of detection of breast cancers in a surveillance programme and the degree of “shift” to earlier stage at diagnosis. As discussed later, we believe the values we have used are realistic but if more optimistic or pessimistic figures are substituted, as shown in table 3, the cost per QALY can range from £13880 to less than £1000. Even the higher figure is well below the £30,000 attributed to the UK National Institute for Clinical Excellence, justifying the adoption of new drugs or procedures<sup>18</sup>.

### **Discussion:**

The costs associated with treatment of breast cancer are not fixed either in time or place. As new drugs emerge, they tend to be increasingly expensive and the indications for their use become ever more circumscribed so that today’s conclusions may be rapidly superseded. Practices and prices vary from country to country so the figures we have calculated for the UK may not apply precisely elsewhere. Nevertheless, the costs presented in Table 2 are in line with those quoted recently for a US health care organisation<sup>19</sup> and with an

earlier US-based study<sup>20</sup>, both of which confirm in particular the extremely high cost of palliative care in the terminal phase of the illness.

We have assumed an incidence of 6 breast cancers per year per thousand women in a “family history” surveillance programme, marginally higher than the figure we actually observed but substantially lower than reported elsewhere<sup>12,21,22</sup>. In the early years of this study, criteria for enrolment in the programme were less strictly applied than currently. We and others have found that investment in checking, extending and validating reported family histories substantially alters the distribution of assessed risk and allows better targeting of screening<sup>8,22,23</sup>. Applying that principle, as we have done since the late 1990’s, should increase the cancer incidence rate among those enrolled in surveillance.

The poor prognosis for breast cancer among young women (unscreened and unselected for family history) is well recognised<sup>25-27</sup> and there is now substantial evidence that pre-menopausal women with a family history of breast cancer, enrolled in an annual screening programme, can expect a much better outcome<sup>7,28</sup>. Our figures of 75% of breast cancers in such women being screen-detected and 77% as small node-negative tumours are conservative in comparison with recently published experience from one large clinic<sup>14</sup>. Five-year disease-free survival is a weak surrogate for long-term “cure” and it can be argued that, through “lead-time bias”, this measure exaggerates the benefits of screening. Nevertheless, pathological stage, particularly nodal status, is strongly correlated with long-term outcome as well as with extent and cost of primary treatment<sup>1</sup>. The marked difference, which

we and others<sup>12</sup> have confirmed, between screened and unscreened cohorts of young women in this respect is therefore a powerful argument in favour of surveillance.

It remains to be demonstrated how much of the “gain” is attributable to the screening programme. Breast cancers in women with a family history of the disease tend to be of lower grade and to have a better predicted prognosis than sporadic tumours<sup>29</sup>. Follow-up of relevant cohorts have generated conflicting findings<sup>30,31</sup>. The largest and most recent report found, in the absence of special surveillance, no survival advantage for women from “low or moderate” risk families compared to age-matched patients from the general population<sup>32</sup>. There are also data supporting the view that screening of women under 50 (irrespective of family history) can achieve a stage-shift in breast cancers at diagnosis<sup>33</sup>. Our analysis of the outcomes for unscreened affected young relatives of our cohort (with comparable familial risk) shows that screening has a large beneficial effect. Of course the comparison is far from ideal; some data on the relatives are missing; 23 of them were diagnosed and treated more than 20 years ago, when management and outcomes were generally less satisfactory than to-day; there might be a greater incentive for women whose relatives had died from breast cancer to seek advice about familial risk compared to those whose relatives had survived; lead time bias could generate an apparent survival gain of up to two years without actually changing the outcome. Nevertheless, taking all of these caveats into account, there is a striking disparity ( $P < 0.025$ ) between the 10 year survival of >85% recorded in the European multi-centre cohort for

mutation-negative women enrolled in annual “family history” surveillance programmes<sup>7</sup> and the corresponding figure for our subgroup of unscreened relatives (54%, at best, if all 9 patients with incomplete follow-up information are assumed to remain disease-free).

Carriers of germ-line BRCA1 mutations appear to represent a distinct subgroup that does not benefit from regular screening as currently practised<sup>7,28</sup>. Although introduction of MRI scanning may change this picture, evidence of survival benefit is awaited. Despite detection of their cancers at an apparently early stage (small, node-negative primaries) recurrence rate is very high. **Chemotherapy regimes designed specifically for BRCA1-associated breast cancer (using, for example, platinum-containing agents or PARP inhibitors) show promise and may alter prognosis substantially but trials are still in their early stages. Their results must be taken into account in due course** but, for the present, these cases should all be counted in the left hand column of Table 2. Note that this does not apply to BRCA2 mutation-carriers who have a good outcome if screened regularly<sup>7</sup>. Only some 10% of the Tayside “breast cancer family” clinic patients carry BRCA mutations, with BRCA1 slightly outnumbering BRCA2 carriers. Five of the 46 observed breast cancers in the screened cohort were known (or later found) to be positive for BRCA1 mutations (and two for BRCA2). Placing all of these 5 in the “late stage” category or removing them from the calculations has only minor effects on the figures presented in tables 2 and 3. However prophylactic surgery (bilateral salpingo-oophorectomy plus bilateral total mastectomy) are not only better options at present for women with known BRCA1 mutations but are

also cost effective, given that the total cost of this surgery is around £11,000 while the “average” cost of management after a breast cancer has been diagnosed is £44728 (from Table 2). Recent data from Norway confirm the very low cost per life year gained when prophylactic surgery is adopted by young carriers of BRCA1 mutations<sup>34</sup>. Women carrying BRCA2 mutations are also advised to consider prophylactic salpingo-oophorectomy with a cost of less than £3000.

Psychological “costs” should not be underestimated. Work in this area suggests that, with support, prophylactic surgery is acceptable to many women at high risk<sup>35,36</sup> but detailed discussion is beyond the scope of this report.

The psychological price of annual screening, with attendant reminders of breast cancer risk and the anxiety that accompanies the wait for results, applies to all women enrolled in a “family history” surveillance programme. It is difficult to quantify but recent reviews conclude that the impact on general anxiety or cancer-specific worry is broadly neutral<sup>37,38</sup> and it is clear that women aware of their possible familial risk of breast cancer strongly favour access to regular mammography, regarding it as a comfort rather than a source of anxiety<sup>39,40</sup>.

Previous attempts to calculate the costs and benefits of management options for women at increased genetic risk of breast cancer have been hampered by paucity of objective data. The pioneering 1999 report<sup>41</sup> of Heimdal and

colleagues from Norway used standard health insurance charges to measure costs of screening and assumed a 75% “cure” rate for women who developed breast cancers while in a surveillance programme – not very different from what has subsequently been observed. However they estimated that early diagnosis resulted in 30 added years of life (rather than 25) and, for simplicity, attributed all of this gain to screening. This resulted in a lower cost per life year gained than we have calculated but there is no fundamental conflict between our datasets.

Two Canadian studies undertaken some ten years ago, and an even earlier UK survey, confirm that costs of management of advanced breast cancer are much higher than for early stage disease but all their figures are considerably lower than reported here, reflecting mainly the subsequent introduction of expensive new agents<sup>42-44</sup>.

Griffith and colleagues<sup>45</sup> undertook a detailed analysis of costs for NHS (UK) cancer genetics services and arrived at figures for QALYs gained through surveillance or prophylactic surgery that, at first sight, appear rather low. However when our own calculations are re-expressed in equivalent terms, the two datasets are consistent. Our estimate of 13.2 QALYs gained per year (1000 screens) reduces to 0.013 QALYs per screen and if each woman in the surveillance program is screened annually for fifteen years, she can expect to gain only 0.19 QALYs. However all of the gain is concentrated in the minority of women (around 9%) in the program who actually develop breast cancer



during the period of surveillance. Griffith and colleagues did not attempt to estimate the cost savings achieved through surveillance programmes.

Other published analyses<sup>19,46,47</sup> have concentrated on carriers of BRCA1 and BRCA2 mutations and, while the advantages of prophylactic surgery (particularly salpingo-oophorectomy) have been emphasised, the important **finding** that regular surveillance has different efficacy for BRCA1 compared to BRCA2 mutation-carriers has not been recognised.

In conclusion, while financial considerations are not of prime concern in this area of health care<sup>48</sup>, they must be recognised when decisions are made about commissioning new services or evaluating existing ones<sup>48</sup>. We believe our detailed, evidence-based evaluation a surveillance programme for women with a family history of breast cancer makes the case for continuing to support this approach.

**Table 1.**

**Characteristics of breast cancers in three cohorts of young women.**

**a)**

	<b>“Surveillance” Group</b>	<b>Unscreened (population)Group</b>
<b>Number in group</b>	<b>46 (42 patients)</b>	<b>40 (40 patients)</b>
<b>No. (%) screen-detected</b>	<b>34 (74)</b>	<b>0</b>
<b>No. (%) “Early stage” (T1/2 N<sup>0</sup>)</b>	<b>36 (78.5)</b>	<b>22 (55)</b>
<b>% Disease-free at 5 yrs</b>	<b>100</b>	<b>Node Negative 92 Node positive 72</b>

**b)**

	<b>Relatives of “surveillance” group</b>
<b>Number in group</b>	<b>37</b>
<b>Mean age (Range)</b>	<b>45 yrs (28-54)</b>
<b>Number (%) alive 5yrs from diagnosis</b>	<b>25 (68)</b>
<b>Number (%) alive 10 yrs from diagnosis</b>	<b>11* (29.7)</b>
<b>Number (%) with incomplete information</b>	<b>9** (24.3)</b>
<p><b>* At least 3 died later from breast cancer.</b>  <b>** 3 with &lt;10 yrs follow-up, 6 no information.</b></p>	

**Table 2.**

**Unit costs for management of breast cancer in NHS and distribution of costs according to stage at diagnosis.**

Component of management and Unit cost	Late stage (T3/4 N+)		Early stage (T1/2 N-)	
	%*	Cost**	%*	Cost**
Initial inpt. stay (5 nights @ £449/nt)	85	£1908	100	£2245
WLE + Ax Surgery, £1673	15	£251	60	£1004
Mx + Ax surgery, £2421	70	£1695	0	£0
Mx + Ax surgery + reconstr, £4513	0	£0	40	£1805
Anthracyclines X 6, £1836	50	£918	60	£1102
FEC x 6, £3155	50	£1577	0	£0
Taxanes, £9160	70	£6412	15	£1374
Herceptin (2 yrs), £44,000	25	£11,000	5	£2200
Bisphosphonates (2 yrs), £4000	50	£2000	10	£400
Tamoxifen (5 yrs), £43	50	£21	50	£21
Radiotherapy (Standard), £1500	100	£1500	60	£900
Palliative radiotherapy, (£400)	70	£280	15	£60
Palliative care in last year of life (includes 15 nights in-patient stay @ £846), £25,380	70	£17766	25	£6435
<b>TOTAL COST</b>		<b>£45328</b>		<b>£17456</b>

\* Percentage of patients in this category requiring this component

\*\*Cost for "typical" patient in this category – i.e. unit cost x % requiring it.

WLE = wide local excision; Ax. surgery = axillary surgery; MX = total mastectomy reconstr = breast reconstruction; FEC = chemotherapy regime using 5-fluorouracil, epirubicin and cyclophosphamide)

**Table 3**

**Effects of changing sensitive parameters (numbers of breast cancers detected per year and percentage of patients who benefit from “stage shift” of their cancer) on cost-effectiveness of surveillance programmes.**

<b>No.Breast Cancers diagnosed/yr</b>	<b>% shift to “curable” stage</b>	<b>No. Ca Br Patients benefitting/yr</b>	<b>QALYs gained*</b>	<b>Annual saving £**</b>	<b>Annual net cost £***</b>	<b>Cost per QALY £</b>
6	22	1.32	13.2	36791	63209	4789
4	22	0.88	8.8	24527	75473	8576
9	22	1.98	19.8	55187	44813	2263
6	15	0.9	9	25084	74916	8324
6	30	1.8	18	50170	49830	2768
4	15	0.6	6	16723	83277	13880
4	30	1.2	12	33446	66554	5546
9	15	1.35	13.5	37627	62373	4620
9	30	2.7	27	75254	24746	916

\*Assumes 10 QALYs per additional patient detected at a “curable”stage.

\*\* Assumes saving of £27872 per additional patient detected at “curable” stage (from Table 2).

\*\*\* Assumes fixed annual screening cost of £100,000 (1000 women screened)

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