EVALUATION OF MAMMOGRAPHIC SURVEILLANCE SERVICES IN WOMEN UNDER 50 WITH A FAMILY HISTORY OF BREAST CANCER

Background, design and protocol of study

Based on an original idea by Howard Cuckle.

Aims

1. To estimate the difference in breast cancer mortality in women under the age of 50 with a significant family history of breast cancer having regular mammography compared to those not being screened.
2. To estimate the cost-effectiveness of regular mammography in this group of women, compared to no screening.

Summary

The identification of two highly penetrative breast cancer susceptibility genes attracted intense media interest. Unrealistic expectations of genetic testing and understanding about the relevance of family history have raised public and professional anxiety. Many women presenting with a family history of breast cancer under the age of 50 are offered mammograms as preliminary retrospective data suggest it is possible to identify impalpable breast cancer in this group with regular mammography. The effectiveness of this service, however, has not been formally evaluated.

We propose to perform such an evaluation in a cohort of 6,000 women under the age of 50 with a significant family history of breast cancer, given regular mammographic surveillance over five years. Comparison of surgical and pathological data with completed and on-going population screening trials using analysis techniques of varying complexity will be performed to obtain an accurate estimate of breast cancer mortality reduction.

The change in health service resource use attributable to mammography will be compared with no screening and costed. Incremental cost effectiveness ratios of implementing the standardised mammography strategy compared with no screening will be presented in terms of the additional cost per cancer detected, per life saved and per life year saved.

Background

In the past five years, the identification of two breast and ovarian cancer susceptibility genes – BRCA1 and BRCA2 – has received a lot of publicity. Public and professional expectations of the availability and utility of genetic testing have been raised and the importance of a family history of breast cancer overemphasised. This has resulted in an increase in the number of women presenting to their general practitioner because they are worried about a family history of breast cancer, many of whom are then referred on for specialist advice. However, the most appropriate way to manage these women is not known.

Familial breast cancer risk

All women with a family history of breast cancer are at increased risk of breast cancer themselves. However the extent of that risk will vary according to the nature of the family history, specifically which relative was affected, their age at diagnosis, the number of relatives affected, as well as the age of the woman concerned. The relative risks associated with different family histories have been summarised in a recent systematic review and meta-analysis.[1] The relative risks associated with various family history categories are: any relative, RR = 1.9; any first degree relative, RR = 2.1; mother, RR = 2.0; sister, RR = 2.3; daughter,

RR = 1.8; mother and sister, RR = 3.6; a second degree relative, RR = 1.5. Risks are increased in subjects under the age of 50 and when the relative had been diagnosed before the age of 50. For example the relative risk to a woman under the age of 50 who has a first degree relative affected before the age of 50 is 3.3.

The risk categories described in most studies are however simple, being usually based on single factors. The risks associated with more complex histories are difficult to establish. For example, it is difficult to estimate with any precision the risk of breast cancer in a 40 year old woman with three sisters, whose mother and oldest sister developed breast cancer at the age of 65 and 51 years respectively.

Management of familial and genetic risk

Although a high proportion of large breast cancer families are due to the inheritance of dominant predisposing genes, the number of such families is small, and there are well established guidelines for the management of unaffected women in these families.[2] In addition, the cost implications of implementing the guideline recommendations are limited.

Of greater concern are those women with a moderate family history, who are unlikely to inherit a mutation in a predisposing gene, but who are at moderately increased risk of breast cancer. Little evidence is available to inform risk management in these women.

There are several potential methods for primary prevention – i.e. reducing the likelihood of developing breast cancer – including chemoprevention, prophylactic mastectomy and lifestyle modification. Possible methods for early detection (secondary prevention) include breast self-examination, clinical breast examination and regular mammography.

Good evidence for the effectiveness of breast self-examination is lacking. The results of observational studies have been conflicting,[3–6] and preliminary results from two randomised controlled trials failed to show benefit.[7,8] Approximately 10% of breast cancers may be detected by clinical examination alone.

The mainstay of early detection of breast cancer is regular screening of the breasts by mammography. Before considering the merits of mammography in those at high risk, the arguments for and against mammographic screening in women of average (or population) risk need to be rehearsed and interpreted with respect to women at increased risk.

The UK National Breast Screening Programme offers three-yearly mammography to women between the ages of 50 and 64. It is planned to extend this to 50–69 by 2004. The effectiveness of mammography for women aged 50–69 of general population risk has been confirmed by several randomised controlled trials. Meta-analyses of these trials have shown that mammography will produce a relative reduction in breast cancer mortality of around 30% in these women.[9] The absolute reduction in risk is however small and it has been argued that the high financial costs of a screening programme outweigh the marginal clinical benefit.[10,11] The effectiveness of mammographic screening in younger women remains controversial. A US National Cancer Institute workshop concluded that there was no proof of benefit for women under the age of 50,[12] though evidence of benefit in women aged 40–49 is mounting[13,24] and some groups, including the American Cancer Society, recommend screening for women aged 40 to 49 years. Even if the relative risk reduction were the same as in older women, the absolute benefit would be considerably reduced because breast cancer is less common in this age group.

The potential harm caused by mammographic screening includes the false reassurance of women with a false negative mammogram, the adverse effects of unnecessary investigation of false positives and a potential increased cancer risk associated with early and repeated radiation exposure.[14]

Perhaps the most serious concern is the generation of false positive results. About 5% of women screened will have a mammographic abnormality, of whom only 10–20% will subsequently be found to have

cancer.[15] A positive or suspicious mammogram inevitably leads to further studies or interventions including fine needle aspiration, core biopsy or open biopsy, all of which have an associated morbidity. Considerable anxiety can be generated by false positive results.[16,17]

The issues discussed above relate to women of population risk, but the benefit harm ratio may be quite different in women at increased risk because of family history. Various authors have argued that because women with a family history are at greater risk it is likely that the absolute benefit will be greater.[2,10,18,19] This is likely to be true if the performance of the screening test is the same in high risk and average risk women. There is, in addition, the possibility of greater harm from mammography in some groups. For example, some genetic alterations may increase susceptibility to ionising radiation, though many experts believe the benefit of early detection will outweigh the risk.[2] It has also been assumed that because the prevalence of cancer will be higher in a high risk group, the problem of false positives will be lessened, but no research data are available to confirm this.

Basic Design

Over the last ten years there has been debate over the method of evaluation of mammographic surveillance in women at moderate familial risk. Despite repeated calls for a randomised study, the majority opinion in those who manage women with a family history of breast cancer is that a randomised study is not feasible. However a recent survey of BASO breast units indicated that 96 of 100 responding units offered regular mammography to women with a family history, although only 84 had written inclusion criteria.[20] Extrapolating anecdotal evidence from several units to the whole population gives an estimate of 30,000 mammograms being performed annually within the symptomatic breast service in the United Kingdom in women under 50. In this area there is a high volume of ongoing activity without adequate evaluation.

In our proposed evaluation, we plan to gather complete family history, screening, intervention and pathological data on a cohort of women between 40 and 49, and compare screening performance with ongoing and completed randomised studies.

The basic design is to follow up for five years 6,000 women offered annual mammography. It is possible that some centres may experience slippage of the interscreening interval, as this has been observed in the NHS Breast Screening Programme. To remain eligible for inclusion, centres must not allow slippage to an average interscreening interval of more than 18 months.

All breast cancers diagnosed in this period of observation will be followed up for breast cancer death, but our primary endpoint will be the tumour incidence rates by size, node status and histological grade of the tumours diagnosed. Rates by these factors, which are well established as predictors of breast cancer death, will be compared with those expected if screening had not taken place. These will be calculated from a contemporaneous comparison group (controls in the UK age trial) and a historical comparison group. Such comparisons will need careful interpretation and will be adjusted for the difference in underlying risk of breast cancer between our cohort and the comparison groups.

Eligibility Criteria

Data will be collected on women between the age of 40 and 49 offered annual mammography (recruited at ages 40–44 to ensure that each subject contributes five years of observation below age 50), who fulfil at least one of the following criteria:[21,22]

Inclusion criteria

- 1 first degree female – breast cancer at age 40 or under
- 1 first degree female – bilateral breast cancer first cancer diagnosed at age 50 or under
- 2 first or 1 first and 1 second degree female – both with breast cancer at age 60 or under (same side of family)
- 1 first or second degree female – breast and ovarian cancer first cancer diagnosed at age 60 or under

- 3 first or second degree female – breast or ovarian cancer at any age (same side of family)
- 1 first degree male – breast cancer at any age
- Paternal history of a minimum of 2 second degree relatives (NB. father's first degree relatives) with breast cancer at or less than age 50, or one with breast cancer at or less than age 50 and an ovarian cancer (any age), or paternal uncle/grandfather with breast cancer <50 years.

A first degree female relative is mother/sister/daughter
A second degree female relative is granddaughter/grandmother/aunt/niece
A paternal relative is on father's side

Exclusion criteria

- Inability to give written informed consent.
- Pregnant women.
- Women below the age of 40.
- Women with proven breast cancer or ductal carcinoma in situ.
- Women who have had bilateral prophylactic mastectomy.
- Women in whom a BRCA1 or BRCA2 mutation is present in the family, but who have been tested negative for the mutation.

Surveillance Strategy

Agreement on an appropriate regime depends on balancing two opposing considerations; a screening interval which is likely to be effective in view of the disease's natural history, and a screening frequency considered radiologically safe. There is considerable evidence that the disease has a shorter preclinical detectable period in women aged under 50,[23] and that mammographic parenchymal patterns in premenopausal women make for poorer sensitivity[24] of mammography in younger women. This suggests that screening every two years or more cannot be expected to make a substantial impact.[1,3,23,26] Two views at first screen will be necessary, and in this age group two views at subsequent screen are desirable. We therefore plan to offer annual two-view (craniocaudal and mediolateral oblique) mammography.

Study Centres And Units

All units offering regular mammography to women with a family history of breast cancer in the United Kingdom subject to certain quality control standards as outlined in this protocol will be invited to contribute data. The units forming the familial breast cancer group will form the core.

Collaborating units are expected to:

(a) operate a breast cancer unit in line with the recommendations of the British Breast Group and the BASO guidelines for surgeons in the treatment of symptomatic breast disease[27]
(b) have experience in mammography in symptomatic women under the age of 50
(c) either participate in the NHS Breast Screening Programme or offer mammographic services at a level consistent with the quality standards set out by the NHS BSP
(d) have a clearly defined referral line for high risk women to a regional clinical genetics service
(e) have at least one member of the multidisciplinary team trained in pedigree construction and interpretation, and risk analysis.

Power Calculation

Assuming it is possible to use the controls in the UK age trial as a comparison group, an important comparison would be the incidence of node positive tumours in our cohort with that expected from the comparison group, taking into account the different incidences in the two groups. From the Swedish Two-County Study controls, we would expect an unscreened tumour series in the age group 40–49 to be node positive in 42% of cases.[28] In the UK age trial control group, with seven years of cancer incidence in 106,000 women, we conservatively expect around 742 cancers, and therefore 311 (42%) node positive tumours.

Results from the Two-County Study suggest a screening sensitivity of 83% and a mean sojourn time (average duration of the preclinical screen-detectable period) of 2.44 years in women aged 40–49.[23] This suggests that with a one-year interval there would be 77% screen-detected, of which 11% would be node positive. We assume that the interval cancers would have the same 42% node positive as an unscreened group, giving an overall 18% node positive.

A study size of 6,000 will confer approximately 90% power to attain significance of the comparison of incidence rates of node positives, allowing for a 5% increase in standard deviation as a result of adjustment for different underlying risk in the two populations. Five years incidence in 6,000 women at around 4 per 1000 per year (due to high familial risk) would yield 120 cancers.

Data Capture

The evaluation requires three types of data. First, basic attributes recorded at baseline for all subjects. This includes family history, demographic and risk-factor data. The second is the screening information for each screening episode for each subject. The third is the cancer data collected for those who develop breast cancer during the five-year study period. Subjects will be flagged with ONS, but in view of the potential delays in cancer registration, centres will be asked to notify the co-ordinator of all breast cancers among recruits as they arise.

The details of the data required are given in the tables below. It is understood that not all the data items specified (notably updates of menopausal factors at each screen) will be available for all subjects, but there should at least be willingness to aim at recording these.

It is also planned to develop a final 'exit' questionnaire for all subjects at the end of their five years in the study. This will be the subject of a separate application for resources and will undergo ethical scrutiny before implementation.

Data will be accepted and processed by the audit co-ordinator in whatever format is most convenient for each centre. For subjects who have been screened before recruitment, screeening histories, again in whatever form is most convenient for each centre, would be welcome. For the most part, it is anticipated that centres will supply baseline and screening data in digital rather than paper format. In terms of the cancers diagnosed, some centres may prefer to supply cancer details in confidence on paper, as the number of cancers per centre is likely to be small. Some centres newly instigating the surveillance programme for purposes of this evaluation or who have previously not kept computerised records may need extra assistance in terms of data retrieval. In such cases, compact database can be supplied by the audit co-ordinator. This will be a simple database set up solely for the purpose of gathering the data listed below, and will not have complex relational links or provide automated prompts for call, recall etc.

1. Baseline data not pertaining to family history recorded at recruitment	
Data item	Content
Name	Full name
Address	Address, excluding postcode
Postcode	Postcode of residence
NHS number	NHS number – for flagging and a double check on identification
Centre	Screening centre
Study number	Identification number. This together with centre uniquely specifies each subject
Date of birth	__/__/____
Date of recruitment	__/__/____ Date of recording these data
BRCA1 identified?	BRCA1 mutation identified in family?
BRCA2 identified?	BRCA2 mutation identified in family?
Personal search	If yes to either of above, has subject been tested for relevant mutation?
Personal BRCA status	If yes, to above, was subject positive for relevant mutation?
Menopausal status	Pre- (regular periods), peri- (7–12 months since last period) or post (>12 months since last period)
Age at menopause (years)	0 if pre- or perimenopausal
Age at hysterectomy (years)	0 if no hysterectomy
HRT use	Never/previously/currently
Parity	Number of pregnancies to at least 30 weeks
Age at first pregnancy	Age at first pregnancy of at least 30 weeks duration
Age at menarche	Age in years at first period
Previous mammography	Screening mammography prior to recruitment (yes/no)?
Time since last mammo	If so, how long since last mammogram (months)?
Breast biopsy	Previous benign breast biopsy? No, ADH, LCIS, Benign NOS
Previous breast surgery?	Yes/no

1a. Family history of breast and ovarian cancer taken at baseline – list only relatives with a diagnosis						
Relative (first or second degree only)	Maternal/ paternal	Breast cancer (Y/N)	Bilateral (Y/N)	If Y, age first diagnosed	Ovarian cancer (Y/N)	If Y, age first diagnosed
How many sisters has the participant?						
How many sisters has the participant's mother?						
How many sisters has the participant's father?						
Has the family history data been verified from medical records?					Yes/no	

2. Screening and assessment data recorded for each screening episode	
Data item	Content
Name	Full name
Address	Address, excluding postcode
Postcode	Postcode of residence
NHS number	NHS number
Centre	Screening centre
Study number	Identification number. This together with centre uniquely specifies each subject
Date of birth	__/__/____
Menopausal status	As in 1
Age at menopause	As in 1
Age at hysterectomy	As in 1
HRT use	As in 1
Date of mammogram	__/__/____
Screening round	Prevalence, second, third…
Suspicion left breast	Five-point score
Suspicion right breast	Five-point score
Mammographic pattern	Fatty/mixed/dense
Recall for assessment	Yes/No
Percutaneous biopsy	Yes/No
Physical examination	Not done/done after mammography result/done before mammography result/ mammography and physical examination results each assessed with knowledge of the other
Palpable lump	Yes/no
Other tests	Specify-use text field for name of test, text field for result. Up to 4 tests
Surgery/open biopsy	Yes/No
Final diagnosis	Breast cancer, BBD, normal- if cancer, form below required

3. Cancer data- all cancers, whether detected by screening or clinically	
Data item	Content
Name	Full name
Address	Address, excluding postcode
Postcode	Postcode of residence
NHS number	NHS number
Centre	Screening centre
Study number	Identification number. This together with centre uniquely specifies each subject
Date of birth	__/__/____
Date of diagnosis	__/__/____ Date of surgery if performed, date of most definitive test otherwise
Mode of detection	Prevalence screen, incidence screen, interval cancer, clinically diagnosed after non-attendance at last scheduled screen
Date of mammogram	__/__/____ Date of mammogram prompting diagnosis if screen detected
Date of last scheduled mammogram	__/__/____ Date of last scheduled mammogram if clinically detected
Date of last actual mammogram	__/__/____ Date of last actual mammogram if clinically detected
Tumour palpable	Is tumour palpable on physical examination?
Symptoms	Does the subject report any symptoms (yes/no)
Invasive status	Invasive/In situ
Neoadjuvant chemotherapy	Preoperative chemotherapy (yes/no)
Tumour size	Pathological size of invasive component (mm)
Lymph nodes examined	Number of lymph nodes examined pathologically
Lymph nodes positive	Number of pathologically examined nodes with tumour
Axillary surgery	None, sentinel only, sampling, clearance (either immediately or after positive sentinel finding)
Histological grade	1, 2 or 3
Histological type	DCIS, invasive ductal, lobular, medullary, tubular, mucinous…
Ultrasound size	Ultrasonically assessed size, if pathology not available (mm)
Mammographic size	Mammographic size if pathology and ultrasound size both unavailable (mm)
Surgery	None, local excision, mastectomy.
Radiotherapy	Yes/no
Hormone therapy	Yes/no
Chemotherapy	Yes/no
Oestrogen receptor status	Positive/negative
Progesterone receptor status	Positive/negative

Data Analysis

The major objective of the analysis will be to estimate the likelihood of death from breast cancer, on the basis of the features of the tumours diagnosed in our cohort, and compare this to that which would be expected if the mammographic surveillance had not taken place. To do this we take two comparison groups, one approximately contemporaneous and of comparable age, the UK Age Trial controls. The second is a historical group breast cancer cases with a family history of breast cancer, from France. The first group has the advantage that it is more comparable in temporal and demographic terms, but it involves adjustment for the fact that it does not have the same familial risk status as our cohort. The second does have at least a similar familial risk status, but is confounded by temporal, geographic and other factors.

Our cohort will consist of 6,000 women aged 40–44 at recruitment, with a significant family history of breast cancer, offered annual mammography and followed up for 5 years. The principal comparison group will be the control group of the UK Breast Screening Age Trial, which comprises 106,000 women aged 40–41 at recruitment, not offered screening, and followed up for seven years. These women are from the general population, so analysis of the data must be adjusted for the higher incidence in our cohort with a family history, and the potentially different distribution of histological type of breast cancer between the two groups.

The difference in underlying risk status between our study population and the comparison group needs careful evaluation in order to be correctly adjusted for. We therefore need an independent measure of average risk on the basis of family history and other risk factors, impartially applied to both groups. We therefore need to data on the family history and a minimal set of other breast cancer risk factors in our cohort and the comparison groups. It might be considered unethical to raise concerns about risk among the Age Trial controls, since this group is being offered no intervention. We therefore propose to estimate their average risk indirectly, by taking the family history and other risk factor information from a random sample of 3,000 members of the Age Trial Study Group, who are invited to annual mammography. The average risk of the control group can be estimated as that of the study group due to randomisation. The same average risk estimation will be performed on our cohort, so that incidence of advanced tumours and projected mortality from this can be compared with the expected incidence and projected mortality in the absence of screening on the basis of the age trial controls' incidence. The comparison will be adjusted for the difference between the two groups in the underlying average risk of breast cancer.

In addition, we have negotiated the use of a historical comparison group from France of 800 breast cancer patients aged 40–49 with a family history of breast cancer but no prior regular mammography. This will have to be adjusted for differences in stage distribution due to temporal and cultural effects. We shall use both published sources and the Age Trial control group to estimate such trends and adjust the comparisons.

The basic analytic strategy is therefore as follows.

1. Direct indicators-primary outcomes

(a) Projection of anticipated incidence of advanced breast cancer if screening had not been introduced, compared with actual incidence of advanced breast cancer since inception of screening by internal estimation.

(b) Projection of anticipated mortality from breast cancer if screening had not been introduced, compared to projected mortality since inception of screening, again using internal estimation.[30]

(c) Direct comparison with a contemporaneous (the controls from the UK Age Trial) unscreened group of rates of cancer by size, node status and malignancy grade, and comparison of the expected mortality from breast cancer as calculated from the size, node status and malignancy grade. These have been shown to be good predictors both of absolute survival of cases, and of the mortality reduction conferred by screening.[32,33] This will be adjusted for the greater incidence in our familial risk group and for the potentially different distribution of histological type in tumours in women with a family history of breast cancer. Centres will be invited to participate in a pathology review where cancers

which develop in either the family history cohort or the UK Age Trial controls will have their pathology reviewed on a research basis by the same team of pathologists organized by the Cancer Screening Evaluation Unit. In addition, the radiologist applicant will convene a radiology quality review.

2. Indirect indicators- secondary outcomes

(a) Sojourn time, lead time achieved, test sensitivity and program sensitivity.
(b) Estimates of over-diagnosis (if any), by comparison with expected incidence in the absence of screening and by reference to the balance of in situ and invasive cancers diagnosed at screening, by type of screen (prevalence or incidence).

3. Basic description- secondary outcomes

(a) Attendance, assessment, percutaneous biopsy and surgical biopsy rates.
(b) Cancer detection rates by age, size, node status and malignancy grade.
(c) Interval cancer incidence by age and time since last negative screen.
(d) Comparison of these with rates observed in the control and intervention groups of randomised screening trials (adjusted for a different incidence rate in this population).
(e) Cancers arising clinically in those not attending for screening (if available), by age and clinico-pathological attributes.

Economic Analysis

The economic evaluation will estimate the costs associated with the change in health service resource use arising as a result of implementing the standard mammographic surveillance strategy as opposed to no screening. The difference in costs will be compared to the estimated change in cancers detected, lives saved and life years gained. It is anticipated that the surveillance strategy will be more effective but also more costly, in which case incremental cost-effectiveness ratios will be presented in terms of the additional cost per cancer detected, per life saved and per life year gained. The findings will be stratified for low to moderate familial risk group and a moderate to high familial risk group using the criteria described above, under statistical analysis.

Psychosocial Study

Several psychological aspects of regular surveillance of at risk women will be examined by the Primary Care Education Research Group under the directorship of Dr Joan Austoker. These proposals, particularly concentrating on the importance of informed consent and the negative psychological consequences of false positive screening results, are outlined in Dr Austoker's application for five yearly programme funding to the CRC Scientific Committee. They are dealt with in a separate protocol.

Radiology And Pathology Reviews

All centres will be invited to take part in radiology and pathology reviews. In the former, all available mammograms from centres participating in the review up to and including the diagnostic mammogram will be reviewed by a panel of expert screening radiologists. In the latter, slides from all malignancies from centres participating in the review will be re-read by an expert panel of breast pathologists.

Basic Work-Plan For Participating Centres

Starting up

1. Obtain LREC approval (with support from the Audit co-ordinator and members of the management group if necessary).
2. Liaise with audit co-ordinator and local cancer research network to establish procedures and responsibilities for data retrieval and transfer.

Recruitment

1. Potential participants should have a risk assessment, including three-generation family history, performed be appropriately experienced member of staff. Subjects already under management at the

centre are eligible, even if they have already been screened (their first study screen should be the one immediately following recruitment, however).
2. First check that inclusion criteria are satisfied (pages 63–64) and that the potential recruit has none of the exclusion criteria (page 64).
3. If eligible, and subject gives consent, recruit.
4. Record baseline data for tables 1 and 1a (pages 66–67).
5. Regularly transfer baseline data to audit co-ordinator.

Screening

1. Invite each subject to annual mammography for five years (six screens in all). Slippage to more than 18 months between scheduled screens should not occur (if a participant fails to attend a screen, invite her again one year later as per protocol).
2. Record the data in table 2 (page 67) for each screening episode. Some of the data (for example the updated menopausal factors) may not be known but the basic screening details and outcomes must be recorded.
3. Regularly transfer screening data to audit co-ordinator.

Cancers

1. Every effort must be made to identify all breast cancers occurring in women recruited, whether detected at screening or not. Regular checks should be made with local pathology laboratories and treatment centres for breast cancers in recruits but diagnosed outwith the screening (e.g. interval cancer and non-attenders).
2. For each centre record data in table 3 (page 68). Some data may not be available, but as a minimum, relevant dates and basic pathology data (invasive status, size, node status, grade) should be recorded.
3. In view of the likely small numbers of cancers per centre, it may be more convenient to transfer cancer data to the audit co-ordinator as each single case arises.

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