

Study Protocol

Evaluation Of Mammographic Surveillance Services In Women Under 50 With A Family History Of Breast Cancer

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AIMS

- i) 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
- ii) 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 10,000 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-analysis¹. 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 families². 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 conflicting³⁻⁶, 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 women⁹. 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 50¹², 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 exposure¹⁴.

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 cancer¹⁵. 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 risk². 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 criteria²⁰. 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 10,000 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 diagnosed at age 40 or less
- 1 first degree female - bilateral breast cancer first cancer diagnosed at age 50 or less
- 2 first or 1 first and 1 second degree female – both with breast cancer diagnosed at age 60 or less (same side of family) (please do not average the ages).

- 1 first or second degree female - breast and ovarian cancer first cancer diagnosed at age 60 or less
- 3 first or second degree female - breast or ovarian cancer at any age (same side of family) (please do not average the ages).
- 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 diagnosed age 50 or less or breast diagnosed age 50 or less and an ovarian cancer (any age), or paternal uncle/grandfather with breast cancer diagnosed age 50 years or less. (please do not average the ages)

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 50²³, and that mammographic parenchymal patterns in premenopausal women make for poorer sensitivity²⁴ 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 disease²⁷.
- 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 cases²⁸. In the UK age trial control group, with seven years of cancer incidence in 130,000 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 40-49²³. 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.

If we require 90% power to attain significance of the comparison of incidence rates of node positives, and we allow for an increase in standard deviation as a result of adjustment for different underlying risk in the two groups, 30 node positive tumours would be required in our cohort, that is we would need 150 cancers in all. Five years incidence in 10,000 women at around 4 per thousand per year (due to high familial

risk) would yield 200 cancers, which leaves a considerable safety margin for other possible complications or refinements in the analysis.

There will also be internal estimation of the benefit³¹.

DATA CAPTURE

Baseline

For each individual offered screening the following baseline data will be collected by the screening centre:

- a) Name, address, postcode, DOB, NHS number, study number, screening centre
Evaluation will be performed on anonymised data.
- b) Family history information – three-generational pedigree with types and age of cancer diagnosis, whether histological or death certificate confirmation;
- c) Genetic information - whether BRCA1 or 2 mutation search initiated
whether BRCA1 or 2 mutation identified in family;
- d) Menopausal status
- e) Number of children
- f) Age at first childbirth
- g) Age at menarche
- h) History of biopsied benign breast disease

Screening

For each screening episode:

- a) Name, DoB, NHS number, study number of person screened centre
(again, only the screening centre and study number will be supplied to the evaluation team).
- b) Attended after invitation (Y/N)
- c) Date of mammogram
- d) Screening round (first, second ...)
- e) Suspicion score for left breast MLO (1-5), CC (1-5)
- f) Suspicion score for right breast MLO (1-5), CC (1-5)
- g) Mammographic appearance
- h) Recalled for further assessment (Y/N)?
- i) Percutaneous biopsy (Y/N)
- j) Surgery/open biopsy (Y/N)
- k) Other tests, including genetic tests

Cancers

It is important to obtain details on all cancers diagnosed in those recruited to the programme, regardless of whether or not diagnosed as a result of a scheduled screen within the programme.

- a) Name, DoB, NHS number, study number
(again, only the screening centre and study number will be supplied to the evaluation team).
- b) Date of diagnosis (usually date of surgery)
- c) Treatment details
- d) Mode of detection (first screen, subsequent screen, clinically in the interval between screens, clinically after non-attendance at last scheduled screen).
- e) If screen-detected, date of mammograms*
- f) If clinically detected, date of last scheduled mammogram*
- g) If clinically detected, date of last actual mammogram*
- h) Pathology data: size, node status, histological grade, histological type

* if screening data in (2) are supplied correctly, these three items can be omitted, but it would be preferable to supply them as a failsafe measure.

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 10,000 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 10,000 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. The potential of the technique is illustrated in appendix 1.

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 estimation³⁰.
- 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 CRUK 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 CRUK Psychosocial and Education Research 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.

REFERENCES

1. Pharoah PDP, Day NE, Duffy S, Easton DF, Ponder BAJ. Family history and the risk of breast cancer: a systematic review and meta-analysis. *Int J Cancer* 1997;**71**:800-809.
2. Burke W, Daly M, Garber J, Botkin J, Ellis Kahn MJ, Lynch P, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. *JAMA* 1997;**277**:997-1003.
3. Foster RSJ, Lang SP, Costanza MC, Worden JK, Haines CR, Yates JW. Breast self-examination practices and breast cancer stage. *N Engl J Med* 1978;**299**:265-270.
4. Greenwald P, Nasca PC, Lawrence CE. Estimated effect of breast self-examination and routine physician examinations on breast cancer mortality. *N Engl J Med* 1978;**299**:271-273.
5. Newcomb P, Weiss N, Storer B. Breast self-examination in relation to the occurrence of advanced breast cancer. *J Natl Cancer Inst* 1991;**83**:260-265.
6. Holmberg L, Ekblom A, Calle E, et al. Breast cancer mortality in relation to self-reported use of breast self-examination. A cohort study of 450,000 women. *Breast Cancer Res Treat* 1997;**43**:137-140.
7. Thomas DB, Gao DL, Self SG, Allison CJ, Tao Y, Mahloch J, et al. Randomized trial of breast self-examination in Shanghai: methodology and preliminary results. *J Natl Cancer Inst* 1997;**89**(5):355-365.
8. Semiglazov VF, Moiseyenko VM, Manikhas AG, et al. Role of breast self-examination in early detection of breast cancer: Russia/WHO prospective randomized trial in St Petersburg. *Cancer Strategy* 1999;**1**(3):145-151.
9. Kerlikowske K, Grady D, Rubin SM, Sandrock C, Ernster VL. Efficacy of screening mammography: a meta-analysis. *JAMA* 1995;**273**:149-154.
10. Wright CJ, Barber Mueller C. Screening mammography and public health policy: the need for perspective. *Lancet* 1995;**346**:29-32.
11. Jatoi I, Baum M. Screening for breast cancer, time to think - and stop? *Lancet* 1995;**346**:436-437.
12. Fletcher SW, Black W, Harris R, Rimer BK, Shapiro S. Report of the international workshop of screening for breast cancer. *J Natl Cancer Inst* 1993;**85**:1644-1656.
13. Feig SA. Increased benefit from shorter screening mammography intervals for women ages 40-49 years. *Cancer* 1997;**80**:2035-2039.
14. John EM, Kelsey JL. Radiation and other environmental exposures and breast cancer. *Epidemiol Rev* 1993;**15**:157-162.
15. Baines CJ, McFarlane DV, Miller AB. Sensitivity and specificity of first screen mammography in 15 NBSS centers. *J Can Assoc Radiol* 1988;**39**:273-276.
16. Ong G, Austoker J, Brett J. Breast screening: adverse psychological consequences one month after placing women on early recall because of a diagnostic uncertainty. A multicentre study. *J Med Screen* 1997;**4**:158-168.
17. Brett J, Austoker J, Ong G. Do women who undergo further investigation for breast screening suffer adverse psychological consequences? A multi-centre follow-up study comparing different breast screening result groups five months after their last breast screening appointment. *J Public Health Med* 1998;**20**:396-403.
18. Hoskins JF, Stopfer JE, Calzone CA. Assessment and counselling for women with a family history of breast cancer: a guide for clinicians. *JAMA* 1995;**273**:577-585.

19. Vasen HFA. Screening in breast cancer families: is it useful? *Ann Med* 1994;**26**:185-190.
20. Mackay J, Macmillan R, Blamey, R. Personal communication.
21. Eccles DM, Evans DGR, Mackay J, and UK Cancer Family Study Group. Guidelines for a genetic risk based approach to advising women with family history of breast cancer. *J Med Genet* 2000;**37**:203-209.
22. Pharoah PD, Stratton JF and Mackay J. Screening for breast and ovarian cancer: the relevance of family history. *Br Med Bull* 1998;**54**:823-838.
23. Chen HH, Duffy SW, Tabar L, Day NE. Markov chain models for progression of breast cancer Part 1: tumour attributes and the preclinical screen-detectable phase. *Epidemiol Biostat* 1997;**2**:9-23.
24. van Gils CH, Otten JD, Verbeek AL, Hendriks JH. Short communication: breast parenchymal patterns and their changes with age. *Br J Radiol* 1995;**68**(814):1133-1135.
25. Hendrick RE, Smith RA, Rutledge JH 3rd, Smart CR. Benefit of screening mammography in women aged 40-49: a new meta-analysis of randomized controlled trials. *J Natl Cancer Inst Monographs* 1997;(22) 87-92.
26. Swedish Cancer Society and the Swedish National Board of Health and Welfare. Breast-cancer screening with mammography in women aged 40-49 years. *Int J Cancer* 1996;**68**(6):693-9.
27. The BASO Breast Specialty Group. The British Association of Surgical Oncology Guidelines for surgeons in the management of symptomatic breast disease in the UK. *Eur J Surg Oncol* 1998 revision;**24**:464-476.
28. Tabar L, Fagerberg G, Chen HH, Duffy SW, Smart CR, Gad A, et al. Efficacy of breast cancer screening by age. New results from the Swedish Two-County Trial. *Cancer* 1995;**75**(10):2507-17.
29. Launoy G, Duffy SW, Prevost TC, Bouvier V. [Detection of cancer, sensitivity of the test and sensitivity of the screening program]. *Rev Epidemiol Sante Publique* 1998;**46**(5):420-6.
30. Chen HH, Thurfjell E, Duffy SW, Tabar L. Evaluation by Markov chain models of a non-randomised breast cancer screening programme in women aged under 50 years in Sweden. *J Epidemiol Community Health* 1998;**52**(5):329-35.
31. Macmillan RD on behalf of The British Familial Breast Cancer Group. Screening women with a family history of breast cancer. *Eur J Surg Oncol* 2000;**26**:149-152.
32. Balslev I, Axelsson CK, Zedeler K, et al. The Nottingham Prognostic Index applied to 9149 patients from the studies of the Danish Breast Cancer Cooperative Group. *Breast Cancer Res Treatment* 1994;**32**: 281-290.
33. Organizing Committee and Collaborators. Breast cancer screening with mammography in women aged 40-49 years. *Int J Cancer* 1996;**68**: 693-699.

Appendix A

An evaluation of regular mammography in women with a family history of breast cancer

Funded by the NHS Research and Development Programme

CONSENT FORM

I confirm that I have read and understood the information leaflet “ Breast Screening for Women with a Family History of Breast Cancer”

I have received sufficient information and have had the opportunity to have my questions answered

I agree to take part in the above study

Full name -----

Address -----

Postcode -----

Date of Birth -----

Name and Address of General Practitioner

Name of Patient

Date

Signature

Name of Person taking consent

Date

Signature

Please return form to the familial breast cancer clinic

Your contact in the clinic is -----

Appendix B

Breast Screening For Women With A Family History Of Breast Cancer

An evaluation funded by the NHS Research and Development Programme (FH 01)

INFORMATION SHEET

You are being invited to take part in a project to evaluate the effectiveness of mammographic screening in women with a family history of breast cancer. Before you decide to take part in the project, it is important for you to understand why the evaluation is being done and what it will involve. Please take time to think about the following information on breast screening and discuss it with others if you wish. If you require further information on breast screening, or on the evaluation project, please ask us. Take time to decide whether or not you wish to take part.

What's The Purpose Of Screening?

The purpose of breast screening is to detect breast cancer as early as possible by picking up changes to the breast that often cannot be seen or felt. In the UK, around one in every 9 women will develop breast cancer at some point in their life-time. Women with a family history of the disease have a higher risk. Early diagnosis of breast cancer offers the best chance of a successful recovery, however it is not known whether or not breast screening is effective in women under 50 with a family history of breast cancer.

What's The Purpose Of The Evaluation?

The purpose of this evaluation is to look at the effectiveness of providing annual mammographic screening in women under 50 with a family history of breast cancer. The evaluation will involve collecting data from 10,000 women aged 40-44 with a significant family history of breast cancer, who are offered regular mammographic surveillance over 5 years.

How does screening work?

X-ray pictures called mammograms are taken of the breast. Two views of each breast are taken at every screening appointment. Women having a mammogram are asked to undress to the waist, so wearing a separate top rather than a dress may be preferable. The actual X-ray only takes a few minutes and the level of radiation is very low.

Who can have screening?

In the UK women aged between 50 and 64 are routinely invited for breast screening every three years by the National Breast Screening Programme. Work is being carried out to extend the programme to all women up to and including the age of 70. Continued three yearly screening from the age of 64 is available in those areas where the programme has not been extended if requested by the woman and for those over 70 where the programme has been extended.

Why does screening not start until the age of 50?

Research studies have shown that screening significantly reduces deaths from breast cancer in women aged 50-64 who attend for screening. For women under 50 the effectiveness of screening is controversial. Experts in the UK currently believe the disadvantages of screening outweigh the advantages for women in the general population under 50, hence it is not routinely offered.

Why am I being offered screening before I am 50?

For younger women who have an increased risk of developing breast cancer on account of their family history, the collective view of experts in the UK is currently that the benefits of screening are likely to outweigh the harms. However, it is important to realise that, as yet, there is no strong evidence to prove whether or not breast screening in younger women with a family history is effective and will reduce deaths from breast cancer.

Is there anything else I need to know?

For the purposes of this evaluation we need to hold personal information on you to issue regular invitations and to check on the performance of the programme. We take great care to keep your personal details confidential and only share information with people who have a statutory or medical requirement for it, for example your General Practitioner.

We are centralising personal data from everyone involved in this evaluation. The data will be held in a database on behalf of the NHS by Breast Test Wales, the Welsh equivalent of the NHS Breast Screening Programme, which is based in Cardiff. These personal details will remain confidential to Breast Test Wales. Only anonymised details will be released to the research teams involved in the evaluation.

If this evaluation provides evidence to the NHS that regular mammography is not beneficial then this will be formally reported to the National Screening Committee who reserve the right to advise that regular mammography will not be available to women under 50.

How reliable is screening?

Mammography is currently the best way of detecting breast cancer early. However, like other screening tests it is not perfect:

- Some cancers are very difficult to see on the X-ray
- Some cancers, even though they are there, cannot be seen on the X-ray at all
- The person reading the X-ray may miss the cancer (this will happen occasionally, no matter how experienced the reader is)

Does screening hurt?

Each breast needs to be held firmly in position and compressed as the X-ray is taken, in order to obtain a clear picture. Some women describe a mammogram as uncomfortable, while others describe it as painful. Any discomfort only lasts for a brief period of time.

At what age does screening start for women with a family history?

In women with a family history screening usually starts at age 40, although in some women with a strong family history, regular mammography will be offered from a younger age.

How often would I have a mammogram?

Screening is currently recommended every year for younger women with a family history. This is because breast cancer in younger women may appear more quickly than in older women.

How would I get my results?

When you have had the mammogram, a member of the screening team will tell you how and approximately when you will get your result.

What does it mean if I am called back for more tests?

Some women (about 1 in every 20 who goes for screening) are asked to come back for a further appointment because the appearance of the X-ray is not completely normal. It may be necessary to perform further mammographic views, or other investigations such as ultrasound or a biopsy may be needed. In the majority of cases, these further tests will show there is nothing to worry about.

What should I do if I notice any breast symptoms?

As breast cancer can occur between screens it is important you see your doctor immediately if you notice any unusual changes in your breasts, even if you have just had a normal screen or are due for a screen in a month or so.

So should I go for screening or not?

To help you decide whether or not **you** want to attend for breast screening, the main advantages and disadvantages of regular mammography in women under 50 with a family history of breast cancer are outlined below:

- Screening is currently believed to provide the best chance of detecting cancers at an early stage when treatment can offer the best chance of a successful recovery. However there is no good evidence that this is the case.

- Around seventy per cent of the cancers found at screening are still small enough to be removed from the breast. This means that the whole breast does not have to be removed.
- Screening will **not** detect all breast cancers, so some cancers will be missed at screening and some women may be falsely reassured.
- Screening will **not** prevent breast cancer from developing.
- Approximately one in every 20 women who go for screening will be called back for further investigations. Most of the women who have further tests will turn out not to have cancer. However, women who are called back often find this a very anxious time.
- Each mammogram gives a small dose of radiation. The expert view is that the dose is so small it is unlikely to cause any harm. However, it is theoretically possible that regular mammography in younger women could actually promote the development of a breast cancer.
- Many women find mammography uncomfortable or painful.

What if I may be/am pregnant?

The radiation dose to the abdomen during mammography is extremely low, so you could still be screened. However, you may prefer to wait until you know you are not pregnant.

What do I do now?

If you would like to be part of the evaluation including regular mammography, please sign the consent form and return it to the person named on the form

What if I do not want regular mammography?

You do not have to choose screening now. You will be invited automatically for screening after the age of 50 by the NHS Breast Screening Programme. If you change your mind before then and decide that you do wish to have screening please contact the person named on the consent form.

How will the evaluation affect me?

Your treatment will not be affected in any way if you participate in the evaluation. You will receive exactly the same mammographic screening if you participate in the evaluation as you would outside the evaluation. You may withdraw from the evaluation at any time if you wish, without this affecting your treatment. Your mammograms and the results of any further tests, which you may have, may be reviewed by a panel of national experts.

Appendix C

Breast Screening for Women with a Family History of Breast Cancer

An evaluation funded by the NHS Research and Development Programme (FH01)

INFORMATION for PRIMARY CARE

The importance of breast screening

In the UK, 1 in 9 women develops breast cancer at some time in her life. Screening by mammography finds early changes that often cannot be seen or felt. Early diagnosis offers the best chance of full recovery. Most cases of breast cancer detected early are successfully treated with the modern treatments now available. Screening does not prevent cancer and like most tests is not 100% accurate. This means that some cancers may not be detected. It also means that some women may receive unnecessary investigations and/or procedures.

Who is offered screening?

The NHS Breast Screening Programme invites all women in the UK between the ages of 50 and 64 for screening mammography every three years. Breast cancer is more common in women over 50 than in younger women (approximately 4 out of 5 women diagnosed with breast cancer are over 50) and screening with mammography has been proven to be effective in this age group. Invitations will continue to be offered up to the age of 70.

Women with a family history of breast cancer

Women with a family history of breast cancer may benefit from starting regular mammography earlier than 50. In order to investigate whether this practice is beneficial or not the NHS Research and Development Programme have funded a large prospective evaluation of regular mammography in women under 50 with a family history of breast cancer.

Eligible women will be offered annual mammography in their local breast care clinic from the age of 40, until they become eligible for the National Programme. Results will be sent by post within 3 weeks to each woman, and a copy sent to their primary care team. If the mammogram shows an abnormality, the woman will be recalled directly for further assessment, including possible biopsy at the breast clinic. Women entering this evaluation give written consent after reading the information leaflet "Breast Screening for Women with a Family History of Breast Cancer". They agree to personal information being stored in a database held on behalf of the NHS by Breast Test Wales in Cardiff. Only anonymous data will be released by Breast Test Wales to research teams involved in the evaluation.

This evaluation will produce evidence to the NHS, which will be reported to the National Screening Committee. If that evidence shows no benefit, the National Screening Committee reserves the right to advise the NHS that regular screening mammography should not be offered to women under 50.