

## ORIGINAL ARTICLE

# The challenge of evaluating annual mammography screening for young women with a family history of breast cancer

The FH01 Management Committee, Steering Committee and Collaborators

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A full list of acknowledgements is given at the end of the paper

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It has been recommended that women aged 40–49 years with a significant family history of breast cancer should be offered annual mammography screening (<http://www.nice.org.uk>). An observational study known as FH01 (<http://www.screeningservices.org/btw/fh01/index.asp>) is evaluating this policy in a cohort of 6000 women at moderately increased risk of breast cancer due to family history. The main aims are to assess the likely impact on breast cancer mortality and cost-effectiveness. Measuring these outcomes is challenging in an environment where a randomized trial is not feasible and there is no natural comparison group. In this paper, we present some approaches to estimating effectiveness and the planned analyses. These involve comparison of disease stage and likely consequent breast cancer mortality in the cohort offered screening with that estimated in the absence of screening. The estimation uses observed outcomes in external populations and estimated outcomes for the hypothetical situation where screening had not taken place.

## INTRODUCTION

It has recently been estimated from randomized trials that invitation to mammography screening in women aged 50–69 years reduces breast cancer mortality by 22% over a period of 12–20 years.<sup>1</sup> Evidence such as this led to the initiation of breast cancer screening programmes in many European countries and recommendations of regular mammography screening in this age group from worldwide health organizations.<sup>2</sup> The benefits for women aged 40–49 years have not been so well defined and access to breast cancer screening in this age group is limited. For example, the UK's policy of three-yearly invitation to mammography screening covers women aged 50–70 years.

Public awareness of breast cancer and the discovery of high-penetrance genes has led to an increase in the number of women seeking advice from their general practitioners due to a family history of breast cancer. While the number of high-risk families with predisposing genes such as BRCA1 and BRCA2 or other genetic factors<sup>3</sup> is small, there are a number of women aged 40–49 years who, although unlikely to inherit such genes, are at elevated risk due to family history.

Women referred to breast services or clinical genetics departments can be classified into three groups. Firstly, women whose family history is not sufficiently strong to indicate a substantial elevation of risk of breast cancer beyond that of the general population need reassurance but no further intervention. Secondly, women with family history so strong as to lead to a serious suspicion of a BRCA1 or BRCA2 mutation may need counselling on the subject of genetic testing and possible prophylactic interventions in the event of a positive test. Finally, there is an intermediate group whose family history is associated with a substantially increased risk of breast cancer, but is not strong enough to indicate a high probability of a BRCA mutation.

Management strategies for this last group include surveillance that is more intensive and earlier in life than provided by the UK National Breast Screening Programme, possibly by magnetic resonance imaging (MRI) in certain risk groups,<sup>4</sup> but more likely by mammography.

Mammographic screening in these younger, moderate-risk women is an attractive approach, but there is limited evidence on whether it would reduce breast cancer mortality in practice. It does appear that faster growing, more aggressive breast tumours tend to be found in women with a family history diagnosed with breast cancer in their 40s, and for screening to be effective in this group, it would necessarily involve annual invitation.<sup>5</sup>

A study was launched in the UK in 2003 to recruit a cohort of 10,000 women, later revised to 6000 when certain requests for subgroup analyses were withdrawn, aged 40–44 years with a moderate family history of breast cancer. This was based on a previous proposal involving a study of 20,000 women.<sup>6</sup> This observational study (known as FH01) is recruiting women referred to breast services and clinical genetics departments, who have been recommended to have annual mammography. Women will be observed for a minimum of five years. The main aims of FH01 are to measure the impact of such an intervention on likely future breast cancer mortality and to evaluate cost-effectiveness. Thus, the FH01 study addresses the recent recommendation by the UK's National Institute of Clinical Excellence (NICE) (<http://www.nice.org.uk/pdf/CG014quickrefguide.pdf>) that 'All women aged 40–49 years satisfying referral criteria to secondary or specialist care should be offered annual mammographic surveillance'.

While it is of key importance to evaluate the impact of such a policy, a randomized trial is not feasible for this group of women both on ethical (lack of equipoise on the basis of a survey of clinicians involved, study length) and practical

grounds (recruitment problems).<sup>6</sup> The FH01 study offers an opportunity to measure the impact of invitation to annual mammography screening in young women with a moderate family history. However, there is no natural comparison group and so alternatives must be found. Here we describe the comparison groups and strategies available to us and outline the planned analyses to estimate the predicted effect of this policy on breast cancer mortality.

## BASIC DESIGN AND DEFINITIONS

The aim of FH01 is to recruit 6000 women aged 40–44 years, and to offer these women annual mammography over five years. Recruitment is scheduled to end in December 2006. At August 2006, there were 5486 recruits. Thus, they will still be aged under 50 years at the conclusion of the study, and any observed benefit of screening will be due to screening activity before age 50. The tumours diagnosed over the five-year period and their pathological characteristics will provide the major information resource for evaluation. Note that women are eligible whether or not they have undergone previous mammographic surveillance. To be eligible for the study, they must satisfy the following family history criteria:

- one first-degree female: breast cancer at age 40 years or under;
- one first-degree female: bilateral breast cancer first cancer diagnosed at age 50 years or under;
- two first- or one first- and one second-degree female: both with breast cancer at age 60 years or under (same side of family);
- one first- or second-degree female: breast and ovarian cancer, first cancer diagnosed at age 60 years or under;
- three first- or second-degree female: breast or ovarian cancer at any age (same side of family);
- one first-degree male: breast cancer at any age;
- paternal history of a minimum of two second-degree relatives (i.e., father's first-degree relatives) with breast cancer at or less than age 50 years, or one with breast cancer at or less than age 50 years and an ovarian cancer (any age), or paternal uncle/grandfather with breast cancer <50 years.

These criteria were developed before the NICE guidelines were available. NICE guidelines drew on these but varied from them slightly in their definition of moderate risk. For high risk (conferring a 20% or more probability of a high-risk gene mutation in the family), stronger criteria would be applied. For example, NICE specify at least two relatives, one of whom must be first degree, with breast cancer at average age 50 or earlier as one of the high-risk criteria.

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 the FH01 cohort, and compare this to that which would be expected if the mammographic surveillance had not taken place.

In the following, 'FH01 cohort' refers to the women recruited to the FH01 study with a moderate family history of breast cancer. There are two comparison groups available to us, known as the 'age trial cohort' and the 'historical cohort'.

The 'age trial cohort' refers to the *control group* of the UK Breast Screening Age Trial. These women, aged 40–41 years at entry into the Age Trial,<sup>7</sup> were randomly assigned to the 'no invitation to mammography' arm and have seven years

follow-up after entry. The 106,000 women in the Age Trial Cohort are from the general population and do not necessarily have a family history of breast cancer, but their age and follow-up period overlap with that of the planned FH01 cohort. There were 755 interim cancers in this group.<sup>7</sup>

From the estimates of disease progression and screening sensitivity in the Swedish Two-County study, we expect 18% of tumours in the FH01 cohort to be node positive. In the UK Age Trial, 41% were node positive. We anticipate 120 cases in total in FH01. On this basis, a comparison on incidence of node-positive disease between the two cohorts would have power in excess of 95%. We expect a reduction of 53% in incidence of node-positive disease, which would imply a 32% reduction in mortality, for survival rates by node-positive status in the Two-County trial.<sup>8</sup> It is planned to analyse the data in 2010, by which time the 120 expected cases will have been amassed to the FH01 cohort.

The 'historical cohort' refers to 800 breast cancer cases clinically diagnosed in the 1980s in French women aged 40–49 years with a family history of breast cancer with no prior regular mammography. The pathology data on these cases are available.

## STATISTICAL ANALYSES AND ESTIMATION OF THE EFFECT OF THE SURVEILLANCE ON MORTALITY

When it is not possible to obtain a direct estimate of the quantity of interest using the ideal design (in this case a randomized controlled trial), a good strategy is to derive more than one indirect estimate. Accordingly, several methods of estimating the likely effect on long-term breast cancer mortality will be used. If results of the various methods agree, we can be fairly confident of their validity. If there is disagreement among the methods, further model and method diagnostics will be indicated. All breast cancers diagnosed in the FH01 study period will be followed up for breast cancer death, but since this population will be subject to intensive early detection, there will be insufficient numbers of breast cancer deaths for a precise estimate of the effect of the screening, even after 10 years. The fundamental question, therefore, is how to estimate the likely effect on future mortality from observations on the tumours diagnosed during the five years of the study.

### Tumour incidence by size, nodal status and histological grade

Table 1 shows the relative risks of node-positive breast cancer in the randomized trials of mammographic screening (study versus control group) and the subsequently observed relative risks of breast cancer mortality. It is clear that the reduction in advanced stage disease is a powerful predictor of the reduction in breast cancer mortality at an ecological level. That this also holds at an individual level is shown in numerous tumour series.<sup>9–12</sup>

It is clear, therefore, that a simple analysis which is in principle predictive of the likely benefit of the surveillance will be the comparison of the incidence of node-positive tumours in the FH01 cohort with that expected in the absence of the mammographic surveillance.

### Comparison of proportions

We therefore propose in the first instance to compare the proportion of node-positive tumours in the FH01 with those observed in the Age Trial Cohort and the French Historical

**Table 1** Relative risks of breast cancer death and relative risks of node-positive tumours, study versus control groups in the randomized trials of screening for breast cancer

RCT	RR mortality	RR node-positive
HIP	0.78	0.85
Malmö	0.78	0.83
Two-County	0.68	0.73
Edinburgh	0.78	0.81
Stockholm	0.90	0.82
NBSS1	0.97	1.20
NBSS2	1.02	1.09
Gothenburg	0.79	0.80

Cohort. Both of these have full pathology data available. We shall repeat the comparison for the proportion of invasive tumours larger than 2 cm in maximum diameter, and investigate the association of histological grade with any differences observed.

While a simple comparison of the proportions of advanced tumours is informative and easy to understand, it is prone to length bias or overdiagnosis. For example, the proportion of node-positive tumours in the FH01 cohort might be artificially reduced by overdiagnosis of node-negative tumours by screening. A second series of analyses will therefore estimate the effect of the mammographic surveillance on the absolute incidence of advanced tumours, whether defined by size, node status or a combination of pathological factors.

We propose several analytical strategies to estimate the effect of the surveillance on absolute incidence of advanced tumours.

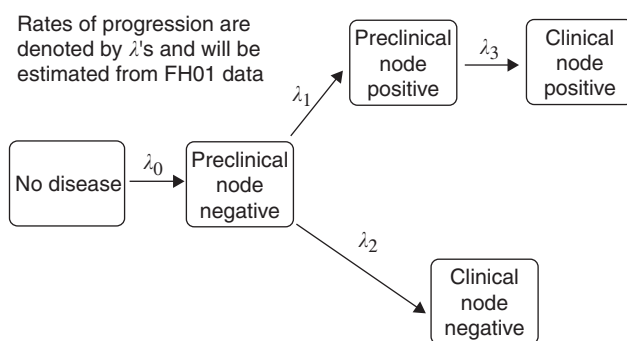
**Internal estimation**

The rates of screen-detected and interval cancers by, for example, node status provide an opportunity to estimate rates of progression from preclinical (i.e., asymptomatic) but screen-detectable disease to overt clinical disease, and from node-negative to node-positive disease. The process may be summarized as in Figure 1. All women begin with no detectable disease, some may progress to preclinical node-negative disease with rate  $\lambda_0$  and some of these may in turn progress to node-positive (rate  $\lambda_1$ ) or clinical disease ( $\lambda_2$ ). When a cancer is diagnosed, it is treated and its natural progress is not observable thereafter. When the progression rates  $\lambda_i$  have been estimated, they can be used to estimate the cumulative rates of node-positive disease expected in the absence of screening.

Chen *et al.*<sup>13</sup> present an example of this in the evaluation of the breast screening programme in women aged 40–49 years in Uppsala, Sweden. In Uppsala, screening was offered to women in this age group every 20 months.

Chen *et al.* fitted the model shown in Figure 1 to this and obtained estimates of the transition rates  $\lambda_i$ . For methodological details, see Chen *et al.*<sup>14</sup> These transition rates translated into annual probabilities of progression, as in Table 2. These progression probabilities can be used to calculate the predicted numbers of node-positive and node-negative cases in the absence of screening. This would predict 79 node-positive cancers in the Uppsala study population in the absence of screening, compared with the 45 observed. Thus the screening is estimated to have brought about a 43% reduction in incidence of node-positive tumours.

A simpler approach would be to assume that the proportion of node-positive tumours prevailing in the



**Figure 1** Disease model of progression from preclinical to clinical disease and from node-negative to node-positive disease.

**Table 2** Estimated progressive probabilities within one year from the data in Uppsala

Progression from	Progression to	Probability (%)
Preclinical node –	Preclinical node +	6
	Clinical node –	25
	Clinical node +	24
Preclinical node +	Clinical node +	97

interval cancers would have been observed in the tumour population as a whole in the absence of screening (although this comparison may be subject to length bias if the interval cancers contain more innately aggressive, high-grade tumours than screen-detected). Of the 71 interval cancers, 32 (45%) were node positive. Applying this to the total tumour population we estimate that 78 ( $172 \times 0.45$ ) tumours would have been node positive in the absence of screening, very similar to the estimate derived from the multistate modelling.

In FH01, we shall similarly estimate the effect on node-positive tumours using both methods.

**Comparison with the Age Trial Cohort**

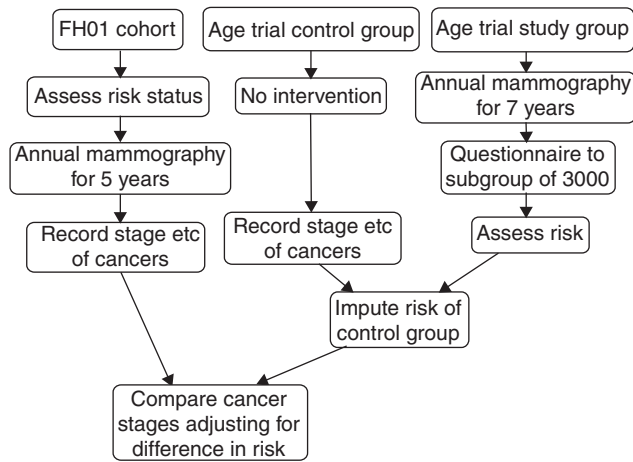
Suppose we observe 0.8 node-positive tumours per 1000 person-years in the FH01 cohort and 0.6 per 1000 in the Age Trial controls. This would give the impression that the screening was actually increasing the rate of advanced tumours with a relative risk of

$$RR_A = 0.8/0.6 = 1.25$$

This, however, ignores the fact that the FH01 cohort has a much higher incidence of breast cancer than the Age Trial Control Group, as a result of the study family history in the FH01 cohort. One way to adjust for this is to divide  $RR_A$  above by  $RR_I$ , the relative risk of breast cancer overall for FH01 compared to Age Trial controls. If, for example, the total incidence of breast cancer in FH01 was four per 1000 and the total incidence in the Age Trial controls was 1.3 per 1000, we would have a corrected relative risk of node-positive disease of

$$RR_C = \frac{1.25}{(4.0/1.3)} = \frac{1.25}{3.08} = 0.41$$

This is a reasonable strategy but may be prone to length bias or its more extreme manifestation, overdiagnosis, in the FH01 cohort. It amounts to comparing the *proportion* of node-positive cancers in the two cohorts. An alternative is to



**Figure 2** Strategy for adjusting comparison of FH01 cohort with Age Trial Cohort for predicted breast cancer risk

use the risk factor status of the individuals in the two cohorts to predict the overall incidence in each independent of screening. This would give an estimate of  $RR_1$  which was not affected by length bias or overdiagnosis. We have developed a method and computer programme for predicting individual risk of breast cancer from family history and other risk factor data.<sup>15</sup> The programme has been validated and shown to be accurate.<sup>16</sup>

The problem with this strategy is that the Age Trial Control Group have not previously been contacted and are having no intervention offered them. It might therefore be unethical to raise anxieties about breast cancer by approaching them with a view to obtaining the same family history and risk factor data as we have for the FH01 cohort. Instead, we propose to contact a subset of the Age Trial Study Group, who are already being offered annual mammography, and to ascertain risk factor status in this subgroup. Because of the randomization, the risk factor status in the Age Trial Study Group will be the same on average as the control group. We can therefore impute the risk factor status and the predicted breast cancer risk in the Age Trial controls. The strategy is illustrated in Figure 2.

We will perform both the simple (observed incidence) and the complex (predicted incidence from risk status) procedure for comparing the two cohorts. Also, by way of sensitivity analysis, we shall repeat the analysis using other risk prediction algorithms for the adjustment.<sup>16</sup>

### Predicted breast cancer mortality

As with the comparison of node status, we shall perform both internal estimation of the benefit of the mammographic surveillance and external comparison of predicted mortality in our cohort with the comparison groups.

Tumour size, lymph node status and histological grade have been shown to reliably predict both individual survival and aggregate mortality reductions conferred by screening.<sup>10,11</sup> The distribution of these factors, as estimated above in 'Tumour incidence by size, nodal status and histological grade', will be used to estimate subsequent breast cancer mortality both in the screened FH01 cohort and in the FH01 cohort had screening not taken place. These estimates will then be compared to predict the change in breast cancer mortality as a result of the surveillance.

Table 3 shows the Uppsala breast cancer cases by node status, and the expected cases in the absence of screening. Applying 10-year death rates to these as observed in the

**Table 3** Observed cases in the Uppsala screened population and expected cases by lymph node status, with corresponding 10-year death rates estimated from the Swedish Two-County Study data

Screening status	Node status	Cases	% 10-year death rate	Predicted deaths
Screened (observed data)	Negative	127	10	13
	Positive	45	40	18
	Overall	172	—	31
Unscreened (predicted data)	Negative	93	10	9
	Positive	79	40	32
	Overall	172	—	41

Swedish Two-County Study,<sup>8</sup> we predict 31 deaths in the Uppsala screened population over 10 years. Applying the same death rates to the expected cases in the absence of screening gives a predicted 41 deaths over 10 years. This therefore suggests a 24% mortality reduction as a result of the screening in Uppsala in women aged 40–49 years.

In our analysis, we will use multivariate prediction of mortality using size, node status and histological grade.<sup>8</sup> The principle, however, is the same.

We shall also estimate the benefit, if any, by external comparison with the Age Trial Cohort and the Histological Cohort. As with the comparison of incidence of node-positive tumours, we shall adjust for the different underlying incidences in the two groups using both observed and predicted incidences.

### Secondary outcomes

#### Rates of attendance, recall and surgical biopsy

These will be reported and compared with those observed in the study groups of the randomized trials and with other service screening programmes.<sup>10</sup> Confidence intervals on these rates will be estimated using the Poisson distribution approximation, and differences from those expected will be assessed using  $\chi^2$ -tests.

However, allowances must be made for the major distinguishing feature of the FH01 cohort, that it is a volunteer population with an underlying risk higher than the general population risk due to family history. As described above, this will be done in two ways: (i) using the empirically observed incidence in the FH01 cohort, and (ii) from the strength of the family histories and with other risk factors using the Tyrer-Cuzick and other methods.

#### Cancer detection rates

These will be reported overall and stratified by tumour size, lymph node status, histological grade and histological type. As above, cancer detection rates will be compared with those reported in the randomized trials and appropriate adjustments made for underlying differences in incidence.

#### Interval cancer rates

These will be reported firstly without transformation or rescaling. Thereafter, proportional interval cancer rates will be calculated in the FH01 cohort. Proportional interval cancer rates are the incidence of interval cancer occurring after a negative screen, divided by the expected incidence in the absence of screening in a group of the same age and risk

profile. The faster this ratio approaches unity, the shorter the screening interval needs to be. Incidence in the absence of screening will be calculated in the two ways described above (i.e. from that observed in the FH01 cohort and that estimated via predictive models).

### Programme sensitivity

Programme sensitivity (PS) is the proportion of cancers in those participating in the screening which are actually detected by screening (as opposed to arising clinically between screens). This can be calculated empirically using the number of screen-detected and interval cancers observed, and using the methods of Launoy *et al.*<sup>17</sup> based on two important indicators of potential effectiveness of a screening programme: mean sojourn time (MST) and test sensitivity ( $S$ ). Mean sojourn time is the duration of the preclinical screen-detectable period (i.e. the window of opportunity for screening to advance the diagnosis). The test sensitivity is the probability that a cancer which is in the preclinical detectable period will test positive by the screening test. MST and  $S$  can be estimated using Markov models.<sup>14</sup> The average lead time achieved is also calculable, since it is the product of the MST and the PS. These methods have been used in the past as part of the evaluation of screening in women at increased familial risk of breast cancer.<sup>18</sup>

### Overdiagnosis

In screening for breast cancer, it is theoretically possible to diagnose cancers which would never have become clinically apparent had screening not taken place (for example, some cases of low-grade ductal carcinoma *in situ* (DCIS) may fall into this category). We shall therefore estimate the proportion of potentially overdiagnosed cases using two approaches based on estimation of incidence. Firstly we will compare the empirical incidence of breast cancer in the FH01 cohort with that expected from the family histories using the previously described predictive models.<sup>15,16</sup> Secondly, we shall use the finding that if there is overdiagnosis or length bias, it tends to occur at the first screen.<sup>9,14</sup> We propose to compare the observed prevalence at first screen with that expected ( $E$ ) from the MST,  $S$  and incidence ( $I$ ) of breast cancer in the FH01 cohort. The expected prevalence,  $E = S \times MST \times I$ . Again, we shall derive two estimates of  $I$ , one empirical and one theoretical from family histories. In addition, we shall monitor detection rates of DCIS and invasive cases separately. Finally, we shall explicitly estimate the incidence of overdiagnosed cases using formal multistate models.<sup>19</sup>

## DISCUSSION

In this paper, we have presented methods to assess the impact of annual invitation to mammography screening for women aged 40–49 years with moderate-high risk due to family history. In particular, outcomes of importance include:

- breast cancer mortality reductions due to the intervention, differences in tumour features such as size, stage, grade and type;
- basic features of a screening programme such as rates of attendance, recall and biopsy, cancer detection rates, interval cancers and investigation of tumour features in non-attenders;

- quality indicators such as MST, sensitivity, PS, average lead-time and potential overdiagnosis.

In the above, we had the necessity to summarize and simplify the proposed analyses to some extent. In addition to the activities described above, there will be separate analyses including and excluding DCIS, use of more than one prognostic index to predict future mortality and a variety of sensitivity analyses investigating departures from the major assumptions.

The results of FH01 are expected to inform policy on the management of this particular risk group. If a substantial benefit is observed, there will be a recommendation to have this annual mammography regime as a national policy for this group. If negative or only weakly positive results are obtained, it will be necessary to consider other management strategies, including surveillance by other imaging techniques or primary prevention.<sup>20</sup>

The methods will make use of previously validated predictive modelling on internal and external comparison groups, together with future observations of the FH01 cohort and appropriately chosen comparative cohorts. While no method is ideal, a variety of methods based around these key concepts will give a number of estimates, which can be compared and carefully interpreted. We feel that this clearly planned analysis meets the challenge of evaluating the policy of invitation to annual mammography screening for young women with a family history of breast cancer.

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