Improvement in risk prediction, early detection and prevention of breast cancer in the NHS Breast Screening Programme and family history clinics: a dual cohort study

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Scientific summary

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Scientific summary

Background

Breast cancer is the commonest cancer in women and incidence continues to increase, with 50,000 women diagnosed annually in the UK. In the UK, women are invited for 3-yearly mammography screening through the NHS Breast Screening Programme (NHSBSP) from the ages of 47–50 years to the ages of 69–73 years. This potentially impacts on early detection of around 50% of breast cancer cases (20% occur < 50 years; 30% occur > 70 years). Women with at least moderate familial breast cancer risk can obtain annual mammography surveillance from 40 years of age and, if they are a carrier or have > 30% risk of a BRCA1 (breast cancer 1 gene)/BRCA2 (breast cancer 2 gene)/TP53 (tumour protein p53) mutation, they can obtain annual magnetic resonance imaging (MRI) screening from the age of 30 years, according to National Institute for Health and Care Excellence (NICE) guidance (NICE. Familial Breast Cancer: Classification and Care of People at Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer. NICE guideline CG164. London: National Collaborating Centre for Cancer; 2013). However, no NHSBSP risk assessment is undertaken. Risk prediction models are able to categorise women by risk using known risk factors such as family history, hormonal/reproductive factors and body mass index (BMI), although accurate individual risk prediction has remained elusive. Identification of mammographic breast density (MD) and common genetic risk variants [single nucleotide polymorphisms (SNPs)] has presaged the likelihood of substantially improved precision of risk prediction models. Models need to accurately predict risk in the family history clinic (FHC) setting as well as in the general population if stratification of risk is to be feasible.

Objectives

1. Identify the best performing model to assess breast cancer risk in the FHC and population settings.
2. Use information from MD and SNPs to improve risk prediction.
3. Assess acceptability and feasibility of offering risk assessment in the NHSBSP.
4. Conduct a preliminary economic evaluation of introducing risk stratified screening.

Methods

Design

Two cohort studies were used to assess breast cancer incidence, using STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. Additionally, case–control series embedded in the cohort studies were utilised to address the utility of SNPs and MD in improving risk prediction. A preliminary model-based cost-effectiveness analysis was used to understand the potential costs and benefits of risk stratified screening.

How the research was conducted

Women were assessed from two groups. The first group was from a FHC at the University Hospital of South Manchester which has assessed breast cancer risk in over 10,000 women. This study [Family History Risk Study (FH-Risk); UK Clinical Research Network identification number (UKCRN-ID) 8611] incorporated a case–control study. Women who had developed breast cancer and had an assessable mammogram either at time of diagnosis or before were the cases, and the controls were selected from the FHC population to have had an assessable mammogram at the same age but were breast cancer free. The larger cohort study, Predicting the Risk Of Cancer At Screening (PROCAS; UKCRN-ID 8080), invited women who were due mammography appointments in Manchester over a 3-year cycle to participate in a questionnaire study.
obtaining standard risk information and consent to use their mammograms to assess breast density. A subset of this population consented to provide a saliva deoxyribonucleic acid (DNA) sample.

Data sources

1. Mammographic density was assessed from an available film (analogue) or digital mammogram through The Nightingale Breast Screening Centre (University Hospital of South Manchester).
2. Breast cancer and vital status were obtained through the North West Cancer Intelligence Service using NHS number and through the NHSBSP.
3. Deoxyribonucleic acid derived from lymphocyte DNA (FH-Risk) and saliva (PROCAS).
4. All other risk factors were identified from questionnaires and entered into a bespoke database.

Study selection

FH-Risk (UKCRN-ID 8611)
All women who had been referred to and assessed at the FHC at the University Hospital of South Manchester between 1987 and 2013 and who did not have breast cancer prior to assessment were included. Women who had developed breast cancer subsequently were identified as cases for a case–control study. For this they required an assessable mammogram at the time of their cancer or before. As analogue mammograms had been destroyed as part of hospital trust policy and raw data from digital mammograms were not saved prior to October 2010, a number of cancer cases were not eligible. All eligible cases were invited to take part. A DNA sample from blood was obtained. Controls were identified from the breast cancer unaffected FHC population who had undergone an assessable mammogram at the same age as the case. Controls were matched on age and type of mammogram on a 3:1 basis.

PROCAS (UKCRN-ID 8080)
Women in the Greater Manchester NHSBSP invited for their 3-yearly mammogram were eligible. As the NHSBSP was not able to identify from the invitation list women who had already developed breast cancer, all women were sent a study information sheet and consent form 1–2 weeks after their NHSBSP invitation. Consent was taken at the screening site by the radiographer. A total of 10,000 women in PROCAS were recruited, by invitation, to a DNA collection study using saliva. All women who developed breast cancer were invited.

Data extraction (and assessment of validity)
The risk information data comprised age at menarche/ menopause, hormone replacement therapy use, family history of breast cancer, weight/height, breast biopsies, age at first assessment/enrolment, and date of last follow-up or death/known last alive were obtained from the relevant FileMaker Pro 12 (FileMaker Inc., Santa Clara, CA, USA) (FH-Risk) and openCDMS (University of Manchester, Manchester, UK) (PROCAS) databases. Existing risk factors were updated using second questionnaires. ‘Impossible’ values, such as BMIs of < 10 kg/m² or > 60 kg/m², were used to change fields to unknown values for risk assessment.

Data synthesis
The risk information data on each individual were downloaded into a data file to include information on cancer and vital status of relatives. These were run through the BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm), Tyrer–Cuzick (TC) and Gail models. Ten-year risks were identified for stratification purposes. Individual risks of breast cancer over the follow-up period in FH-Risk were derived using a date of 1 August 2011 if no recent follow-up was identified, as this represented the date of cancer registry check. Breast cancer dates were derived from cancer diagnosis at the University Hospital of South Manchester or from the cancer registry. All prevalent cancers were excluded, including those identified at prevalence appointment. Observed versus expected (O : E) cancers were obtained for the whole cohort and within risk groups identified. The Manual model was run on 8824 women and TC and Gail were run on 9527 women (the latter number is larger as further follow-up had elapsed). Owing to identification of pedigree information, BOADICEA could be run only on single proband
families \((n = 6268)\). In PROCAS, as there was not a valid last follow-up date, it was therefore too early to assess \(O : E\) ratios.

**Breast density assessment**

**Analogue**

All had visual assessment score (VAS; percentage white area) score and stepwedge assessment.

**Digital**

All had VAS and two automatic methods, Volpara™ (version 1.4.5, Volpara Solutions, Wellington, New Zealand) and Quantra™ (version 2.0, Hologic, Inc., Marlborough, MA, USA). The most recent versions of these two tools were run (June 2014).

Case–control series of both analogue and digital methods were undertaken using the gold-standard Cumulus assessment.

**Deoxyribonucleic acid studies**

Single nucleotide polymorphisms were analysed from lymphocyte/saliva DNA using a SNPlex (Applied Biosystems, ThermoFisher Scientific Inc., Waltham, MA, USA) for 18 SNPs identified in 2010 as being associated with breast cancer risk (SNP18). A polygenic risk score (PRS) was derived based on a multiplicative model with per SNP odds ratios (ORs) to derive an overall relative risk (RR), compared with the general population. The assessment of SNPs based on cumulative risk of breast cancer by quintiles/quartiles was used to assess validity.

**Incorporation of single nucleotide polymorphisms/mammographic density into best model**

The best performing MD assessment tool was introduced into the best performing model using weighted analysis. The PRS and density residual (DR) scores were incorporated to provide a new 10-year risk assessment.

The models were compared using a number of statistical methods, including the c-statistic of the area under the curve (AUC) of receiver operating characteristic curves, which assesses the trade-off between sensitivity and specificity. A score of 0.5 represents a random chance association.

**Preliminary model-based cost-effectiveness analysis**

A systematic review was used of published economic evaluations relevant to breast screening in a general population of women, with input from clinical experts, to inform the development of the model structure to conduct a preliminary cost-effectiveness analysis of risk stratified screening for breast cancer as part of the NHSBSP, compared with the current screening programme. The data from PROCAS, supported by systematic reviews of the published literature, were used to populate the preliminary model-based cost-effectiveness analysis.

**Results**

**FH-Risk cohort (UKCRN-ID 8611)**

Since 1987, 10,177 women have been assessed in the FHC at the University Hospital of South Manchester. Assessment of \(O : E\) ratios in 8824 women with the Manual method model gave a ratio of 1.05 [95% confidence interval (CI) 0.95 to 1.16]. The risk precision was accurate in all risk groups. The assessment of TC and Gail carried out on 9527 women gave \(O : E\) ratios of 1.09 (95% CI 0.98 to 1.20) and 1.01 (95% CI 0.91 to 1.11) for 446 incident breast cancers in 97,958 years of follow-up. Gail significantly overestimated risk in women with a 10-year risk of > 12% and underestimated this in 2826 women with a < 2% 10-year risk. TC was accurate in all but the lowest risk group (1175 women with a < 1% 10-year risk). BOADICEA was accurate across all risk groups in the 6624 assessable single
proband women with an O : E ratio of 0.97 (95% CI 0.84 to 1.11). As BOADICEA could not be run on the whole population, modelling with both SNPs and MD was carried out on TC.

**FH-Risk case–control**

Owing to the loss of mammograms, only two small case–control studies could be carried out on 82/82 matched cases/controls on analogue films and on 48/144 cases/controls with digital mammography. Cumulon was found to be predictive in the analogue series, and both Cumulus and VAS were found to be predictive in the digital series using quartiles. Mammograms were destroyed if they were > 3 years old owing to space considerations, although some cancer-related ones were preserved. This meant that few controls were available for analogue films and the ones available were more recent.

**Single nucleotide polymorphisms analyses**

Single nucleotide polymorphism testing was carried out in four studies. A total of 462 and 445 women with a confirmed pathogenic mutation in *BRCA1* and *BRCA2*, respectively, were included in the analyses. SNP18 was not predictive of breast cancer risk for *BRCA1* (p = 0.25). This was not improved by using the three SNPs linked to breast cancer risk, and predictions showed a reverse prediction. Nonetheless, for *BRCA2* there was a significant difference in age at the development of breast cancer between the risk groups for SNP18 (p < 0.001) and a clear trend for reducing hazard with reducing overall PRS (increasing quintile). In 6954 women from PROCAS, including 673 with breast cancer, there was a clear increase in overall PRS in those with breast cancer. Median (mean) PRS in breast cancer cases was 1.00 (1.15), compared with 0.90 (1.02) for those without. The distribution was also shifted to the right in all categories using > 8% 10-year risk group, where NICE guidelines advise offering chemoprevention with tamoxifen or raloxifene. Adding a SNP67 to TC increased the proportion eligible substantially, from 0.77% to 2.85%.

Finally, analysis in the FH-Risk case–control series showed that SNP18 added significant discrimination to TC in non-*BRCA1* women. DNA was tested in 1701 individuals and 18SNP PRSs were generated. A significantly higher proportion of cases, 33 out of 359 (9.2%), had RRs of > 2, compared with controls (56/1079, 5.2%; p = 0.01). The inclusion of SNP18 in TC improved the AUC from 0.59 to 0.62.

**PROCAS (UKCRN-ID 8080)**

As of 30 June 2014, 53,596 women had been recruited to PROCAS, representing 37% of the 68% of women attending for NHSBSP screening. There was wide variation in uptake by age, deprivation status and site. The highest uptake was 56% in Oldham Integrated Care Centre, and was 47% in women invited for their first screen aged 46–49 years in phase 2. Uptake was higher, at 60%, when a study representative was present. Of the recruits, 95% wished to know their risk. Risk feedback was offered to women at high (> 8% 10-year risk) and low (< 1% 10-year risk) risk. A total of 513 out of 689 (74.5%) high-risk women and 105 out of 192 (55%) low-risk women took up the offer of risk assessment (p < 0.01). Reattendance at subsequent mammogram was not affected in low-risk women (43/53, 81%), while 200 out of 202 high-risk women reattended (99%; p < 0.0001).

At the time of assessment (12 March 2014), 632 prospective breast cancers had occurred in 53,184 women. This met the original power calculation target of 600.

Mammographic density was assessed in both analogue (n = 8511) and 38,861 digital films. Raw data were lost in 4200 women owing to non-saving in the first 6 months of the study. Case–control studies were carried out on 324 breast cancer cases with digital mammograms and 972 matched controls. VAS gave the best prediction with an OR of 3.59 (95% CI 2.37 to 5.43) between upper and lower quartiles. There was a dose–response relationship with increasing density (χ² trend 33.3; p < 0.0001). This was superior to Cumulus (1.93, 95% CI 1.12 to 3.34) and Volpara (2.33, 95% CI 1.46 to 3.72). Volpara percentage breast density had a dose–response relationship with increasing density (χ² trend 9.2; p = 0.002), but this was inferior to VAS. Quantra had no correlation for either glandular volume or percentage density. In the light of these results, and because VAS was available for all subjects, VAS was incorporated into the risk prediction models.
The DR score was derived to determine VAS, compared with an average woman of the same age, BMI and menopausal status. DR score was highly predictive of breast cancer incidence and increased stage at diagnosis. The Gail model achieved an AUC c-statistic of 0.54, and TC was better, at 0.57. Incorporating DR score to the models significantly improved the discrimination to a c-statistic of 0.58 for Gail and 0.60 for TC. In particular, using the best-fitting model adjusted for DR, 18 out of 272 (6.6%) of breast cancers had high stage at diagnosis in women with an adjusted TC score of < 3.5% 10-year risk, whereas 28 out of 222 (12.6%) of those with TC 10-year risks of > 3.5% had high-stage cancers (p = 0.029). The annual risks were assessed: women with < 3.5% 10-year risk had a breast cancer rate of 1.3 per 10,000 per year, compared with 4.76 per 10,000 annually (p < 0.001) in moderate women. TC predicted that only 29.8% of the population have a 10-year risk of > 3.5%.

A preliminary model-based cost-effectiveness analysis suggested that a risk-based stratified screening programme may be an effective use of health-care resources, but this was an early economic analysis that relied on currently available data and there was extensive uncertainty around some key inputs into the model.

Conclusions

Implications for health care
This programme grant has shown that addition of MD and SNPs to the TC model substantially improves risk prediction in the general population. This allows better risk stratification such that women at high and moderate risk will potentially gain better access to additional surveillance and preventative strategies.

The research indicates that 3-yearly screening is sufficient for ≈70% of the population with average/below average risks, but that more frequent screening may be justified in those with a MD-adjusted 10-year risk of > 3.5%. The current level of uncertainty in the available evidence base to identify the incremental costs and benefits of a risk-based screening programme, compared with the current programme, suggests that more research is required before its introduction at a national level.

Research recommendations

1. A pilot study of risk provision in real time in the NHSBSP.
2. Development of a better risk prediction automatic MD model.
3. Validation studies of SNP67 in the screening population and FHCs.
5. Studies to show whether or not increased screening frequency will down-stage breast cancers in women predicted by MD and TC to have a risk of > 3.5%, or whether further strategies such as tomosynthesis or MRI may be required.

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