Research Article

Cancer Prevention Research

Assessing Individual Breast Cancer Risk within the U.K. National Health Service Breast Screening Program: A New Paradigm for Cancer Prevention

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Abstract

The aim of this study is to determine breast cancer risk at mammographic screening episodes and integrate standard risk factors with mammographic density and genetic data to assess changing the screening interval based on risk and offer women at high risk preventive strategies. We report our experience of assessing breast cancer risk within the U.K. National Health Service Breast Screening Program using results from the first 10,000 women entered into the "Predicting Risk Of breast Cancer At Screening" study. Of the first 28,849 women attending for screening at fifteen sites in Manchester 10,000 (35%) consented to study entry and completed the questionnaire. The median 10-year Tyrer–Cuzick breast cancer risk was 2.65% (interquartile range, 2.10–3.45). A total of 107 women (1.07%) had 10-year risks 8% or higher (high breast cancer risk), with a further 8.20% having moderately increased risk (5%–8%). Mammographic density (percent dense area) was 60% or more in 8.3% of women. We collected saliva samples from 478 women for genetic analysis and will extend this to 18% of participants. At time of consent to the study, 95.0% of women indicated they wished to know their risk. Women with a 10-year risk of 8% or more or 5% to 8% and mammographic density of 60% or higher were invited to attend or be telephoned to receive risk counseling; 81.9% of those wishing to know their risk have received risk counseling and 85.7% of these were found to be eligible for a risk-reducing intervention. These results confirm the feasibility of determining breast cancer risk and acting on the information in the context of population-based mammographic screening. *Cancer Prev Res; 5(7); 943–51. ©2012 AACR.*

Introduction

Over the past 20 years, deaths from breast cancer in the United Kingdom have declined by 40% in women under the age of 70, which is attributed to the introduction of breast screening by mammography, more widespread use of adjuvant systemic therapies, and general improvements in care (1, 2). However, the incidence of breast cancer continues to rise and is a major public health problem. Preventive measures based on chemoprevention and lifestyle change are possible but not feasible on a population basis, in part, because of the difficulties of identifying women at risk in the general population. Here we evaluate whether such an approach can be introduced as part of a national breast screening program. In the United Kingdom approximately 70% of the population of women between the ages of 47 and 73 years regularly attend a screening mammogram. Currently no public health measures are introduced at this time, and we hypothesize that this is a great opportunity to introduce measures that may help prevent breast cancer and improve the screening program based on assessment of risk of breast cancer at the screening episode.

Unlike most screening programs in other countries, which typically use 1 or 2 yearly intervals, the interval between mammograms in the National Health Service Breast Screening Program (NHSBSP) is 3 years, possibly partly as a result of this, 40% of tumors arise in the interval between mammograms. These cancers have a poorer prognosis and reduce the potential effectiveness of the program (3, 4). Identification of women likely to develop interval cancers and offering them tailored screening and preventive interventions may be a way to reduce the incidence of interval cancers. There is evidence to suggest that women

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at high risk of breast cancer are more likely to develop interval cancers. The Swedish 2-county study showed that women with a family history of breast cancer were significantly more likely to develop breast cancer in the interval between 2 yearly screens than equivalent women with no family history (5). High mammographic breast density also considerably increases the risk of developing interval breast cancer (6, 7). A screening program adapted to risk may therefore improve the effectiveness and efficiency of the NHSBSP. For women at very low risk of developing breast cancer, the screening interval might be extended or no screening conducted–-thereby safely reducing the numbers needing to be screened.

Breast cancer risk is generally assessed using models that include a combination of known risk factors, such as a family history of the disease, reproductive and hormonal history (age at first pregnancy, for example; refs. 8–11), and perform well at predicting the overall number of breast cancer cases arising in a particular population but are poor at identifying the specific individuals (8). In the United States, the Gail model, based on age, first-degree family history, the number of surgical biopsies of the breast and reproductive factors such as age of menarche, of first pregnancy, and age of menopause is widely used (10, 11). In a comparison of various breast cancer risk prediction models using observed data from the United Kingdom, we showed that for women with a family history of breast cancer the Tyrer–Cuzick model performed better than the Gail model (12). The former model is based on a more extensive familial component, HRT use, and height and weight also being included (9). Nevertheless, most breast cancers arise in women with none of the commonly assessed risk factors (12).

Assuming that the association between breast density and breast cancer risk is causal, mammographic density is the single assessable risk factor with the largest population attributable risk and may also have a substantial heritable component (13, 14). The difference in risk between women with extremely dense, as opposed to predominantly fatty breasts is approximately 4- to 6-fold (15). Incorporation of density into the standard risk prediction models is associated with some improvement in risk prediction (16, 17). Mutations in breast cancer genes such as *BRCA1* and *BRCA2* are too infrequent to affect risk prediction appreciably in the models for the general population. However, recently identified single nucleotide polymorphisms (SNP) in some genes (about 20 to date; ref. 18–20), which individually confer small changes in risk, may prove useful in predicting larger differences in risk when considered together.

At present no attempt to routinely collect risk information has been made in the NHSBSP. The main aim of this study is to assess the feasibility of (i) collecting information on standard breast cancer risk factors, mammographic density, and SNPs within the context of a conventional population-based breast screening program and (ii) offering counseling and risk-reducing interventions to women found to be at high risk, and (iii) to assess, later, the feasibility of adapting the mammographic screening interval based on risk

Another aim of the study is to further develop and validate the Tyrer–Cuzick breast cancer risk evaluation model so that it will include mammographic density and SNPs, in addition to the current breast cancer risk factors, to determine whether the discriminatory power could be improved Here, we report the feasibility of the approach in 10,000 women entered into the study of Predicting Risk Of Breast Cancer At Screening (PROCAS).

Materials and Methods

We devised a 2-page questionnaire to collect family history, hormonal, and lifestyle information (see http://www.uhsm.nhs.uk/research/Documents/PROCAS%20Questionnaire.pdf; refs. 21). All sequential women in 15 screening areas across Greater Manchester, who had been invited for routine mammographic screening, were identified through the U.K. NHS Breast Screening Program and mailed the questionnaire, study information, and a consent form before their attendance. Women gave consent to the study at the screening unit and brought their completed questionnaires with them. Information on each questionnaire was scanned into the Cardiff Teleform software package, imported into the study database, and the risk estimated automatically using the Tyrer–Cuzick model (9). All had at least 2 opportunities to opt out of receiving risk information; firstly at initial consent and, subsequently, by contacting the study coordinator at any time. Women with a 10-year risk of developing breast cancer of 8% or more per the Tyrer–Cuzick model, or of 5% to 8% 10-year risk with at least 60% mammographic density, were invited to receive risk counseling and were given another chance to opt out of receiving risk information when they received their invitation. Risks were discussed either in person or on the telephone by 2 experienced clinicians in risk communication (DGRE, AH). Women who were not invited to risk counseling were informed of their risk by letter toward the end of the study. The study was approved by Central Manchester Research Ethics Committee (Ref: 09/H1008/81).

Assessment of mammographic density

Mammographic density (percent dense area) was estimated by visual assessment during film reading by 12 film readers (7 radiologists, 2 breast physicians, and 3 advanced radiography practitioners), working independently in pairs. Using a preprinted form showing a line with 0 marked at one end and 100 at the other, readers marked the place on the scale corresponding to their assessment of the density. The paper forms were then scanned and read by specially designed software to give a measure of percent dense area. Each breast and view was assessed separately. There were, therefore, 8 separate assessments of mammographic density per woman. Here overall density score was taken to be the average. The radiologists at our center were trained in this method during the CADET-1 trial (22) and their performance was shown to be comparable with interactive

thresholding software (Cumulus), with regard to predicting breast cancer risk when the assessment was based on both the mediolateral and craniocaudal views (23), and the process incorporated into usual practice.

DNA testing

Women have been approached by a combination of random approach to those attending at screening mammography by a study researcher and also by invitation to already enrolled women to attend a study day to provide saliva samples for DNA extraction. Five genome-wide association studies (GWAS; refs. 18–20, 24, 25) have found common genetic variants (SNPs), each carried by 6% to 44% of the population associated with a 1.07 to 1.43 relative risk of breast cancer. These variants were identified at 18 loci. When combined in an individual by multiplying the risks associated with each allele together, they can give an overall genetic risk of breast cancer (26). A subset of the PROCAS population (those attending one center) was invited to attend a drop-in day and provide a saliva sample for DNA extraction. Women giving their consent were provided with an Oragene kit (DNA Genotek) to collect a saliva sample. DNA was extracted according to manufacturer's protocols, and 18 known validated breast cancer SNPs (only one for each genetic locus) associated with breast cancer were typed (Table 1). Genotyping was carried out as multiplexed assays using the Sequenom MassARRAY iPLEX Gold system, therefore reducing the costs and time associated with the genetic analysis to sample sets of 384 being analyzed and scored in less than 5 days. Chips were run on a matrix-assisted laser desorption/ionization—time-of-flight mass spectrometer and the mass automatically converted to the allele call. One of the SNPs (rs10931936) was genotyped using a TaqMan SNP genotyping allelic discrimination assay (C___2960444_10). Reactions were carried out at standard conditions and analyzed using SDS software. Quality checks including duplicate samples, water, and positive controls were undertaken. Using the published estimates of per allele ORs for breast cancer from the most recent GWAS (18) for the majority of the SNPs (all except rs713588), we calculated the relative risk of developing breast cancer for each genotype. For example, for FGFR2 the published relative allele frequency (RAF) of the risk allele T is 0.42 and the per-allele OR is 1.43. The frequency of genotypes TT, TC, and CC is therefore 0.17 (0.42^2), 0.49 ($2 \times 0.42 \times 0.58$), and 0.34 ($0.58^2$), respectively, the average population risk relative to genotype CC is 1.39 ($0.17 \times 1.43^2 + 0.49 \times 1.43 + 0.34 \times 1.00$), and the risk relative to the general population for each of the 3 genotypes is 1.47 ($1.43^2/1.39$), 1.03 (1.43/1.39), and 0.72 (1/1.39), respectively. We then calculated a combined risk score for each woman, on the basis of her SNPs, by multiplying her individual risk ratios together.

Power calculation

The study was powered to identify 5 to 600 breast cancers over 2 screening rounds and therefore 60,000 women were required to deliver this over a 3-year screening round.

Table 1. Breast cancer susceptibility SNPs, published risk allele frequencies and associated ORs, and observed genotype frequencies in the 478 participants who have provided a DNA sample

		Published risk alleles, risk allele frequencies, and per allele ORs for developing breast cancer			Genotype frequencies among the 478 who provided DNA samples		
SNP	Gene/locus	Risk allele	RAF (18)	OR (18)	0 risk alleles, %	1 risk allele, %	2 risk alleles, %
rs2981579	*FGFR2*	T	0.42	1.43	35	50	15
rs10931936	*CASP8*	C	0.74	0.88	8	37	55
rs3803662	*TOX3*	T	0.26	1.3	55	38	7
rs889312	*MAP3K*	C	0.28	1.22	51	39	10
rs13387042	*2q*	A	0.49	1.21	25	52	23
rs1011970	*CDKN2A*	T	0.17	1.09	70	28	2
rs704010	*10q22*	A	0.39	1.07	38	48	14
rs1156287	*COX11*	A	0.71	1.1	8	36	56
rs11249433	*NOTCH*	C	0.42	1.08	35	45	20
rs614367	*11q13*	T	0.15	1.15	72	25	3
rs10995190	*10q21*	G	0.85	1.16	2	23	75
rs4973768	*3p24*	T	0.47	1.16	32	48	20
rs3757318	*ESR1*	A	0.07	1.3	89	11	0
rs1562430	*8q24*	G	0.42	0.85	41	43	16
rs8009944	*RAD51L1*	A	0.75	0.88	7	41	52
rs909116	*LSP1*	T	0.53	1.17	21	51	28
rs9790879	*5p12*	C	0.40	1.1	34	51	15
rs713588	*10q*	A	0.60	0.86	16	48	36

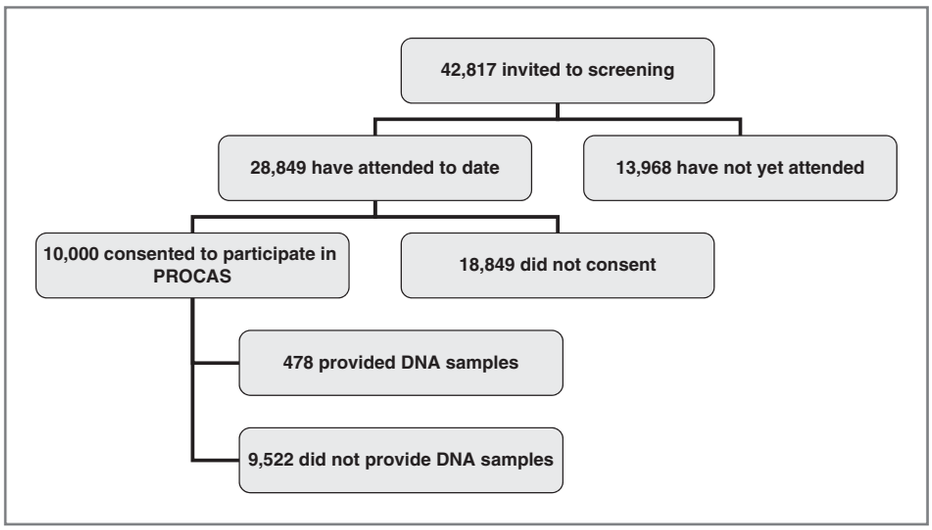


Figure 1. Consort diagram showing recruitment into PROCAS via the NHS Breast Screening Program in Manchester.

Socioeconomic class

Socioeconomic class was assessed using deprivation scores. Deprivation was assessed from participants' postcodes using the English Indices of Multiple Deprivation 2010 (http://www.imd.communities.gov.uk/; ref. 27). This is an area-based measure of socioeconomic status, specifically "material deprivation," high levels of which are associated with low uptake of a wide range of health services.

Results

We report the feasibility of collecting risk information in the context of the NHSBSP, presenting results for the first 10,000 recruited women. A consort diagram showing the numbers eligible and recruited into PROCAS and the DNA substudy are given in Fig. 1. A total of 42,187 women were invited for screening of which 28,849 (68.4%) attended. Average uptake to the study was 34.7% (10,000 attending women gave informed consent and entered the study), but having an additional member of staff, dedicated to study recruitment, based at the screening site increased average uptake from 31% to 50% at 3 sites where we were able to facilitate this. Analysis of average uptake and deprivation, by screening site, suggests a strong (negative) correlation between mean deprivation score and uptake to PROCAS (Pearson correlation coefficient, $\rho = -0.73$, 95% Class Interval $= -0.91$ to -0.37), that is, uptake is generally lower in areas with the greatest deprivation. The median deprivation score in all women who were approached to join PROCAS (i.e., screening attendees) was 23.0 [interquartile range (IQR) 13.1–42.8], but in those who chose to participate in PROCAS, it was 18.5 (IQR, 11.2–35.7), and in those who chose not to participate, it was 25.8 (IQR, 14.0–44.8). The difference is significant ($P < 0.0001$, Mann–Whitney test). The median age of participants was 58 years (IQR, 52–64) with the distribution evenly spread across the screening age range but with some tailing off in the youngest and oldest age groups, and a peak (31%) at age 50 to 54 years. The percentage of participants in the age groups 45 to 49 years, 50 to 54 years, 55 to 59 years, 60 to 64 years, 56 to 69 years, and 70 or more years, respectively, was 7%, 31%, 20%, 20%, 16%, and 6%. The majority (91%) were white and the remainder mainly Black/Black British (1.3%) or Asian/British Asian (1.5%). A minority of women (4%) gave no answer to the ethnicity question. Of 10,450 women aged 47 to 52 invited for their first screen 6,895 (66%) attended for screening and of those 2,971 (43%) joined PROCAS. Since the first 10,000 recruits, overall recruitment of attendees has increased to between 41% and 45%, with the highest proportion (52%) again in the youngest age group. Women could state whether they wished to be informed of their breast cancer risk; 94.96% indicated that they did, 0.68% indicated no preference, and 4.36% did not wish to know their risks. Subsequently, 29 of those originally indicating that they would like to be informed of their risks decided that they did not wish to know. On the basis of the information provided by participants via the questionnaires, the median 10-year risk of breast cancer in the 10,000 women, generated from the Tyrer–Cuzick program, was 2.65% with a range of 0.76% to 24.3% (IQR, 2.10–3.45). The distribution of the Tyrer–Cuzick risk estimates is shown in Fig. 2. One hundred and seven women (1.07%) had a 10-year risk of 8% or more and therefore have a high breast cancer risk (i.e., would be classified as high risk according to the U.K. NICE guidelines; ref. 28), with a further 8.20% having moderately increased risk (5% to 8%). A total of 19.84% of women had risks below 2%. Mammographic percent dense area, assessed visually and recorded using the Visual Analogue Scale, ranged from 0.63% to 97.25% (Median, 25.4%; IQR, 14.0–40.1). The distribution of mammographic percent dense area is shown in Fig. 3. Percent dense area was 60% or greater in 8.3% of women.

Identification and counseling of high-risk women

Two groups of women were identified as having a high breast cancer risk; 107 with a Tyrer–Cuzick 10-year risk of 8% or higher and 64 with a Tyrer–Cuzick risk of 5% to 8%,

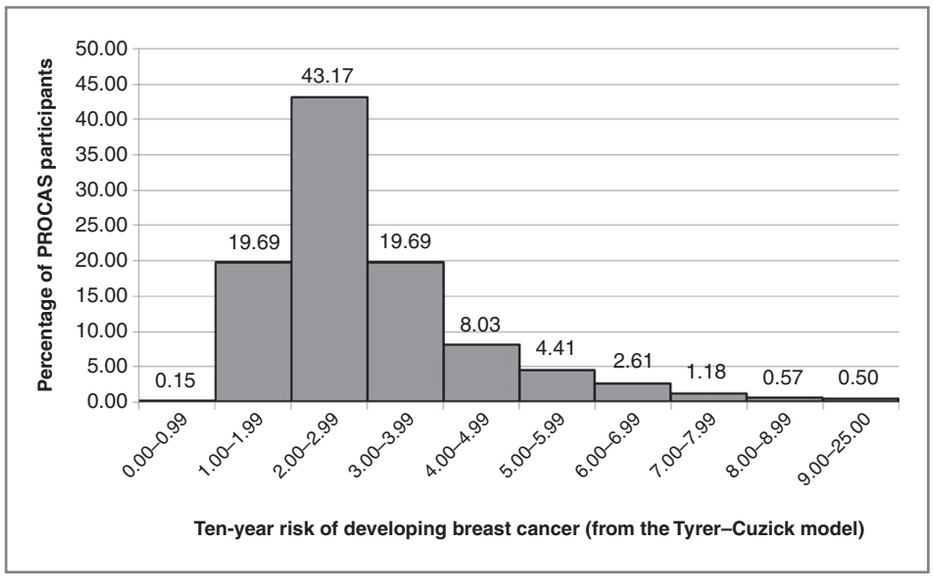


Figure 2. Predicted 10-year risk of developing breast cancer for the first 10,000 PROCAS participants (calculated from risk assessment questionnaires using the Tyrer–Cuzick model).

and mammographic percent dense area 60% or more. Thus, 1.71% of the participants were identified as having a high breast cancer risk and considered eligible for an invitation to discuss their risk with a clinician (DGRE/AH). A summary of the numbers identified, numbers invited, numbers attending, and numbers eligible for risk-reducing interventions are given in Fig. 4. The majority of women (91.8%) had indicated, when consenting to the study, that they wished to be informed of their risk, but some later changed their minds (9 of 149, 6.04%), failed to attend (2 of 149, 1.34%), or have not yet responded to the invitation (16 of 149, 10.74). To date, 121 women have undergone risk counseling, either by telephone or at a clinic appointment, during which the details provided on the questionnaire (information on family history, individual hormonal, and lifestyle factors) were verified. As a result, a number of women (16 of 121, 13.22%) were reassessed as moderate risk. The women confirmed as high risk (105 of 121, 86.78%) were all offered tailored risk-reducing advice, such as to lose weight if overweight or to consider stopping hormone replacement therapy following consultation with their GP. Those eligible for risk-reducing interventions were identified and the appropriate options discussed. These were one or more of the following; referral for 18 monthly screening, participation in a weight loss study (http://www.genesisuk.org/media-centre/articles/The%20Intermittent%20diet%20.html; ref. 29), or participation in IBIS-II (a randomized chemoprevention study of anastrazole vs. tamoxifen, http://www.ibis-trials.org/; ref. 30). As a result, several women have chosen to participate in IBIS-II [11 of

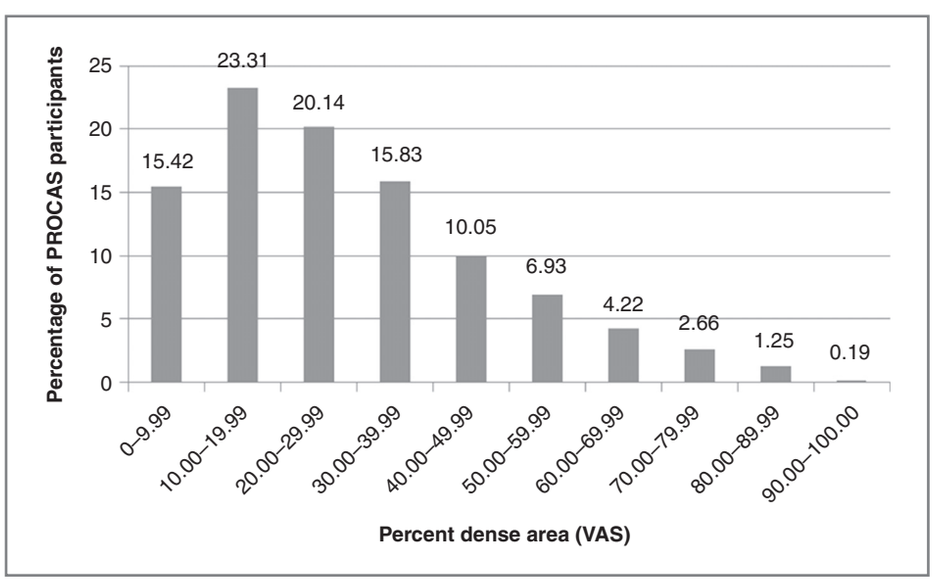
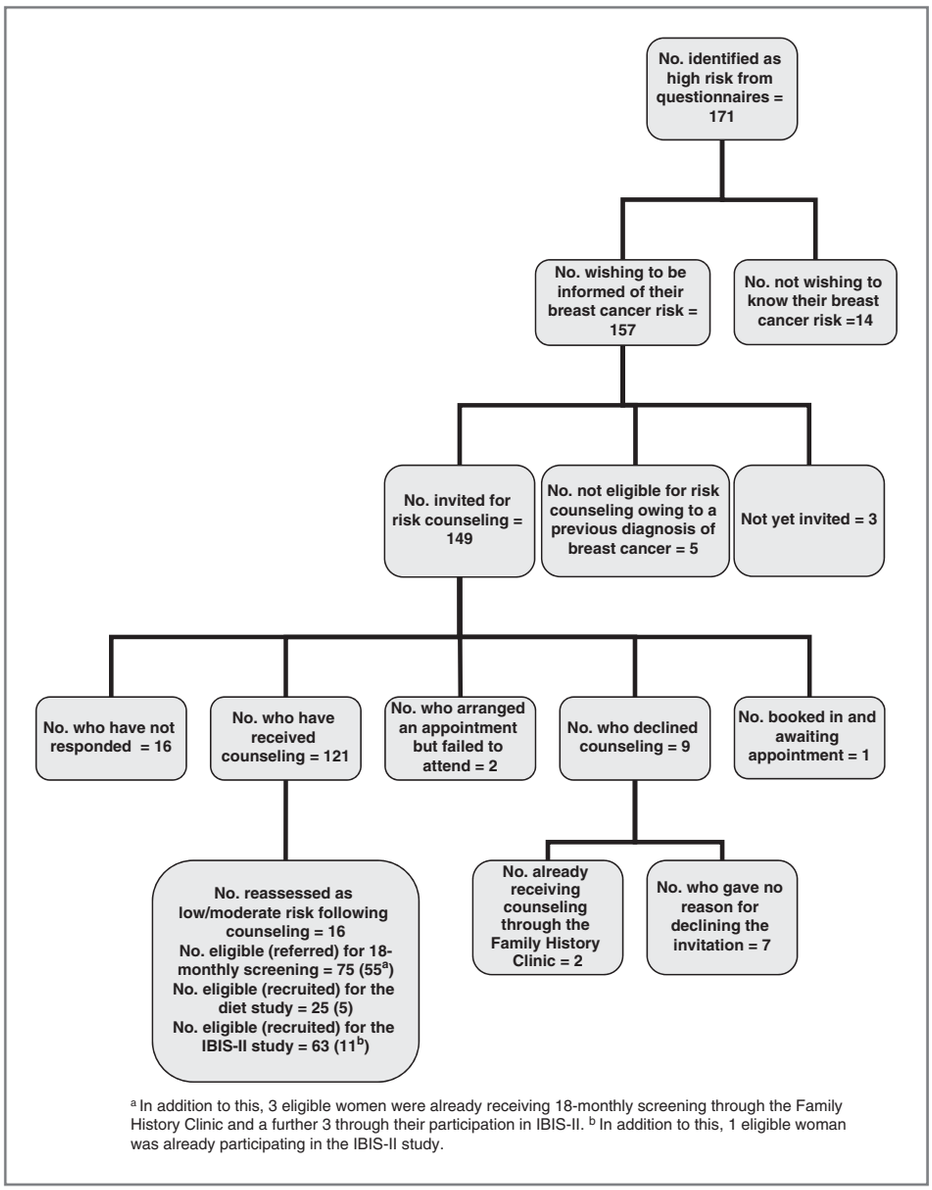


Figure 3. Distribution of mammographic density in the first 10,000 participants, as assessed by the Visual Analogue Scale (VAS).



[a] In addition to this, 3 eligible women were already receiving 18-monthly screening through the Family History Clinic and a further 3 through their participation in IBIS-II. [b] In addition to this, 1 eligible woman was already participating in the IBIS-II study.

Figure 4. Consort diagram showing numbers identified as having a high risk of developing breast cancer, take-up of invitation to counseling, and risk-reducing interventions.

63 eligible (17%)] or a dietary intervention study [5 of 25 eligible (20%); Fig. 4], and a larger number (75 of 121) have been offered 18 monthly screening.

SNPs

So far, 478 of the first 10,000 PROCAS participants have consented to enter the DNA substudy and provided a saliva sample for DNA testing. The overall risk score for each woman (her estimated relative risk of developing breast cancer compared with the general population) was obtained by multiplying her individual per allele relative risks together. The IQR for this SNP-based estimate of breast cancer relative risk was 0.66 to 1.20, whereas for the same 478 women, the Tyrer–Cuzick estimate of breast cancer risk, relative to the population average of 2.7%, was 0.84 to 1.51. The IQR of the corresponding Tyrer–Cuzick estimates of absolute breast cancer risk was 2.26% to 4.07%. If it was assumed that every woman has a 10-year absolute risk of developing breast cancer of 2.7% (i.e., roughly the population average), adding the SNPs information gave modified individual risk estimates with an IQR of 1.78% to 3.24%. Using the individual risk estimates from the Tyrer–Cuzick model, instead of the population mean, to represent the underlying risk led to modified individual risk estimates with an IQR of 1.83 to 4.37. The distribution of these SNP-based risk estimates together with those obtained from the Tyrer–Cuzick model are shown in Fig. 5. The addition of SNPs to the Tyrer–Cuzick model broadened the distribution of risk estimates so that fewer individuals are in the average risk category. Furthermore, greater numbers were

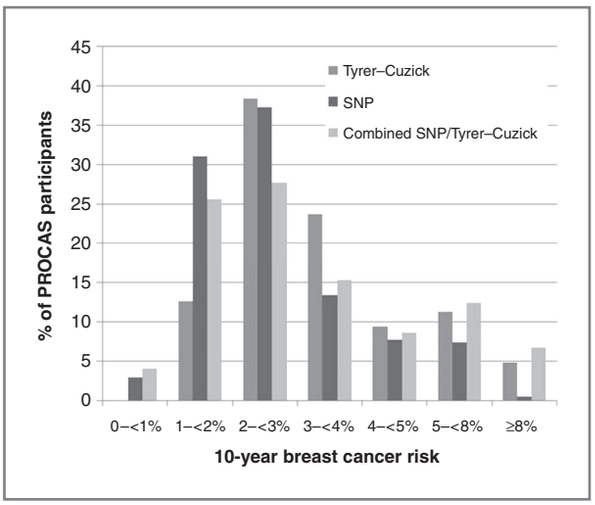


Figure 5. Predicted breast cancer risk from the Tyrer–Cuzick model (based on classic breast cancer risk factors), predicted breast cancer risk based on the SNPs alone (assuming that each woman has average breast cancer risk), and predicted breast cancer risk from the Tyrer–Cuzick model (crudely adjusted to take account of individual SNPs) for the 478 women who provided DNA samples.

assigned to both the highest and lowest risk categories, suggesting that the incorporation of SNPs information into the Tyrer–Cuzick model may lead to better discrimination. Overall, in the 478 who provided a DNA sample, there was no correlation between the SNPs based risk estimates and those from the Tyrer–Cuzick model ($\rho = 0.02$), between the SNPs based risk estimates and mammographic density ($\rho = -0.09$), or between the risk estimates from the Tyrer–Cuzick model and mammographic density ($\rho = 0.07$). We have since typed a further 515 women (later recruits) for the SNPs and had very similar results.

Discussion

In this ambitious entirely population-based study, we show that it is feasible to undertake detailed individual breast cancer risk evaluation and feed this back to high-risk individuals in the context of the U.K. NHSBSP. Average uptake to the study was 35%, somewhat lower than in the CADET II study (31), which obtained average recruitment of 46% using a very similar process to recruit participants, but higher than the U.K. Collaborative Trial of Ovarian Cancer Screening in which uptake averaged 25% (32). As in CADET II, we found that recruitment was increased when an additional member of staff was based at the screening site. Although the uptake of 35% is potentially disappointing in terms of wide-scale population applicability, it represents a pragmatic approach largely depending on an "opt in" rather than a proactively offered intervention. Later we predict greater uptake if the program is introduced more widely and screening interval depends upon risk assessment. Unsurprisingly, there was also a clear association between uptake and social deprivation. The recruitment rate among screening attendees in the area where the mean deprivation score for study participants was the lowest was 60% higher than in the area where the mean deprivation score was the greatest. This is consistent with a number of other studies involving uptake of health screening and interventions (33–36) but is of concern because although women in the most deprived social groups have a lower incidence of breast cancer (37), they also have poorer survival (38). Any introduction of risk-adjusted breast screening must, therefore, consider how to minimize the potential health-care inequality that might result. Ethnic minorities seem to be reasonably well represented in our study. Mid year population estimates for 2009 from the Office for National Statistics on the ethnicity of female residents aged 50 to 70 in the 5 primary care trusts that the Greater Manchester Breast Screening Program covers (Manchester, Oldham, Salford, Tameside and Glossop, and Trafford; ref. 39) suggest that 90.7% of the population from which we recruited are White British or Irish. In our study 91% self-reported as belonging to this category, but a further 4% did not answer the ethnicity question, so there is some uncertainty about this. Furthermore, these population estimates are experimental. Nevertheless, there is no evidence to suggest that women from ethnic minorities are underrepresented. In terms of our "vision" of offering risk assessment at inception of screening at 47 to 50 years of age, the uptake in this age group is by far the highest without a proactive approach, which we believe would result in an uptake among screening acceptors of close to 80%. Attempts at "opportunistic" health interventions are notoriously unreliable and without the organization of a national screening program would never approach the levels of uptake and would be even more likely to result in biases toward higher socioeconomic classes. There are initiatives in the United Kingdom to address the uptake of screening in lower socioeconomic classes and in ethnic minorities.

The range of 10-year risks identified by the Tyrer–Cuzick program in 10,000 women is quite narrow with 43.2% of all women having a 10-year risk between 2% and 3%. These risks are calculated from family history information as well as standard reproductive risk factors, but when risk information from SNPs was added to that from the Tyrer–Cuzick model a wider spread was generated, suggesting that adding SNPs to the Tyrer–Cuzick model might lead to better discrimination. Two other studies using 7 (40) and 15 susceptibility SNPs (41) also found no association between being assessed as high risk using one of the established breast cancer risk prediction models, such as the Gail (10, 11) and Tyrer–Cuzick (9), and being assessed as high risk on the basis of SNPs. The addition of SNPs information to the Gail model led to better discrimination (40, 42), although the magnitude of the improvement was small; for one study (40), the area under the curve (AUC) increased from 0.557 to 0.594 with the addition of SNPs to the classic Gail risk model ($P < .001$) and for the other, adding 7 SNPs to the National Cancer Institute's Breast Cancer Risk Assessment Tool increased the AUC from 0.607 to 0.632 (42). The fact that there is little association between the 3 methods of

assessing breast cancer risk (percent dense area, Tyrer–Cuzick model, and SNPs) is promising as it suggests that the addition of mammographic density and SNPs to the Tyrer–Cuzick model may lead to improved overall performance (by adding new, independent, information). The issue of how information on mammographic density and SNPs might be used to further develop the Tyrer–Cuzick model will be explored in detail, and the predictive ability of the expanded model assessed, when the data from this study are suitably mature and a sufficient number of breast cancers have occurred.

We have also shown that the assessment of mammographic density can be incorporated into routine screening practice. It is likely that addition of mammographic density to standard risk factors and DNA testing will further improve the precision of risk assessment, although ideally this will involve an automated measure of mammographic density that can be made on digital mammograms that are now carried out in many areas of the NHSBSP. We are currently evaluating 3 automated methods of measuring density and comparing these with a well-established computer-assisted approach (Cumulus 4.0 software, Martin Yaffe, Sunnybrook Health Sciences Center, Toronto, Canada). The goal of incorporating mammographic density into risk models has so far had limited success with the Gail model (16, 43).

Another feature of this study has been the ability to deliver risk counseling to those at highest risk. Although the population has been already self-selected to some extent, the uptake of risk information has been very high, even though women had at least 2 opportunities to opt out of receiving counseling. To our knowledge, this is the first time that personalized risk prediction and personalized delivery have been incorporated into a population screening program. We have also shown that acceptance of more intensive mammographic screening is high (81% of eligible women), and that uptake to prevention studies is relatively low (17%–20%) in the women we identified as high risk. Nevertheless, uptake to PROCAS and to the preventive interventions offered was considerably greater than in a recent study on risk assessment in a population setting from Germany (44) in which 17.7% ($n = 446$) of participants met the eligibility criteria for IBIS-II, but only 202 of 445 (45%) wished to be informed of their breast cancer risk and only 0.7% (3/446) eventually entered IBIS-II.

Ultimately the incorporation of risk SNP results and mammographic density into current risk prediction models will require further ongoing research and the maturation of prospective data from this and other cohorts. We have shown that it is feasible to undertake detailed breast cancer risk assessment within the context of a National Screening program (the NHSBSP) and also that this is acceptable to women, and that those identified as high risk are willing to act on the information given. Further research is already underway on the methodologic issue of how the SNP results and assessments of mammographic density might be incorporated into the Tyrer–Cuzick model. The performance of this and existing risk prediction models will be assessed when this study has sufficient follow-up data from this and other planned studies.

Disclosure of Potential Conflicts of Interest

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Authors' Contributions

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