Breast Cancer Risk in Young Women in the National Breast Screening Programme: Implications for Applying NICE Guidelines for Additional Screening and Chemoprevention

D. Gareth Evans, Adam R. Brentnall, Michelle Harvie, Sarah Dawe, Jamie C. Sergeant, Paula Stavrinou, Susan Astley, Mary Wilson, John Ainsworth, Jack Cuzick, Iain Buchan, Louise S. Donnelly, and Anthony Howell

Abstract

In the United Kingdom, women at moderate and high risk of breast cancer between the ages of 40 and 49 years are eligible for annual mammographic screening and preventive therapy with tamoxifen. Here, we estimate the numbers of women in a population eligible for this service and the proportion of breast cancers detected in this group compared with the whole population. Women <50 attending for mammographic screening in the National Health Service Breast Screening Programme (NHSBSP) completed a risk questionnaire. The proportion at moderate and high risk according to National Institute of Health Care Excellence (NICE) guidelines was estimated. An estimate was also made using a different model of risk estimation (Tyrer–Cuzick). The numbers of cancers detected in the moderate/high risk groups were compared with numbers detected in the whole population. Completed questionnaires were available for 4,360 women between ages 46 and 49 years. Thirty women (0.7%; 95% confidence interval [CI], 0.5–1.0%) were at high risk and 130 (3.0%, 2.5–3.5%) were at moderate risk according to NICE guidelines. Thirty-seven cancers were detected by mammography in the whole group. Five of these were found in the moderate-/high-risk group giving a 3.2-fold increase in detection compared with the standard risk group. More women were assigned to the moderate- or high-risk group using the Tyrer–Cuzick model (N = 384), but the numbers of cancers in this group were not appreciably increased (N = 8). Systematic assessment of family history in primary care or through population-based screening will identify appreciable numbers of women in their forties, eligible for additional surveillance and chemoprevention.

Introduction

Breast cancer is a major burden to society and individuals with 49,936 women developing the disease in the United Kingdom (population 60 million) in 2011, and 11,684 dying (1). Although deaths from breast cancer have been decreasing in many Western countries, the incidence of the disease continues to increase. In particular, in countries with historically low incidence breast cancer rates are rising rapidly, making it now the most prevalent cancer in the world. The increase in incidence may well be related to changes in weight and reproductive patterns associated with Western lifestyles. Indeed, there is evidence from genetic studies in the United States, Iceland, and the United Kingdom (2–4) of a 3-fold increase in incidence not only in the general population but also in those at the highest level of risk with BRCA1 and BRCA2 mutations in the last 80 years (4). Breast cancer rates are also rising in women who have not generally been screened, such as those in their forties (1). Although cure rates continue to improve, the cost of treating breast cancer is considerable for both the women concerned and the health service. Therefore, there is a need not only to predict which women will develop the disease but also to apply drug and lifestyle measures to prevent the disease.

Currently, women ages 47 to 73 years are invited for breast screening with 3-yearly mammography in the United Kingdom.
Kingdom. A recent review of the National Health Service Breast Screening Programme (NHSBSP) estimated that it saved around 1,300 lives annually (5). Although, the vast majority of women in the United Kingdom receive only 3-yearly screening invitations, more frequent screening has been recommended by the National Institute of Health Care Excellence (NICE; ref. 6) since 2004 for those at increased familial risk. This includes annual mammography ages 40 to 49 years for women at moderate risk and annual screening ages 40 to 60 years in those at high risk (annual MRI is recommended ages 30 to 50 years in mutation carriers and those with at least a 30% chance of a mutation in BRCA1/2 or TP53). This guidance has just been updated and the high-risk recommendations are already being implemented in the NHSBSP as highlighted recently (7). Recent evidence suggests that stratification of risk and screening frequency is likely to be more cost effective (8–10). A substantial amount of breast cancer is preventable but chemoprevention has, thus far, not been applied to moderate-/high-risk UK women outside randomized trials. Chemoprevention involves 5 years of the selective estrogen receptor modulators (SERM) tamoxifen or raloxifene, which reduce risk by 35% to 40% (11–13). NICE have reviewed chemoprevention for women at moderate/high familial breast cancer risk (≥17% lifetime). Final guidance states: “offering/considering” tamoxifen/raloxifene for women at high/moderate risk (13, 14). It is difficult to apply the NICE guidelines for additional surveillance or offer of chemoprevention within the NHS because there is currently no systematic mechanism for identifying moderate-/high-risk women. Many/most moderate-/high-risk women remain unaware of their breast cancer risk and only those women who present with concerns about family history get referred to Family History Clinics (FHC) where they receive additional screening (every 12–18 months) and could now be offered chemoprevention.

We are undertaking an NIHR funded study (PROCAS, Predicting Risk Of Cancer At Screening) in Greater Manchester, which is investigating the feasibility of assessing and communicating breast cancer risk to women in the NHSBSP (15). More than 53,000 women have been recruited to date from those invited for mammography (39% uptake). Interestingly, 95% of recruited women indicated that they wished to know their risk of breast cancer. Because risk is not estimated in the general population, it has not been possible to assess the proportion of women in the National Screening Programme who are at moderate or high risk by NICE criteria, or by models of risk, which include additional factors to family history. An important age group in respect of the NICE guidance are those ages 40 to 49 years. Of these women, those identified as moderate/high risk would gain access to annual mammography screening as well as being considered for chemoprevention with tamoxifen. The greatest population impact of tamoxifen would be in this age group, with long-term risk reduction and fewer risks of serious complications such as endometrial cancer and thromboembolism (11–13). In PROCAS, we have assessed family history by questionnaire in 4,360 women attending the NHSBSP ages 46 to 49 years, and identified those that meet either the NICE algorithm for moderate or high risk, or who meet the 10-year risk thresholds at age 40 years of 3% for moderate risk and 8% for high risk, assessed using the Tyrer–Cuzick model. We also assessed whether women were diagnosed with breast cancer in the first 3 years of PROCAS and whether women had previously had risk assessment in the genetic and family history services.

Materials and Methods

We devised a two-page questionnaire to collect family history, hormonal, and lifestyle risk factors for breast cancer (15). Women invited for routine mammographic screening across 15 screening areas in Greater Manchester were mailed the questionnaire, study information, and a consent form. Consent was obtained at the time of screening. Information on each questionnaire was imported into the study database (and checked for inconsistencies) and the risk estimated automatically using the Tyrer–Cuzick model (16). The study was approved by the Central Manchester Research Ethics Committee (ref: 09/H1008/81). Only women <50 years of age were included for the main analysis for reasons given above.

The NICE algorithms (Appendix; ref. 6) were used to assess whether first-degree relative (FDR) or combined FDR and second-degree relative (SDR) family history met either the high- or moderate-risk criteria. NICE guidance advises to use a woman’s 10-year risk at their current age in their mid to late forties adjusted to the 10-year risk at age 40 years (6). Four examples in Table 1 compare risk from NICE guidelines and Tyrer–Cuzick. The high-risk examples show that the Tyrer–Cuzick relative risk decreases as a woman gets older. The moderate-risk examples show that the relative risk is more constant as a woman gets older. Partly on this

<table>
<thead>
<tr>
<th>NICE</th>
<th>Mother age</th>
<th>Sister age</th>
<th>10-year risk age 40</th>
<th>10-year risk age 49</th>
<th>Relative risk age 40</th>
<th>Relative risk age 49</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>35</td>
<td>35</td>
<td>8.6%</td>
<td>7.8%</td>
<td>5.4</td>
<td>3.0</td>
</tr>
<tr>
<td>High</td>
<td>45</td>
<td>45</td>
<td>4.8%</td>
<td>6.3%</td>
<td>3.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Moderate</td>
<td>50</td>
<td>50</td>
<td>3.7%</td>
<td>5.8%</td>
<td>2.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Moderate</td>
<td>35</td>
<td>—</td>
<td>3.3%</td>
<td>4.8%</td>
<td>2.0</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Table 1. Examples to compare examples of family histories that meet moderate and high risk in NICE algorithm with the equivalent risk in Tyrer–Cuzick from an example pedigree.
basis the following strategy was used to convert a risk age 46 to 49 years to a high or moderate category, based on the NICE guidance for a woman ages 40 years. First, an absolute risk of 8% was taken for high risk, as although the baseline incidence increases due to age, relative risk from family history decreases as a woman gets older as she is less likely to have inherited a genetic predisposition. Second, the boundary for moderate risk was taken to be the same relative risk for each year at ages 46 to 49 as 40 years. For example, the population 10-year risk at age 46 years is 2.25% and, therefore, the 10-year moderate-risk threshold with a 1.9-fold risk would be 4.3% (Table 2). The population risk in the Tyrer–Cuzick model age 40 years was approximately 1.6%, so moderate risk is taken to be a relative risk more than 1.9 (3.0/1.6) but an absolute risk less than 8.0%. The absolute risk cutoffs used are shown in Table 2, for other ages the same strategy of multiplying the population 10-year risk by 1.9 could be used to determine moderate risk. A sensitivity analysis of the high-risk group was undertaken by plotting the percentage of women and breast cancers diagnosed for different 10-year cutoffs.

Breast cancers in all women [ICD10 codes C50 and D05; invasive and ductal carcinoma in situ (DCIS)] were actively sought through the NHSBSP reporting system. Breast cancer rates, sensitivity, and specificity were assessed in each risk category and by closeness of affected relatives. In addition, we interrogated our FHC attendance against the local population estimates from the National Census to assess the number of women who have already identified themselves or more distant relatives affected. To date, 37 breast cancers have been detected in this population; 24 of which occurred at the prevalent screen; 4 were interval cancers, and 9 were detected at the second mammography screen.

Table 2 shows the main results by NICE and Tyrer–Cuzick categories. Thirty women [0.7%; 95% confidence interval (CI), 0.5%–1.0%] met the NICE algorithm for high risk and 130 (3.0%; 95% CI, 2.5%–3.5%) were moderate risk. Using the Tyrer–Cuzick algorithm the 10-year high risk threshold of 8% was met by 37 women (0.8%; 95% CI, 0.6%–1.2%) and 347 (8.0%; 95% CI, 7.2%–8.8%) met the moderate-risk category. Thus, around 3.7% (95% CI, 3.1%–4.3%) of women ages 46 to 49 years would meet NICE moderate-/high-risk criteria following the NICE algorithm; 8.8% (95% CI, 8.0%–9.7%) when using Tyrer–Cuzick.

The largest difference was that 240 women were identified by the Tyrer–Cuzick groupings to be at moderate risk that were not identified by the NICE algorithm. However, the proportion of breast cancer events was similar in both the NICE and Tyrer–Cuzick categories. The OR in the NICE moderate or above category versus other was 4.2 (95% CI, 1.4–10.0); for the Tyrer–Cuzick model it was 2.9 (95% CI, 1.2–6.1). Furthermore, with the NICE algorithm the 160 (3.7%) in the moderate- or high-risk groups identified 5 of 37 (13.5%; 95% CI, 5.1%–26.8%) of the breast cancers occurring after enrollment. The Tyrer–Cuzick group of 384 (8.8%) moderate or high risk identified 8 of 37 (21.6%, 95% CI, 10.5%–36.5%) of the breast cancers occurring after enrollment. These compared with 20 of 37 (54.1%; 95% CI, 38.1–69.4) of cancers that occurred in 1,327 (30.4%) of women with any blood relative, including 5 with only third or more distant relatives affected.

The distribution of reproductive risk factors in all women identified by one or both risk assessments as being at least moderate risk are shown in Table 5. This table also shows correlations between risk categorization between NICE algorithm and Tyrer–Cuzick 10-year risks. The NICE categorization does not use parity, age at menarche, or menopause. It can be seen that these factors explain some of the difference in categorizations with Tyrer–Cuzick. For example, women who were found to be moderate risk by Tyrer–Cuzick but not by the NICE algorithm were more likely to be nulliparous (OR, 1.5; 95% CI, 1.1–2.1).

The Tyrer–Cuzick model provides a continuous range of absolute risks, and so it is possible to explore the effect of different cutoffs in absolute risk for any age. If a 3% 10-years risk is used as the threshold at all ages (rather than the 3% 10-year risk at age 40 years) then 17 of 37 (45.9%, 95% CI 30.6%–61.9%) of the cancers are identified by assessing 1,269 women (29.1%; 95% CI, 27.8%–30.5%). Conversely, no breast cancers occurred to date in 583 women (13.4%; 95% CI, 12.4%–14.4%) with a Tyrer–Cuzick 10-year risk of

### Table 2. Ten-year risk at age in forties in Tyrer–Cuzick with equivalent risks ages 46 to 49 years

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Age 40</th>
<th>Age 46</th>
<th>Age 47</th>
<th>Age 48</th>
<th>Age 49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>3.0</td>
<td>4.3</td>
<td>4.5</td>
<td>4.6</td>
<td>4.8</td>
</tr>
<tr>
<td>High</td>
<td>8.0%</td>
<td>8.0%</td>
<td>8.0%</td>
<td>8.0%</td>
<td>8.0%</td>
</tr>
</tbody>
</table>
<1.8% at initial assessment. Using the 2.5% 10-year risk cutoff suggested by Cambridge (17), 23 of 37 (62.2%; 95% CI, 46.1%–76.6%) of the cancers are identified by assessing 2,243 women (51.4%; 95% CI, 50.0%–52.9%). A sensitivity analysis of the Tyrer–Cuzick high-risk group is available in the Supplementary Figure.

In our FHC that covers Central and South Manchester and Trafford, we compared the number of women we currently see who have been identified with at least moderate risk by NICE criteria ages 40 to 49 years against the Census record of women in that age group. In Trafford, there are currently 203 women at moderate risk representing 1.2% of the population. In Central and South Manchester, there are 213 women representing 0.8% of the population. Of the 160 women meeting NICE guideline criteria only 28 (17.5%; 95% CI, 12.2%–23.9%) had been seen in the FHC or clinical genetics service previously, indicating that only one sixth of those at moderate or high risk of breast cancer had come forward for assessment. This dropped to only 2 of 31 (6.5%; 95% CI, 1.1%–18.6%; P = 0.02) of those whose family history risk was predominantly paternally related. Of those at high-risk, 10 of 30 (33.3%; 95% CI, 18.3%–51.1%) had been previously assessed compared with 19 of 130 (14.6%; 95% CI, 9.3%–21.4%) of those at moderate risk, so those at high-risk had a 2.9 (95% CI, 1.2–7.1)-fold likelihood of being FHC assessed.

To assess whether women identified at increased risk may have gone for breast cancer risk assessment elsewhere, we checked for this in the 257 women at 8% 10-year risk in the whole PROCAS cohort who had been interviewed by study clinicians (D.G. Evans and A. Howell). Although only 46 of 257 (18%) had been assessed previously in our FHC, none of the remaining women were aware of their high-risk status or had undergone a risk assessment elsewhere. A small proportion of women interviewed at both high and low risk had minor adjustments made to their 10-year risks based on a few inaccurate details on their questionnaire. However, 95% remained in the same risk category. Women at high-risk received a detailed letter outlining their risks and potential options to deal with these. Copies of these letters were sent to the primary care physicians.

We finally assessed the potential impact in North America of using the 1.65% 5-year threshold approved by the FDA in North America for chemoprevention with tamoxifen. Of note, 961 of 4,360 (22%) of women reached the equivalent 3.3% 10-year risk threshold in Tyrer–Cuzick. This would have identified 13 of 37 (35%) of the breast cancers. In the whole dataset of enrollees ages 46 to 73 years 14,281 (29%) of 49,288 women without breast cancer at entry met the 3.3% threshold. Of women >65 years of age, 3,526 of 11,146 (32%) met tamoxifen criteria. Again in the expanded full population 637 (1.3%) met the high-risk 8% 10-year NICE threshold.

Discussion

Only one study to our knowledge has identified the proportion of the female population who are at moderate or high risk of breast cancer and, hence, eligible for increased surveillance and the offer of chemoprevention as per NICE guidance (18). We have shown that among women entering the PROCAS population-based screening cohort study in Greater Manchester, 0.7% met high- and 3.0% moderate-risk criteria. Only 5 of 37 (13.5%) of the
breast cancers would have been identified in 160 women if just these elevated risk women had been screened from age 46 years onwards. The odds of breast cancers was 5.7 (95% CI, 1.9–14.7) times higher than 17 of 3,033 (0.6%) of those diagnosed in women with no family history of breast cancer. These finding are at an early stage in follow-up and more time is required to assess whether with further cancers NICE guidance on extra screening is justified (7).

The present study has highlighted a disparity between the NICE algorithm and the 10-year risk thresholds as calculated by Tyrer–Cuzick. This is not surprising as the NICE algorithm was set to identify women based on family history alone who would usually meet the 10-year threshold. The additional numbers identified by Tyrer–Cuzick are those who in addition to a less significant family history had additional risk factors such as the three that developed breast cancer with a single FDR aged in their forties. The number of relatives of breast cancer patients was assessed the number of relatives of breast cancer patients in the Netherlands and using UK criteria of the time (22). They found that would meet familial breast cancer screening criteria at the time (22). This was based on only 196 replies in this age range and the criteria were then stricter than NICE as there was a necessity for an average age of <60 years when there were two affected relatives. In a study of 8,019 practice patients ages 35 to 69 (21), only 4.8% admitted to having an FDR with breast cancer, age <70 years. This was somewhat less than the 9.2% with any FDR in the present study, although this reduces to 8.0% when the 53 mothers with breast cancer age of >70 years were excluded. The general practice (GP) survey was based on nurses asking family history in those attending for health checks and may, thus, have some biases to a more health aware population. A different approach was taken by a Dutch study (23) that assessed the number of relatives of breast cancer patients that would meet referral criteria for referral in the Netherlands and using UK criteria of the time (22). They found that 0.25 FDRs would have met eligibility criteria per case of breast cancer in a series of 1,060 breast cancer–affected women. If one assumes that 12.5% women develop breast cancer in their lifetime (1), this might translate to 12.5/0.25 = 3.1% almost identical to the number found at moderate risk in the present study.

Table 3. Baseline characteristics of 4,360 women joining PROCAS ages 46 to 49 years

<table>
<thead>
<tr>
<th>Number</th>
<th>46–47</th>
<th>48–49</th>
<th>Age at Menarche</th>
<th>Parous</th>
<th>Premenopausal</th>
<th>FDR with BC</th>
<th>SDR with BC</th>
<th>More distant history of BC</th>
<th>BMI</th>
<th>HRT use</th>
</tr>
</thead>
<tbody>
<tr>
<td>4,360</td>
<td>1,385</td>
<td>2,983</td>
<td>&lt;12</td>
<td>3,618</td>
<td>3,219</td>
<td>410</td>
<td>649</td>
<td>268</td>
<td>&lt;21</td>
<td>Current use:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>952</td>
<td>(83%)</td>
<td>(74%)</td>
<td>(9.4%)</td>
<td>(14.9%)</td>
<td>(6.1%)</td>
<td>313</td>
<td>304 (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12–13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Previous use:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1,814</td>
<td></td>
<td></td>
<td>1,325</td>
<td></td>
<td></td>
<td></td>
<td>207 (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;13</td>
<td></td>
<td></td>
<td>&gt;25</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1,501</td>
<td></td>
<td></td>
<td>2,330</td>
<td></td>
<td></td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(35%)</td>
<td></td>
<td></td>
<td>400</td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviation: BC, breast cancer.

A number of articles have recommended risk-stratified breast screening (9, 10, 17). One of these suggested using a threshold of 2.5% 10-year risk to start breast screening (17). This would have resulted in 38% of the breast cancers being identified outside screening while excluding 49% of the population ages 46 to 49 years from screening. This is little different to the overall assessments of 24% fewer women being eligible for screening at a cost of 14% fewer screen-detectable cases, although the assessments for the article included women ages 35 to 79 years (17). There have been some previous attempts to assess family history of breast cancer in women at the population level (20, 21). In a study using questionnaires in a general practice (20), 42.0% of patients responded and 1.6% were found to meet familial breast cancer screening criteria at the time (22). This was based on only 196 replies in this age range and the criteria were then stricter than NICE as there was a necessity for an average age of <60 years when there were two affected relatives. In a study of 8,019 practice patients ages 35 to 69 (21), only 4.8% admitted to having an FDR with breast cancer, age <70 years. This was somewhat less than the 9.2% with any FDR in the present study, although this reduces to 8.0% when the 53 mothers with breast cancer age of >70 years were excluded. The general practice (GP) survey was based on nurses asking family history in those attending for health checks and may, thus, have some biases to a more health aware population. A different approach was taken by a Dutch study (23) that assessed the number of relatives of breast cancer patients that would meet referral criteria for referral in the Netherlands and using UK criteria of the time (22). They found that 0.25 FDRs would have met eligibility criteria per case of breast cancer in a series of 1,060 breast cancer–affected women. If one assumes that 12.5% women develop breast cancer in their lifetime (1), this might translate to 12.5 × 0.25 = 3.1% almost identical to the number found at moderate risk in the present study.
We have also assessed the potential impact of using a risk algorithm in the general population in North America. More than 30% of the UK population sampled aged >64 years would have been eligible for tamoxifen use using the FDA threshold. A study from North America has shown that Tyzer–Cuzick substantially outperformed the Gail model (24). Using the similar population structure and breast cancer incidence between the UK and North America it is likely that a similar proportion of North Americans would qualify for chemoprevention. In a study from British Columbia of 4,266 women surveyed, 3.5% of women aged 40 to 79 years were found to have the 8% 10-year risk of developing breast cancer. In our expanded UK population was not overrepresented with family history and that eligibility for chemoprevention and MRI screening may be even higher in North America (25, 26).

A number of breast cancer risk models have been developed in the last 25 years (27). These incorporate known genetic, reproductive, and other risk factors to a greater or lesser extent (Table 6). Gail and colleagues (28, 29) described a risk assessment model, which focuses primarily on nongenetic risk factors with limited information on family history. A model of relative risks for various combinations of the used risk factors (Table 6) was developed from case-control data from the Breast Cancer Detection Demonstration Project (BCDDP). Individualized breast cancer probabilities from information on relative risks and the baseline hazard rate are generated. These calculations take competing risks and the interval of risk into account. The data depend on having periodic breast surveillance. The Gail model was originally designed to determine eligibility for the Breast Cancer Prevention Trial, and has since been modified (in part to adjust for race) and made available on the National Cancer Institute Website (28). The model has been validated in a number of settings and probably works best in general assessment clinics, in which family history is not the main reason for referral (29–31), although it should also be useful in general population screening programs. The major limitation of the Gail model is the inclusion of only FDRs, which results in underestimating risk in the 50% of familial risk with cancer in the paternal lineage and also takes no account of age of onset of breast cancer.

The Claus model (31) and BRCAPRO (32) are primarily genetic models calculating a likelihood of either a putative high-risk dominant gene (31) or of BRCA1 (32). Breast

Table 4. Number identified by family history criteria and risk category with proportions with breast cancer in each risk category, sensitivity, and specificity

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>n (%)</th>
<th>95% CI</th>
<th>BC (%)</th>
<th>Sensitivity (%)</th>
<th>95% CI</th>
<th>Specificity (%)</th>
<th>95% CI</th>
<th>PPV (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE high</td>
<td>30 (0.7)</td>
<td>0.5–1.0</td>
<td>1 (3.3)</td>
<td>0.3–13.9</td>
<td>2.7</td>
<td>0.3–11.4</td>
<td>99.3</td>
<td>99.1–99.5</td>
<td>3.3</td>
</tr>
<tr>
<td>TC high</td>
<td>37 (0.8)</td>
<td>0.6–1.2</td>
<td>1 (2.7)</td>
<td>0.3–11.4</td>
<td>2.7</td>
<td>0.3–11.4</td>
<td>99.2</td>
<td>98.9–99.4</td>
<td>2.7</td>
</tr>
<tr>
<td>NICE moderate</td>
<td>130 (3.0)</td>
<td>2.5–3.5</td>
<td>4 (3.1)</td>
<td>1.0–7.0</td>
<td>10.8</td>
<td>3.5–23.4</td>
<td>97.1</td>
<td>96.6–97.6</td>
<td>3.1</td>
</tr>
<tr>
<td>TC Moderate</td>
<td>347 (8.0)</td>
<td>7.2–8.8</td>
<td>7 (2.0)</td>
<td>0.9–3.9</td>
<td>18.9</td>
<td>8.6–33.4</td>
<td>92.1</td>
<td>91.3–92.9</td>
<td>2.0</td>
</tr>
<tr>
<td>FDR BC</td>
<td>410 (9.4)</td>
<td>8.6–10.3</td>
<td>6 (1.5)</td>
<td>0.6–2.9</td>
<td>16.2</td>
<td>6.8–30.2</td>
<td>90.7</td>
<td>89.8–91.5</td>
<td>1.5</td>
</tr>
<tr>
<td>SDR BC</td>
<td>649 (14.9)</td>
<td>13.8–16.0</td>
<td>9 (1.4)</td>
<td>0.7–2.5</td>
<td>24.3</td>
<td>12.5–39.6</td>
<td>85.2</td>
<td>84.1–86.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Any Rel BC</td>
<td>1327 (30.4)</td>
<td>29.1–31.8</td>
<td>20 (1.5)</td>
<td>0.9–2.3</td>
<td>54.1</td>
<td>38.1–69.4</td>
<td>69.8</td>
<td>68.4–71.1</td>
<td>1.5</td>
</tr>
<tr>
<td>No FH BC</td>
<td>3033 (69.6)</td>
<td>68.2–70.9</td>
<td>17 (0.6)</td>
<td>0.3–0.9</td>
<td>45.9</td>
<td>30.6–61.9</td>
<td>30.2</td>
<td>28.9–31.6</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Abbreviations: BC, breast cancer; PPV, positive predictive value; Rel, relative; T–C, Tyzer–Cuzick.

Table 5. Hormonal and reproductive risk factors in those found in each risk category by NICE algorithm and Tyzer–Cuzick 10-year risks

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>TC</th>
<th>n (%)</th>
<th>BC (%)</th>
<th>Parous (%)</th>
<th>Age birth</th>
<th>Pre-meno (%)</th>
<th>Age meno</th>
<th>Menarche</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td>Other</td>
<td>3,960 (90.8)</td>
<td>29 (0.7)</td>
<td>3,307/3,932 (84.1)</td>
<td>25.2 (5.5)</td>
<td>2,902 (73.3)</td>
<td>44 (5.6)</td>
<td>13.0 (1.7)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Other</td>
<td>16 (0.4)</td>
<td>0 (0.0)</td>
<td>16/16 (100.0)</td>
<td>19.1 (5.7)</td>
<td>10 (62.5)</td>
<td>45 (7.7)</td>
<td>13.1 (1.6)</td>
</tr>
<tr>
<td>Other</td>
<td>Moderate</td>
<td>240 (5.5)</td>
<td>3 (1.2)</td>
<td>184/240 (76.7)</td>
<td>29.0 (5.3)</td>
<td>200 (83.3)</td>
<td>45 (4.3)</td>
<td>12.6 (1.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate</td>
<td>104 (2.4)</td>
<td>3 (2.9)</td>
<td>81/104 (77.9)</td>
<td>28.7 (5.4)</td>
<td>72 (69.2)</td>
<td>45 (3.7)</td>
<td>12.8 (1.8)</td>
</tr>
<tr>
<td>High</td>
<td>Moderate</td>
<td>3 (0.1)</td>
<td>1 (33.3)</td>
<td>3/3 (100.0)</td>
<td>25.7 (1.5)</td>
<td>2 (66.7)</td>
<td>44 (–)</td>
<td>13.3 (0.6)</td>
</tr>
<tr>
<td>Moderate</td>
<td>High</td>
<td>10 (0.2)</td>
<td>1 (10.0)</td>
<td>7/10 (70.0)</td>
<td>32.4 (4.9)</td>
<td>9 (90.0)</td>
<td>45 (–)</td>
<td>12.3 (1.2)</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>27 (0.6)</td>
<td>0 (0.0)</td>
<td>20/27 (74.1)</td>
<td>28.0 (7.2)</td>
<td>24 (88.9)</td>
<td>44 (3.6)</td>
<td>11.9 (1.2)</td>
</tr>
</tbody>
</table>

NOTE: For all age categories median age with 95% CI is quoted.

Abbreviations: BC, breast cancer; Meno, menopause.
cancer risks are imputed from this calculation. As such given the rarity of BRCA1/2 or the putative dominant gene in the Claus model these models are only useful in the familial setting and not relevant to this study. BOADICEA (33) is another model primarily developed to assess genetic risk, but has been validated in a population-based series of breast cancers. Although inclusion of nongenetic risks is anticipated, these are not yet available in the online model.

The Cuzick–Tyrer model (16) based partly on a dataset acquired from the International Breast Intervention Study and other epidemiologic data incorporates both familial and no genetic risk factors in a comprehensive way (16). The major advantage over the Claus model and BRCAPRO is that the model allows for the presence of multiple genes of differing penetrance. It does give a read-out of BRCA1/2, but also allows for a lower penetrance BRCAX. As such the Cuzick–Tyrer model addresses many of the pitfalls of the previous models, significantly, the combination of extensive family history, endogenous estrogen exposure, and benign breast disease (atypical hyperplasia). It is unsurprising, therefore, that the model performs better than the simpler Gail model and this is particularly so in the familial setting (19).

Mammographic density is the single assessable risk factor with the largest population attributable risk and also has a substantial heritable component (34, 35). The difference in risk between women with extremely dense, as opposed to predominantly fatty breasts is approximately 4- to 6-fold (36). Incorporation of mammographic density into standard risk prediction models has been associated with some improvement in precision of risk prediction (37, 38).

The present study has important implications for GPs, the NHSBSP, genetics centers and those working in breast cancer FHCs. The release of NICE guidelines created a lot of publicity over the potential for use of chemoprevention (39). On the basis of the self-reported risk questionnaires at least 3.7% of women would meet criteria to be offered or considered for chemoprevention (NICE criteria). This rises to 8.8% if the 3% 10-year risk at age 40 years is used in the Tyrer–Cuzick program. We are planning a further feasibility study (PROCAS-II) to provide women with their

### Table 6. Known risk factors and their incorporation into existing risk models

<table>
<thead>
<tr>
<th>Prediction</th>
<th>RR at extremes</th>
<th>Gail</th>
<th>Claus</th>
<th>BRCAPRO</th>
<th>Ford</th>
<th>Cuzick–Tyrer</th>
<th>BOADICEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal information</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (20–70)</td>
<td>30</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Body mass index</td>
<td>2</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
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<tr>
<td>Alcohol intake (0–4 U) daily</td>
<td>1.24</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>Hormonal/reproductive factors</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of menarche</td>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Age of first live birth</td>
<td>3</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Age of menopause</td>
<td>4</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<td>HRT use</td>
<td>2</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>OCP use</td>
<td>1.24</td>
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<td>No</td>
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<tr>
<td>Breast feeding</td>
<td>0.8</td>
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<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Plasma estrogen</td>
<td>5</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td></td>
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<tr>
<td>Personal breast disease</td>
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<tr>
<td>Breast biopsies</td>
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<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
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<tr>
<td>Atypical ductal hyperplasia</td>
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<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
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<tr>
<td>Lobular carcinoma in situ</td>
<td>4</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Breast density</td>
<td>6</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<td>Family history</td>
<td></td>
<td></td>
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<tr>
<td>FDRs</td>
<td>3</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>SDRs</td>
<td>1.5</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Third-degree relatives</td>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Age of onset of breast cancer</td>
<td>3</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Bilateral breast cancer</td>
<td>3</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Ovarian cancer</td>
<td>1.5</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Male breast cancer</td>
<td>3–5</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Genetic testing</td>
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<tr>
<td>BRCA1/2</td>
<td>15</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>SNPs</td>
<td>6</td>
<td>No</td>
<td>No</td>
<td>Soon</td>
<td>Soon</td>
<td>Soon</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HRT, Hormone replacement therapy; OCP, Oral Contraceptive Pill.
risk feedback within 6 weeks of their screening mammo-
gram with a letter outlining their risk category and an-
information leaflet describing their options. It is anticipated
that women at moderate/high will access FHC and genetics
services to discuss chemoprevention and extra screening
through their GP.

There are some limitations to the present study. The
attendance at breast screening in this age group was only
61.0% and only 46.4% of this population joined the study.
As such it is possible that family history is overrepresented
in the sample because those with such a history may have
had greater interest in joining the study. However, our
internal assessment showed that despite already screening
around 1% of the female population ages 40 to 49 years
in our catchment area in our moderate-/high-risk clinics, we
were aware of <20% of the women identified in the same
area as being at moderate-/high-risk. As such this could
indicate that as many as 5% to 6% of the female population
may be eligible for additional screening ages 40 to 49 years
based just on the NICE algorithm. A further limitation
of our study is that due to the offer of screening in the NHSBSP
only starting ages 46 to 49 years, questionnaire data were
not available on those ages 40 to 45 years. Nonetheless, the
data most likely reflect the proportion that would be classed
with at least moderate risk at some time in their forties. Our
study also represents by far the largest assessment of family
history of breast cancer in women in their forties. This also
has resonance in North America and Europe that have
similar criteria for assessing increased risk based on family
history and in which screening ages 40 to 49 years is not now
completely endorsed for the average risk.

Initiatives are under way in other countries to collect risk
information data at national screening, in addition to the
British Columbia study (18), a large-scale study in Sweden
called Karma is under way (40).

Conclusions

From a large population-based assessment of breast can-
cer risk in women in their forties 3.7% (95% CI, 3.1%–
4.3%) of women ages 46 to 49 years met NICE moderate-/ 
high-risk criteria following the NICE algorithm; 8.8% (95% 
CI, 8.0%–9.7%) using Tyner–Cuzick. These women would
meet the new NICE criteria for additional mammography
screening and consideration of chemoprevention with
tamoxifen. The great majority of such women are likely to
be unaware of their eligibility for these interventions as only
17.5% (95% CI, 12.2%–23.9%) had been seen in the FHC
or clinical genetics service previously.

Disclosure of Potential Conflicts of Interest

J. Cuzick received speakers’ bureau honoraria from AstraZeneca. No
potential conflicts of interest were disclosed by the other authors.

Disclaimer

The views expressed are those of the author(s) and not necessarily those of
the NHS, the NIHR, or the Department of Health.

Authors’ Contributions

Conception and design: D.G. Evans, S. Astley, M. Wilson, J. Cuzick,
A. Howell

Development of methodology: D.G. Evans, S. Astley, M. Wilson, J. Cuzick,
A. Howell

Acquisition of data (provided animals, acquired and managed patients,
provided facilities, etc.): D.G. Evans, S. Dawe, P. Stavrinou, A. Howell

Analysis and interpretation of data (e.g., statistical analysis, bio-
statistics, computational analysis): D.G. Evans, A.R. Brentnall, J.C. Sergeant,
J. Cuzick, I. Buchan, A. Howell

Writing, review, and/or revision of the manuscript: D.G. Evans,
A.R. Brentnall, M. Harvie, J.C. Sergeant, S. Astley, J. Cuzick, I. Buchan,
L.S. Donnelly, A. Howell

Administrative, technical, or material support (i.e., reporting or orga-
nizing data, constructing databases): D.G. Evans, A.R. Brentnall, S. Dawe,
P. Stavrinou, M. Wilson, J. Ainsworth

Study supervision: D.G. Evans, A. Howell

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Conception and design: D.G. Evans, S. Astley, M. Wilson, J. Cuzick,
A. Howell

Development of methodology: D.G. Evans, S. Astley, M. Wilson, J. Cuzick,
A. Howell

Authors’ Contributions

Conception and design: D.G. Evans, S. Astley, M. Wilson, J. Cuzick,
A. Howell

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