

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

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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 *Cancer Prev Res*; 7(10); 993–1001. ©2014 AACR.

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

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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 ($\geq 17\%$ 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 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

NICE	Mother age	Sister age	10-year risk age 40	10-year risk age 49	Relative risk age 40	Relative risk age 49
High	35	35	8.6%	7.8%	5.4	3.0
High	45	45	4.8%	6.3%	3.0	2.4
Moderate	50	50	3.7%	5.8%	2.3	2.2
Moderate	35	—	3.3%	4.8%	2.0	1.9

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 with at least moderate risk. Profile likelihood confidence intervals were used for ORs and binomial parameters.

Results

Sixty-one percent of the general population of Greater Manchester ages 46 to 49 years and unaffected by breast cancer who were invited for breast cancer screening attended, and 46.1% of these ($n = 4360$) enrolled in PROCAS (Fig. 1). Although there have been some potentially expected issues with women's responses to some questions, overall the questionnaires were filled in to completeness by the vast majority of women and 10-year risks were readily identifiable. As in our initial article, women entering PROCAS were more likely to come from less deprived areas (15). Baseline characteristics of the sample are in Table 3. Some 30.4% (1,327) indicated on their questionnaire that they had a relative with breast cancer: 9.4% (410) with one FDR or more, 14.9% (649) not having an FDR but at least one SDR and 6.1% (268) with a third or more distant relative with breast cancer. 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 4 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-year 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

	Age 40	Age 46	Age 47	Age 48	Age 49
Moderate risk	3.0	4.3	4.5	4.6	4.8
High risk	8.0%	8.0%	8.0%	8.0%	8.0%

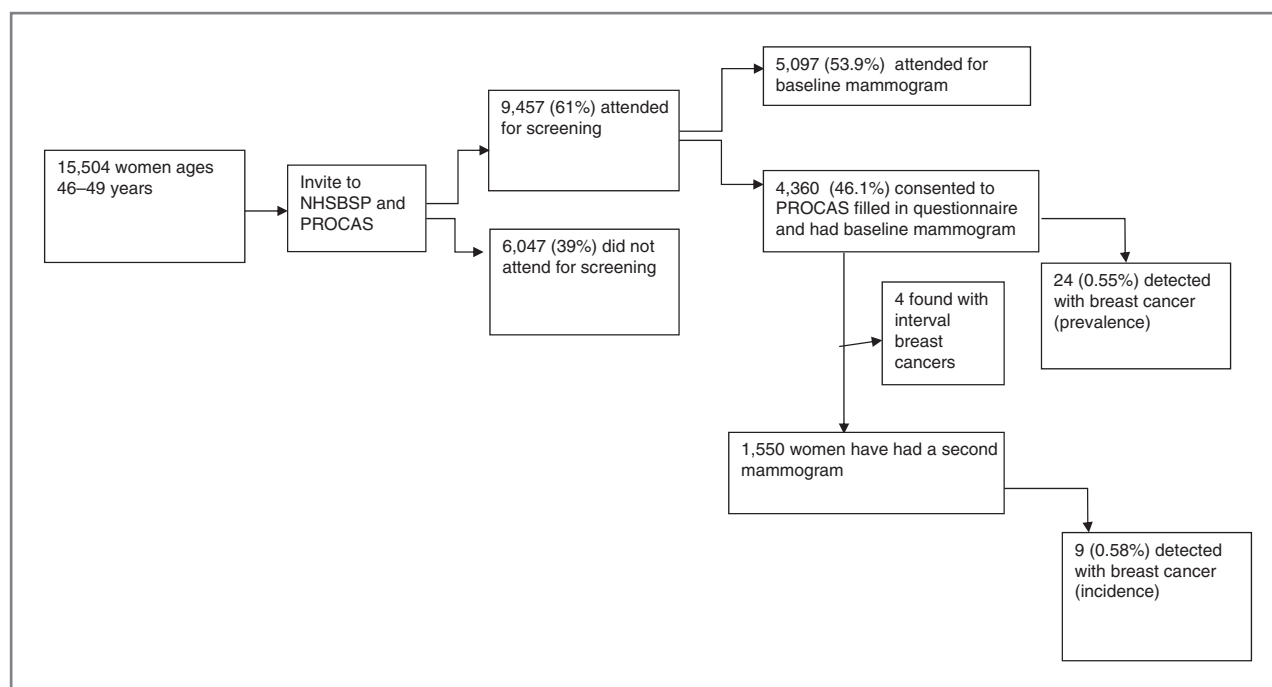


Figure 1. Consort diagram of the PROCAS study.

<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

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

Number	46–47	48–49	Age at Menarche	Parous	Premenopausal	FDR with BC	SDR with BC	More distant history of BC	BMI	HRT use
4,360	1,385	2,983	<12	3,618	3,219	410	649	268	<21	Current use:
			952	(83%)	(74%)	(9.4%)	(14.9%)	(6.1%)	313	304 (7%)
			(22%)						(8%)	Previous use:
			12–13						21–25	207 (4.7%)
			1,814						1,325	
			(43%)						(33%)	
			>13						>25	
			1,501						2,330	
			(35%)						(59%)	
									Unknown	
									400	

Abbreviation: BC, breast cancer.

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 findings 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 fifties. Primary care physicians and all others undertaking risk assessment need to be aware that moderate risk can be achieved with less significant family history if there are other adverse risk factors. 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. Thus, up to 8.8% of the female population in their forties could be offered annual mammography as per moderate risk screening recommendations.

We have previously shown that Tyrer–Cuzick is accurate in risk assessment (19) in the FHC setting and indeed three breast cancers were identified in women with single FDRs affected in their fifties who did not meet NICE algorithm criteria. However, this would have been at the cost of significantly lower specificity in the moderate-risk group: 92.1% (95% CI, 91.3–92.9) versus 97.1 (95% CI, 96.6–97.6). Although there was less agreement between NICE algorithm and Tyrer–Cuzick for moderate risk, there was good agreement at the high-risk level with 27 of 30 (90%) meeting both

high-risk criteria. 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 $12.5 \times 0.25 = 3.1\%$ almost identical to the number found at moderate risk in the present study.

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

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

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

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 age >64 years would have been eligible for tamoxifen use using the FDA threshold. A study from North America has shown that Tyrer-Cuzick substantially outperformed the Gail model (24). Given 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 ages 40 to 79 years were found to have the 8% 10-year risk of developing breast cancer using the Tyrer-Cuzick model and this dropped to 1.1% using the Gail model (18). In our expanded UK population ages 46 to 73 years, this was only 1.3%, which suggests that our 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). Some of the difference may also be accounted for by the different age structures of the populations and using Tyrer-Cuzick v.7 in the Canadian study (18).

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 *BRCA1/2* (32). Breast

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

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

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

Abbreviations: BC, breast cancer; Meno, menopause.

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

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

Abbreviations: HRT, Hormone replacement therapy; OCP, Oral Contraceptive Pill.

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

risk feedback within 6 weeks of their screening mammogram 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 cancer 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 Tyrer–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.

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