Detection and management of women at increased risk of breast cancer

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Practice Points

- Women at high and moderate risk of breast cancer should be referred to their local family history clinic or cancer genetics clinic if requested.
- If above a proscribed risk threshold at-risk women should be offered screening, preventive measures and the possibility of joining research studies.
- Risk thresholds are defined in local and national guidelines.
- The probability of being a *BRCA1*, *BRCA2* or *TP53* gene carrier is estimated for women with a strong family history.
- Gene testing will usually be undertaken if the index case in the family has a 10% (Europe) or 20% (UK) chance of carrying a mutation.
- Carriers (and noncarriers) should be counseled and offered appropriate screening and risk reduction measures.
- Risks may be reduced by breast or ovarian surgery and the use of tamoxifen or raloxifene (USA).
- Observational data suggest that lifestyle change may be helpful.

SUMMARY In this article we give a practioner's perspective concerning the management of women at increased risk of breast cancer. Such women are usually identified because of a family history of breast cancer. However, there are a number of other risk factors including age of first pregnancy, age of menopause and use of hormone-replacement therapy that can be taken into account and incorporated with family history into predictive models. Prediction

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is important because it determines management. For example, women with mutations in the *BRCA1* and *BRCA2* breast cancer genes have greater survival with appropriate screening and surgical and medical preventive measures. There is evidence to suggest that survival may also be improved with optimal management in the larger group of women without mutations but at increased risk of breast cancer for other reasons.

The aim of this article is to outline the problem of women at increased risk of breast cancer, to indicate current management algorithms and current research strategies and to speculate how improvements in clinical practice may be made in the future. The argument for detecting carriers of mutations in the dominant breast cancer genes *BRCA1* and *BRCA2* is strong since there is evidence to suggest that, with appropriate screening and preventive measures (mainly surgical), women may expect to have a normal lifespan [1]. The evidence of benefit for intervention in high- and moderate-risk nongene carriers is also available [2]. Some data indicate that screening by mammography improves survival in these groups [3,4] and randomized, placebo-controlled trials indicate that the selective estrogen receptor modulators – tamoxifen [5], raloxifene [6] and lasafoxafine [7] – reduce breast cancer risk by approximately 50% and the aromatase inhibitor, exemestane, by approximately two-thirds [8]. However, because we currently cannot predict risk precisely, the number of women needed to treat to prevent one breast cancer is high and thus the risk:benefit ratio is relatively low. Observational studies indicate that weight loss reduces the risk of postmenopausal breast cancer [9,10] and exercise reduces the risk of pre- and post-menopausal breast cancer [11]

Incidence of breast cancer

Breast cancer is the most common cancer in women. Although the mortality from breast cancer has declined over the past 20 years (by up to 50% in some groups) in most western countries, the incidence of the disease continues to rise [101]. A reduction of incidence occurred after the results of the Women's Health Initiative trials were published in the USA in 2002, indicating that combined hormone-replacement therapy (HRT) increased breast cancer risk. Large numbers of women stopped taking HRT and the incidence declined in the USA [12]; however, a nonsignificant increase in incidence is reported in the latest Surveillance Epidemiology and End Results Program of the National Cancer Institute from 2005 [102].

In Iceland, where there are good long-term records, there was a fourfold increase in breast cancer (from 2.6 to 10.7%) between 1920 and 2002 [13]. Interestingly, there was also a fourfold increase in the penetrance of the founder Icelandic *BRCA2* mutation (from 18.6 to 71.9%). The changes are too rapid to be related to genetic change and thus the increases in both sporadic and genetic breast cancer are thought to be related to lifestyle change (e.g., later age of first birth, smaller family size and positive energy balance).

Over the 30-year period between 1979 and 2008 the annual number of breast cancer cases in England almost doubled from 23,876 to 46,537, and now in the UK, breast cancer accounts for 31% of all female cancers [101]. In 2008, it was estimated that 1.38 million women were diagnosed with breast cancer worldwide representing nearly a quarter (21%) of all female cancers worldwide. The rates of increase of breast cancer incidence are highest in areas such as Africa and Asia where traditionally the incidence was low [14].

The widespread increase in breast cancer incidence has led to extensive research efforts aimed at improving prediction of breast cancer risk and introducing measures, such as risk-reducing surgery, preventive therapy (chemoprevention) and lifestyle changes, to help reduce the incidence of the disease.

Management guidelines

The management of women at increased risk of breast cancer is described in several local and country-specific guidelines. The major guideline is published by NICE in the UK [103] and by National Comprehensive Cancer Network (NCCN) in the USA [104]. An extract of the NICE guidelines for referral to family history clinics (FHCs), which deal with moderate risk women (a one in four to six lifetime risk), and

Clinical Genetics Services, which deal with women at high genetic risk, are shown in Box 1.

Risk estimation

The simplest risk information, and perhaps the most understandable, is to give a lifetime risk of breast cancer. In the UK, the lifetime risk of breast cancer is approximately a one in ten chance of developing the disease. Higher estimates have been given (e.g., one in eight) but these assume that all women live until 85 years of age and includes second primary breast cancer; both factors have the effect of inflating risk [15]. Risks are increased by family history and several other hormonal and lifestyle factors (Table 1). However, clinical referrals are usually based on family history only. Women may be referred in the UK if they have a lifetime risk of one in six or more of breast cancer, which is equivalent to having one affected first-degree relative below age 40 years.

Two probabilities are usually estimated in the clinic. One is the lifetime and 5- and 10-year risk of developing breast cancer, based on family history and other risk factors, and the second probability is the chance of carrying a mutation in the risk genes *BRCA1*, *BRCA2* and *TP53*. This is based on the strength of the breast cancer family history and the presence of additional cancers in the family such as ovarian, prostate and male breast cancer.

Several models have been published to compute general risk [16–20]. In the USA, the Gail model is most widely used whereas the Tyrer-Cuzick model appears more appropriate in the UK. The Gail model gives 5-year and lifetime risks based on consideration of age, first-degree family history, number of breast biopsies and age of first full-term pregnancy, while the Tyrer-Cuzick model is based on estimation of risk from a more extensive family history and information concerning age of menarche, first full-term birth and menopause, as well as height, weight, pathology and HRT use. A comparison of several risk prediction models in our clinic indicated that the Tyrer-Cuzick model predicted breast cancer risk optimally for our population of women [21]. Other risk prediction models have also been assessed [22–25].

A major need in the clinic is to decide whether the family history is strong enough to warrant genetic testing of the index case with cancer. Several models are used to predict the probability of the presence of a *BRCA1* or *BRCA2* mutation in the family. In Europe and the USA, genetic testing is undertaken if there is at least a 10% probability of a mutation in the index case, whereas in the UK, this figure is 20% [103,104].

We have developed a simple scoring system (the Manchester score) that enables prediction of the mutation probability in the busy clinic. The scoring system is shown in Table 2 and integrates the numbers of affected members of the family and age of onset of the cancers. As with BOADICEA, discrimination may be improved

Box 1. NICE UK National Health Service guidelines.

Familial breast cancer 2006 (abbreviated extract)

- Family history referral from primary care
  - Risk assessed in primary care: refer greater than one in six risk
  - No indication to actively seek women at risk
  - Protocols with local clinics should be developed
- Care on referral
  - Psychological support should be available
  - All women aged 40–49 years to be offered annual mammography if at greater than one in six risk
  - Must be given information about the risks and benefits
  - Women with *BRCA1/2* mutations from 30 years of age or *TP53* mutation from 20 years of age to be offered annual MRI
  - MRI also offered to women aged between 30 and 39 years if 10-year risk of >10% and from 40 to 49 years if 10-year risk >20% or if mammograms very dense and >12% 10-year risk
  - Offer genetic testing as appropriate
  - Offer risk-reducing surgery as appropriate

Table 1. Risk factors for breast cancer.

Factor	Effect	Ref.
Age	One in 215 women develop breast cancer by the age of 39 years and one in 13 by age 69 years	[101]
Menarche	RR reduced by 4% for each year of delay	[101]
First full-term pregnancy	RR increased by 3% for each year of delay	[101]
Breastfeeding	RR reduced for each year	[55,56]
Menopause	RR increased for each year of delay	[101]
Physical activity	RR reduced by approximately 20% >2 h/week	[11]
Weight gain	RR×2 for 20 kg versus no gain	[10]
Weight loss	RR reduced by approximately 25% if >5% maintained reduction	[9]
Mammographic density	RR approximately 5 comparing least to most dense	[57]
Atypical ductal hyperplasia	RR×4	[58]
Alcohol	RR 7–12% for 10 g alcohol per day	[61]
Family history	RR×2 for one and RR×3 for two first-degree relatives	[25,59]
HRT	No risk E only Combined HRT RR×2	[62] [12,60]

E: Estrogen; HRT: Hormone-replacement therapy; RR: Relative risk; RR×2: Twofold relative risk; RR×3: Threefold relative risk; RR×4: Fourfold relative risk.

Table 2. Manchester scoring system for determination of probability of carrying a *BRCA1* or *BRCA2* mutation.

Cancer; patient age (years)	*BRCA1*	*BRCA2*
FBC; <30	6	5
FBC; 30–39	4	4
FBC; 40–49	3	3
FBC; 50–59	2	2
FBC; >59	1	1
MBC; <60	5 (if *BRCA2* tested); for combined, score = 5 without prior testing	8
MBC; >59	5 (if *BRCA2* tested); for combined, score = 5 without prior testing	5
Ovarian cancer; <60	8	5 (if *BRCA1* tested); for combined, score = 5 without prior testing
Ovarian cancer; >59	5	5 (if *BRCA1* tested); for combined, score = 5 without prior testing
Pancreatic cancer	0	1
Prostate cancer; <60	0	2
Prostate cancer; >59	0	1

Scores are added for each cancer in a direct blood lineage (cancers on the same side of the family). The combined score is determined by adding both the *BRCA1* and *BRCA2* scores without consideration for prior testing, thus MBC scores five points for *BRCA1*, and ovarian cancer scores five for *BRCA2*. A combined score of 16 points can be used as a 10% threshold, and 20 points as a 20% threshold in nonfounder western populations. In families with no unaffected females, a lower threshold could be used. Other tumor types such as cholangiocarcinoma and ocular melanoma can contribute to the *BRCA2* score, but the numbers of these tumors are too low to validate a precise score.
FBC: Female breast cancer; MBC: Male breast cancer.

by incorporating details of the pathology of the tumor of the index case in the family [26,27].

Problems with risk prediction

It is important to understand that, although we can detect women at increased risk, most women who develop breast cancer do not have many or any of the known risk factors. In addition, although we can say with some confidence that a woman has, for example, a one in four lifetime risk of breast cancer we cannot tell whether she is the one who will develop cancer and the three women who will not. Several groups have attempted to improve prediction by adding other known risk factors such as the extent of mammographic density and estimation of the 18 known 'risk' single nucleotide polymorphisms (SNPs) to standard risk prediction models. Unfortunately these efforts have to date led to only minor improvements in prediction [24,28–34].

Another problem is that most referrals are based on family history but a woman may be at risk because she has several nonfamilial risk factors, which are outlined in **Table 1**. In order to determine risk in the general population, we assessed the risk in over 40,000 women who attend for screening mammography in the National Health Service Breast Screening Programme. The distribution of risks computed using the Tyrer-Cuzick model is shown in **Figure 1**. Women at very low risk often have an early age of first birth and an oophorectomy in their third or early fourth decade. Women at high risk may have a late age of first pregnancy, be nulliparous, have a late menopause or be taking combined HRT. In the UK, NICE guidelines indicate there is "no indication to actively seek women at risk" [103]. However, we asked over 40,000 women undergoing mammography in the National Health Service Breast Screening Programme by questionnaire whether they wished to know their risk of breast cancer and over 94% wished to do so [27].

The FHC model

FHCs were first set up in the 1980s in response to women's increasing awareness of their genetic risk of breast cancer [35]. Clinics generally offer risk information, mammographic and other screening, and advice concerning the appropriateness of particular preventive interventions for women [35]. Information about the probability of carrying a mutation in a cancer gene is given, genetic testing is offered to the family if appropriate [22,23,26,27,36,37] and assessment of overall risk of breast cancer for noncarriers produced by combining genetic and other risk factors by the use of models such as Gail and Tyrer-Cuzick is given [16,20]. FHCs are available throughout the UK and are run according to national guidelines produced by the UK NICE [103]. An abbreviated part of the guideline is shown in **Box 1**, which outlines some referral guidelines and standards of care once referred.

Screening

It is customary to offer annual screening by mammography to women at increased risk from the age of 40 years although the effectiveness of screening with regards to reducing breast cancer mortality has been assessed in randomized controlled trials [4]. We compared the survival of women undergoing 12–18-monthly mammography and who developed breast cancer in our FHC with patients in the same age range who presented symptomatically at our surgical clinic

over a 10-year period. After correction for lead time bias, survival (hazard ratio: 0.24; 95% CI: 0.08–0.43; p = 0.005) and disease-free survival (hazard ratio: 0.25; 95% CI: 0.11–0.57; p < 0.001) were significantly improved in the FHC group compared with women who presented symptomatically to the same breast unit [2]. More recently, in a multicenter study in 76 FHCs in the UK, the outcomes of 6710 women who had annual mammograms aged 40–49 years demonstrated that screening in this age group is likely to improve breast cancer survival. The relative risk reduction was 0.80 (95% CI: 0.66–0.96; p=0.022) compared with controls from other trials, which suggests that annual mammography in FHCs is likely to prevent deaths from breast cancer [3]. Other studies in *BRCA1* and *BRCA2* mutation carriers indicate that risk-reducing oophorectomy and mastectomy are also associated with improved survival compared with no surgery groups, although recent modeling indicates that focused screening by mammography and MRI may be as effective as bilateral prophylactic mastectomy [1,38,39].

While the service outlined above is available to younger women with a family history of breast cancer, there are fewer data relating to defining risk, adapting screening to risk and offering preventive approaches to postmenopausal women who represent the group where 80% of breast cancers develop. In the UK, women aged between 47 and 73 years are offered mammographic screening every 3 years. This national program is largely successful and it is estimated that there is an approximately 30% improvement in breast cancer survival relative to nonscreened women.

However, mass screening is by definition inefficient and thus controversial. In the UK National Health Service Breast Screening Programme, approximately seven cancers (five invasive and two *in situ*) are discovered for every 1000 women screened at the expense of approximately 50 women per 1000 being recalled for further assessment and approximately half of these require an additional needle biopsy or, rarely, an open biopsy. Because mammography is every 3 years nearly four interval cancers present between screens for every 10,000 women [40].

PROCAS

In an attempt to begin to investigate how we might predict risk more precisely in older women so that high-risk women can be offered preventive interventions, we have instituted a study (PROCAS) in 60,000 women in the screening program in Manchester, UK [27,34]. Each woman is asked to complete a questionnaire concerning standard risk factors before her mammogram and her risks are computed using the Tyrer-Cuzick model (Figure 2), mammographic density (Figure 3) is estimated by a variety of methods and a proportion tested for the currently available SNPs shown to predict risk [24,28,29,30–34]. The overall aim of the study is to determine the optimal model of risk prediction by combining standard risk factors, a measure of density and the SNPs for predicting the cancers that arise during the program. It is of interest that 94% of women who join the program (~40% of the screened population) indicate that they wish to know their risk. Currently, most women at high risk (≥8% 10-year risk) attend for counseling and advice concerning potential preventive measures such as chemoprevention with raloxifene or tamoxifen, and lifestyle interventions such as dietary energy restriction and exercise. Assessments of Tyrer-Cuzick risk and visual analog mammographic density scores (VASs) have been reported for the first 10,000 women and SNP information is available on 983 women [27]. The median 10-year breast cancer risk was 2.65% (Figure 4) and the median VAS was approximately 25% (Figure 3). Interestingly, when the top 5% of women for Tyrer-Cuzick risk, VAS and SNPs were compared, there was little overlap in the populations identified suggesting that the three methods detect different at-risk populations.

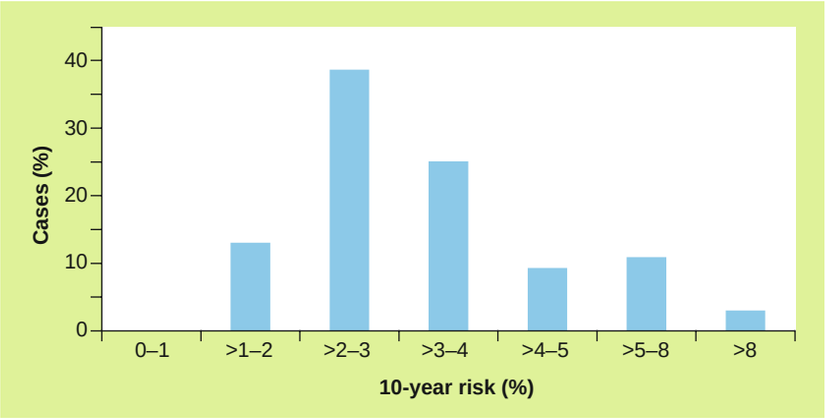

Figure 1. 10-year risk distributions. Tyrer-Cuzick risks of breast cancer in 10,000 women screened in the UK between the ages of 47 and 73 years. The proportion of women at high risk (>8% 10-year risk) is approximately 2.5% and at moderate risk (>5% 10-year risk) is approximately 11% of the population [34].

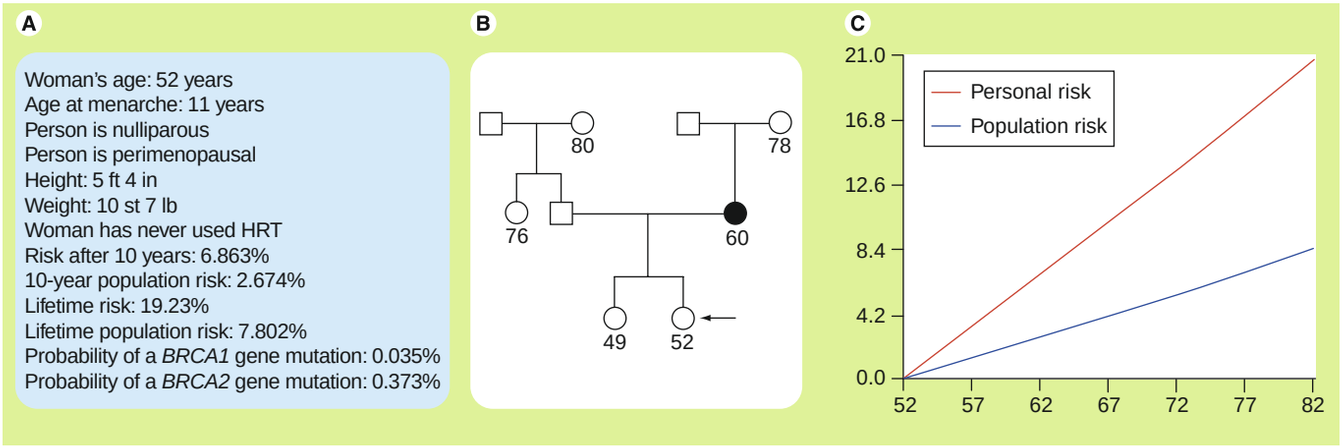

Figure 2. The Tyrer-Cuzick model for breast cancer risk assessment. (A) The information input panel concerning the risk factors for breast cancer for a women aged 52 years when seen. **(B)** Part of the output giving 10-year and lifetime risks of breast cancer. **(C)** Visual output of risks over time for the individual (upper line) compared with risk in the general population (lower line) [20].
HRT: Hormone-replacement therapy.

Women with a 10-year risk of ≥8% or with a 10-year risk of 5–7.9% and with a VAS of ≥60% were invited to attend or be telephoned to be counseled concerning their risk in our FHC. Over 80% have been counseled to date and 18.8% of 85 eligible women at high risk entered a randomized prevention study. Thus, to date, results from the PROCAS study indicate that it is feasible to assess breast cancer risk and offer risk information and risk-reducing advice within the context of the population mammographic screening. The utility for improved risk calculation by combining standard risk factors in the Tyrer-Cuzick model, mammographic density and SNP estimations will be assessed after each individual's second mammogram at 3 years when we expect approximately 600 tumors in the population of 60,000 women enrolled [27]. A similar program to PROCAS, known as KARMA, involving 100,000 women has been initiated in Sweden [Hall *et al.*, Pers. Comm.].

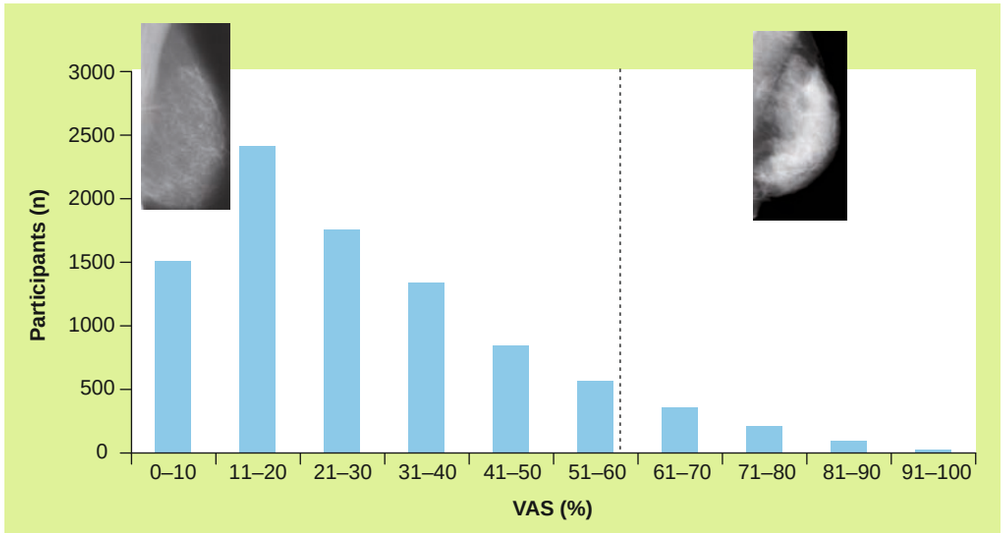

Figure 3. Distribution of mammographic density estimated by using a visual analog scale in 7810 women between the ages of 47 and 73 years in the UK National Health Service national screening program. Relatively few women have high density [34].
VAS: Visual analog mammographic density score.

Breast cancer prevention

The question arises concerning the effectiveness of currently available preventive measures and how we might target the appropriate at-risk population more accurately. Three main preventive avenues of investigation have been undertaken; surgery, the use of endocrine-blocking agents (mainly antiestrogens and aromatase inhibitors), and lifestyle change (particularly weight loss and exercise).

Surgical prevention

Women who carry mutations in *BRCA1* or *BRCA2* have up to an 80% chance of developing breast cancer during their lifetime and up to a 30% chance of ovarian cancer [38]. Since ovarian cancer screening is relatively ineffective, the majority of women elect to have bilateral oophorectomy, which is usually advised after childbearing is completed. It is usual to advise the option of hysterectomy as this reduces the small risk of tumors arising in the endometrium and allow for estrogen-only replacement therapy, which appears safe in younger women. In our clinic, approximately 50% of women elect to undergo bilateral risk-reducing surgery, usually with implants but also reconstruction of the breast with abdominal or latissimus dorsi flaps. The other 50% elect to continue intensive screening with alternating mammography and MRI [41,42]. Kurian *et al.* have modeled that these surgical and screening procedures are likely to result in a normal lifespan [1]. The authors have also produced a useful decision aid to help women and their clinicians make the complex decisions required in carriers [1,39].

Endocrine prevention

Recent reviews summarize the data indicating the effectiveness of preventive therapy (chemoprevention) of breast cancer [5,43,44]. The agents already shown to be effective include tamoxifen and raloxifene [5,6,45–48]. More recently the aromatase inhibitor exemestane was reported to give greater risk reduction than placebo [30]; a further study of anastrozole versus placebo (IBIS II) is in progress [49].

Cuzick *et al.* performed an overview of the four randomized, placebo-controlled trials of tamoxifen and reported an overall risk reduction of 38% [5]. In the IBIS I trial, the long-term effect of 5 years of tamoxifen and a further 5 years of follow-up showed that the curves for placebo and treated groups continued to diverge so that there was a 20% greater preventive effect at 10 years compared with the effect determined at 5 years [46]. In the STAR trial, women were randomly assigned to receive either tamoxifen or raloxifene for 5 years [6]. The risk ratio (raloxifene vs tamoxifen) for invasive breast cancer was 1.24 (95% CI: 1.05–1.47). The greater effectiveness of tamoxifen was associated with a higher incidence of side effects so that the risk:benefit ratio favored raloxifene in women with a uterus and was equivalent to tamoxifen in women without a uterus, indicating the important negative effect of tamoxifen on the endometrium [6].

Aromatase inhibitors are more effective for the prevention of relapse after breast cancer diagnosis compared with tamoxifen and the early results of a comparison between exemestane versus placebo for prevention of breast cancer in women at high risk show a 62% reduction in risk (odds ratio: 0.35; 95% CI: 0.18–0.70) with few differences in the side-effect profiles between exemestane and placebo [8]. However,

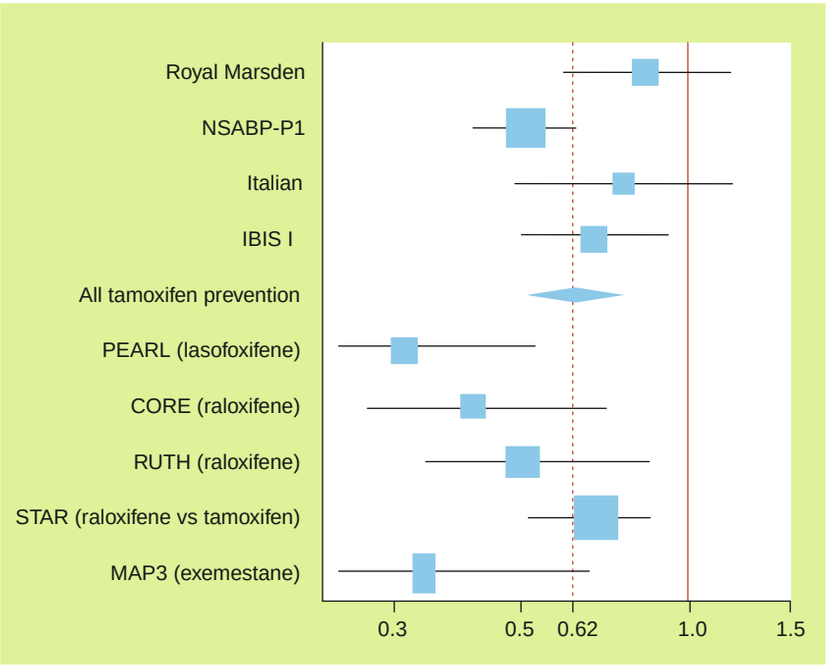

Figure 4. Results of randomized trials of chemoprevention of breast cancer. The size of the boxes is proportional to numbers in the trial and the horizontal bars are 95% CIs. The Royal Marsden, NSABP-P1, Italian and IBIS I trials compared tamoxifen with placebo [5,45,47]. The PEARL trial compared lasofoxifene with placebo [7]. The CORE and RUTH trials compared raloxifene with placebo [48,49]. The STAR trial compared tamoxifen and raloxifene and both reduced breast cancer incidence by approximately 50% [6]. The MAP3 trial compared the aromatase inhibitor exemestane with placebo [8].

the estimated number needed to treat to prevent one breast cancer was projected to be 25. These and other number needed to treat data [50] indicate the need for more precise prediction of risk, for more effective agents and for biomarkers to predict women most likely to benefit from preventive therapy [51]. Currently, tamoxifen is the preventive treatment of choice for premenopausal women and raloxifene for postmenopausal women. Aromatase inhibitors, although promising, require further investigation on their risk:benefit ratio.

Lifestyle change

There are few randomized data to support a positive effect of lifestyle change in relation to breast cancer prevention. However, observational data indicate that lifestyle, mainly caloric excess and exercise deprivation, increases the risk of breast cancer and that risk can be reduced by decreasing weight and increasing physical activity. Two large prospective studies [9,10] demonstrate that weight reduction in mid-life or after the menopause decrease the risk of postmenopausal breast cancer by approximately 25–50% as does weight reduction related to bariatric surgery. The results of other observational studies of weight reduction are mixed, possibly reflecting the small size of some and lack of data on maintained weight loss in the reported studies (summarized in [52,53]). Reduction in fat intake without appreciable calorie restriction has only a minor effect on risk as shown in the Women's Health Initiative large randomized trial [54]. This study also demonstrated that increased intake of vegetables, fruit and grain does not appear to reduce breast cancer risk.

A meta-analysis of 73 papers reporting the effect of physical activity on breast cancer incidence indicated an overall risk reduction of approximately 25% in both pre- and postmenopausal women [11]. The risk reduction was greatest in women with a normal BMI suggesting that the optimal approach to lifestyle reduction of breast cancer risk is to combine weight control and appropriate physical activity.

Conclusion

The increasing incidence of breast cancer highlights the need for prevention and improved early detection of the disease. FHCs are models for management of younger women who are at risk but could potentially be used for older women determined to be at high risk. Models such as Gail and Tyrer-Cuzick predict general risk well but have low discriminatory power for individuals. The models may (or may not) be improved by adding other risk factors such as mammographic density and measurement of breast cancer risk-associated SNPs. Surgery is successful in preventing breast and ovarian cancer in carriers of mutations. Clinical trials of endocrine-blocking agents have demonstrated that it is possible to prevent breast cancer using preventive therapies and observational studies suggest that lifestyle changes may also reduce risk, although ideally we need appropriate randomized trials to test these assumptions. The early results of the Manchester PROCAS study suggest that it may be feasible to introduce risk prediction and prevention strategies in the context of a population-based mammographic screening program and thus to focus preventive approaches and possibly introduce risk-adapted screening.

Future perspective

■ 'Genetic' breast cancer

The management of women with *BRCA1* or *BRCA2* mutations will be further refined. The penetrance of both genes is variable and this will be predicted using 'risk' SNPS and other measures. It seems unlikely that other high-risk genes will be discovered but other rare risk genes and SNPs will be tested for routinely.

■ 'Nongenetic' high-risk breast cancer

Risk prediction will improve by combining known and as yet unknown additional markers of risk. With improved predictive methods there will be more widespread use of surgery, chemoprevention and lifestyle change. New preventive therapies such as PARP inhibitors will enter the risk clinic. Approaches that help prevent other diseases as well as breast cancer (e.g., raloxifene and lifestyle change) will be more widely utilized.

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