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Breast cancer prevention in high-risk women

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A B S T R A C T

Women at high risk of developing breast cancer are a heterogeneous group of women including those with and without high-risk germline mutation/s. Prevention in these women requires a personalised and multidisciplinary approach. Preventive therapy with selective oestrogen receptor modulators (SERMs) like tamoxifen and aromatase inhibitors (AIs) substantially reduces breast cancer risk well beyond the active treatment period. The importance of benign breast disease as a marker of increased breast cancer risk remains underappreciated, and although the benefit of preventive therapy may be greater in such women, preventive therapy remains underutilised in these and other high-risk women. Bilateral Risk-Reducing Mastectomy (BRRM) reduces the risk of developing breast cancer by 90% in high-risk women such as carriers of *BRCA* mutations. It also improves breast cancer-specific survival in *BRCA1* carriers. Bilateral risk-reducing salpingo-oophorectomy may also reduce risk in premenopausal *BRCA2* carriers. Further research to improve risk models, to identify surrogate biomarkers of preventive therapy benefit and to develop newer preventive agents is needed.

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It is currently estimated that 1.6 million breast cancer cases occur worldwide each year, making it the commonest cancer in women today [1] and breast cancer incidence continues to rise. Substantial improvements in cancer treatments over past few decades have reduced breast cancer mortality in the well-developed regions of the world, yet it remains a major cause of death. Primary prevention of breast cancer remains one of the most effective, yet underutilised strategy in reducing breast cancer burden [2]. In this review of evidence and approaches for breast cancer prevention in high-risk women, we discuss breast cancer risk factors and genetic predisposition, risk prediction models, prevention strategies including therapeutic and surgical approaches, barriers to implementation of these strategies as well as research priorities. The discussion will specifically focus on prevention in high-risk women; a detailed discussion on surveillance in these women for early detection of breast cancer is outside the scope of this review.

Breast cancer prevention can be achieved either through intervention in the entire population or by implementing strategies in women at an increased risk of breast cancer. A reduction in breast cancer incidence of 25% (Fig. 1) can be achieved either through an intervention that reduces risk by 25% applied to the entire population (Fig. 1A) or by implementing an intervention that reduces risk by 42–45% in 20% or 10% of women at the highest risk (Fig. 1B). Apart from being more feasible than an intervention in the entire population, the latter strategy also provides the best benefit-harm balance at an individual level, particularly if such interventions have significant adverse effect implications.

Breast cancer risk factors

Several modifiable and non-modifiable factors are associated with breast cancer risk (Box 1). Many of these, e.g. weight, physical activity and alcohol consumption fall in the category of lifestyle modifications and should be applicable to all individuals including those at a higher risk of breast cancer. On the other hand, for high-risk individuals where majority of their risk is driven by non-modifiable risk factors such as family history with or without known genetic predisposition, high mammographic breast density (MBD) or history of benign breast disease (BBD), interventions other than lifestyle modifications would also need to be considered to reduce their risk of developing breast cancer.

Breast cancer risk models

It is amply clear from the above discussion that successful implementation of breast cancer prevention requires accurate stratification of breast cancer risk. Several risk models (Box 2) have been developed to specifically predict an individual's breast cancer risk and some of these also predict the probabilities of germline *BRCA1* and *BRCA2* mutations. These include the Gail Model [12], Tyrer-Cuzick Model [16], BSCS model [17,18], Colditz and Rosner model [19], Claus model [20], BRCAPRO model [21] and BOADICEA [22]. Manchester Scoring System [23] and the Breast Cancer Genetics Referral Screening Tool (B-RST™) [23] provide probabilities of *BRCA* mutations to guide referral to genetic services. It is

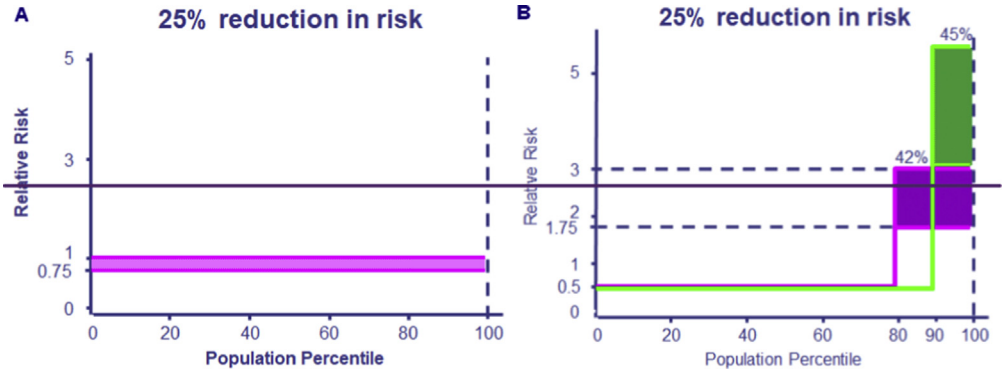

Fig. 1. Prevention strategies based on risk-stratification.

Box 1
Breast cancer risk factors

- **Non-Modifiable** Factors
  - Sex and age
  - Family history of breast cancer (1FDR* 2-fold, 2FDRs 3-fold and 3FDRs 4-fold) [3,4].
  - Major inheritance susceptibility.
  - Breast density [5].
  - BBD (a spectrum of pathologies) [6].
- **Modifiable** Factors – **Increased** Risk
  - Hormone Replacement Therapy (RR^{Ω} 1.2 to 1.3 for oestrogen-only, 1.6 to 2.1 for combined) [7].
  - Ionizing radiation ($RR^{\Omega} = 6$) [8,9].
  - Obesity (dependent on menopausal status) [10].
  - Alcohol (7% increase per unit/day) [11].
- **Modifiable** Factors – **Decreased** Risk
  - Early pregnancy (50% decrease as compared to >35 or nulliparous) [12].
  - Breast-feeding (Risk reduced by 4% for every year breastfed and 7% for each birth) [13].
  - Exercise (30–40% reduction) [14,15].

* FDR: First-degree relative; Ω: Relative Risk.

Box 2
Breast cancer risk models

- IBIS Breast Cancer Risk Evaluation Tool (Tyrer-Cuzick Model)
- The Breast Cancer Risk Assessment Tool (BCRAT or Gail Model)
- Breast Cancer Surveillance Consortium (BSCS) Risk Calculator
- Colditz and Rosner model
- Claus model
- BRCAPRO model
- Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm [BOADICEA] model
- Manchester Scoring System
- Breast Cancer Genetics Referral Screening Tool (B-RST™)

worth noting that the accuracy [16,24–26] of these models including models that incorporate genotype information and MBD is moderate; expressed in terms of an area under the curve (AUC), it ranges between 0.55 and 0.70 [16,26] when simply flipping a coin has an AUC of 0.50.

Breast cancer risk categories

Different regions of the world define breast cancer risk groups differently. In the USA, women with a 5-year risk of 1.67% or higher are classified as 'high-risk'. In the UK, the National Institute for Health and Care Excellence (NICE) has defined risk categories [27] as high-risk for women with 30% or greater chance of developing breast cancer in their lifetime, or 8% or greater chance of developing breast cancer between the ages of 40 and 50. Those with greater than 17% but less than 30% lifetime risk, or 3–8% chance of developing breast cancer between the ages of 40 and 50 are classified as moderate-risk group.

The importance of benign breast disease as a risk factor

Certain types of BBD are associated with an increased risk of breast cancer (Table 1). The importance of this risk factor is often underappreciated [6] even though in some ways this is the easiest group of

Table 1
Risks of subsequent breast cancer for different types of benign disease.

Type	Study (reference)	N (cancer)/N (group)	OR (95% CI)
Atypical Hyperplasia (AH)	Nashville [83]	30/232	4.40 (3.10–6.30)
	Mayo [31,84,85]	143/698	4.34 (3.66–5.12)
	Henry Ford [86]	29/246	4.74 (2.81–7.84)
	Nurses' health Study [87]	96/160*	4.11 (2.90–5.83)
	McDivitt [88]	66/26*	2.60 (1.60–4.10)
Hyperplasia - no atypia	McDivitt [88]	124/68*	1.80 (1.30–2.40)
Fibroadenoma (FA) –Clinical only	Ciatto [89]	31/2603	0.97 (0.70–1.40)
FA- all histology	Ciatto [89]	41/1335	2.00 (1.40–2.70)
	Dupont [90]	87/1835	1.61 (1.30–2.00)
FA – no hyperplasia	Dupont [90]	51/1177	1.48 (1.10–1.90)
	McDivitt [88]	64/42*	1.70 (1.10–2.50)
FA – hyperplasia without atypia	Dupont [90]	12/162	2.16 (1.20–3.80)
	McDivitt [88]	21/6*	3.70 (1.50–9.20)
FA – with AH	Dupont [90]	3/19	4.77 (1.50–15.0)
	McDivitt [88]	14/2*	6.90 (1.50–30.6)
Aspirated Cysts – No histology	Dixon [91]	65/1374	2.81 (2.17–3.59)
	Bundred [92]	14/352	4.40 (2.41–7.38)

Reprinted from Cuzick J, Sestak I, Thorat MA. Breast 2015;24. https://doi.org/10.1016/j.breast.2015.07.013. [6] under the terms of the Creative Commons Attribution License (CC BY).
* Case–control.

increased risk patients to whom preventive intervention can be offered, because these women have already entered the treatment pathway. Among the spectrum of BBD, lobular carcinoma *in situ* (LCIS) is associated with the highest risk but fortunately this is rare. Atypical hyperplasia (AH), which carries a 4- to 5-fold risk of breast cancer, is more common. Hyperplasia of the usual type, which carries a roughly two-fold risk, is even more common. Not all risk models with the exception of the Gail Model [12], BSCS model [17,18] and the Tyrer-Cuzick Model [16], particularly the latter allow for capturing information regarding a range of BBD to refine risk estimates. However, further validation [28] of these models when both AH and other important risk factors are present is needed because the Gail model [29] tends to underestimate, whereas the Tyrer-Cuzick Model [28,30] appears to overestimate risk in such women.

Long-term follow-up data from Mayo Clinic and Nashville cohorts suggest that AH alone is associated with a 30% cumulative risk of breast cancer over a 25-year period [31], thus these women should automatically be assigned to the high-risk group. Also underappreciated is the fact that combination of BBD with family history (Table 2) would assign a significant proportion of such women to the high-risk group.

Hereditary breast cancer susceptibility

A vast majority (90%) of breast cancers are sporadic, i.e. they develop as a result of somatic mutations arising during an individual's lifetime [32]. A proportion of the remainder of breast cancer cases is

Table 2
Breast cancer risk in patients with benign breast disease with or without family history.

Benign Disease	Age	No Family History		1 First-Degree relative affected	
		Gail	Tyrer-Cuzick	Gail	Tyrer-Cuzick
No	50	12.1	12.9	17.3	27.4
	40	13.6	14.7	19.3	28.7
Yes, not AH	50	14.2	24.1	20.1	**48.1**
	40	16.5	27.2	23.2	**50.0**
Yes, AH	50	25.6	**39.9**	**35.0**	**39.9**
	40	29.5	**42.8**	**39.8**	**42.8**

Note: Tyrer-Cuzick Model version 7; assumptions - menarche: 12–13 years; First Childbirth: ≥30 years; Ethnicity: White; Biopsy: 1 (where applicable); FH: Mother breast cancer at 55 years.

individuals with a known heritable germline mutation, the most common of these being mutations in the *BRCA1* and *BRCA2* genes involved in DNA repair [33–36]. Such individuals inherit a single defective (heterozygous) copy of the gene, and acquisition of mutation in the second copy results in the loss of tumour suppressor function leading to the development of malignancy; homozygous inherited loss of *BRCA2* function results in Fanconi Anaemia [37]. *BRCA1* and *BRCA2* are high-penetrance genes [36] i.e. the risk of developing breast cancer is very high as a large majority of mutation carriers (69–72%) will also acquire a mutation in their second copy, thus developing breast cancer in their lifetime (Table 3) [38]. The frequency of these mutations in the general population ranges between 1 in 200 and 1 in 400, whereas these are much more frequent (1 in 40) in certain populations like Ashkenazi Jewish populations [39]. *BRCA* mutation carriers are also at an increased risk of ovarian, pancreatic and prostate (men) cancer [35,40], particularly ovarian cancer with risk estimated to be 44–59% in *BRCA1* and 16–17% in *BRCA2* carriers by 70 years [38,41].

Other genes with less frequent prevalence of mutations as well as lower estimated relative risk of developing breast cancer are *p53, PTEN, CDH1, STK11, PALB2, CHECK2, ATM* and *NF1*. The relative risks and absolute risks of developing breast cancer to the age of 80 years for genes where these can be reliably estimated, are given in Table 3. It is worth noting that as more well-curated data become available, particularly through international collaborative projects, this list and risk estimates continue to get refined. Of particular note are some specific syndromes associated with these mutations such as the Li-Fraumeni syndrome, caused by the loss of function of the p53 tumour suppressor gene [42,43] with median age of onset of breast cancer in early 30s. Germline mutation of STK11 results in the Peutz-Jeghers syndrome, whereas those in PTEN lead to PTEN Hamartoma Tumour Syndrome which includes the Cowden syndrome [44].

Breast cancer prevention in high-risk women – general considerations

Women with a known genetic predisposition and those without

It is important to recognise that the group of women at a high risk of developing breast cancer comprises of women with a known genetic predisposition and those without. The perception of risk, psychological impact of stratification into the high-risk group, and acceptability of intervention and its adverse effects vary between these 2 subgroups of women; and therefore the need for a personalised approach to prevention in these women cannot be overemphasised.

Multidisciplinary approach

The magnitude of intervention in high-risk women is often substantial and irreversible, for example, risk-reducing surgery. Therefore, it is of utmost importance that care of such women should be undertaken by a multidisciplinary team that includes clinical geneticists, radiologists, psychologists, specialist nurses, breast surgeons, gynaecologists and plastic surgeons.

Table 3
Genes with established association between mutations and breast cancer risk.

Gene	Estimated RR (95% CI)	Absolute Risk by 80 years (%)	Median age*
BRCA1	11.4	75	42
BRCA2	11.7	76	45
CDH1	6.6 (2.2–19.9)	53	53
PALB2	5.3 (3.0–9.4)	45	–
CHEK2	3.0 (2.6–3.5)	29	–
ATM	2.8 (2.2–3.7)	27	–
NF1	2.6 (2.1–3.2)	26	–

Adopted and expanded from Easton DF, Pharoah PDP, Antoniou AC, Tischkowitz M, Tavtigian S V, Nathanson KL, et al. N Engl J Med 2015;372:2243–57. https://doi.org/10.1056/NEJMsr1501341. [33].

* Median age for the development of breast cancer.

Lifestyle modifications

Women with high risk of breast cancer will often opt for a preventive intervention/s, however, these should not be considered as a substitute for lifestyle modifications, particularly because some residual risk of developing breast cancer persists even after major preventive intervention/s. The importance of lifestyle modifications should be appropriately discussed at available opportunities, for example, surveillance visits and surgical follow-up consultations.

Initiation of risk management

The age at which risk management in a high-risk woman should start is guided by her genetic predisposition, and the age of diagnosis in her youngest affected relative. The UK-NICE [27] recommends that MRI surveillance should commence at the age of 20 years in *p53* carriers and at 30 years in *BRCA* carriers. On the other hand, the EUSOMA working group [45] recommends that MRI surveillance should commence at an age 5 years prior to the age of diagnosis in the youngest affected relative. Initiation of surveillance offers the opportunity to begin multidisciplinary management, including discussion and sequencing of preventive interventions and lifestyle modifications. It is also important to recognise that the median age of development of breast cancer varies (Table 3) by gene mutations, and therefore, major interventions need to be timed accordingly, for example, earlier risk-reducing surgery in *BRCA1* carriers as compared with *BRCA2* carriers.

Surgical approaches to prevention

BRRM and bilateral risk-reducing salpingo-oophorectomy (BRRSO) are the surgical interventions used in women with high-risk gene mutations to reduce the risk of breast cancer; the latter is mainly employed to reduce the risk of ovarian cancer. The evidence to support the use of these interventions comes from non-randomised studies.

Bilateral Risk-Reducing Mastectomy (BRRM)

BRRM reduces the risk of developing breast cancer by approximately 90% [46–52]. Although sometimes called prophylactic mastectomy, BRRM is a more accurate terminology. *BRCA* mutation status was not known in the earliest of studies [49], therefore the expected breast cancer risk and benefit of intervention may have been overestimated. However, a large body of observational evidence supports substantial reduction in breast cancer risk [52]. BRRM has also been shown to reduce the number of breast cancer deaths and improve breast cancer-specific survival, particularly in *BRCA1* mutation carriers [52,53]. Women undergoing BRRM generally report reduction in anxiety, satisfaction with respect to psychosocial outcome but less satisfaction with cosmetic outcomes [52].

The age at which BRRM (and BRRSO) is considered depends on the patient's completion of family (childbearing), median age to breast cancer development in that gene mutation group and the age of onset in the youngest affected family member. This requires careful discussion and planning, and the discussion process should be initiated by the multidisciplinary team as early as possible in the risk management pathway.

The most commonly performed procedure is subcutaneous/nipple-sparing mastectomy (NSM) through inframammary, radial or lateral approach, often accompanied by immediate reconstruction. Nipple-sparing BRRM is generally thought to provide better cosmetic and psychosexual outcome than skin-sparing or total mastectomy, and approach is guided by the patient's breast size, ptosis and desired breast size following reconstruction; free nipple graft may need to be employed in certain situations.

Immediate reconstruction in the form of implant-based reconstruction or autologous reconstruction using free tissue transfer is commonly employed, although some patients may elect to have delayed reconstruction or no reconstruction at all. More recently, availability of acellular dermal matrix (ADM) has made implant-based reconstruction [54,55] a fairly common procedure. Autologous reconstruction using free tissue transfer is a more extensive procedure and may not be feasible in all

patients. The most commonly used source for autologous free tissue is abdominal wall – transverse rectus abdominis myocutaneous flap or deep inferior epigastric perforator flap [56]. Other free tissue flaps used are superior gluteal artery perforator flap, transverse myocutaneous gracillis flap, profunda artery perforator flap and latissimus dorsi flap.

Bilateral risk-reducing salpingo-oophorectomy (BRRSO)

BRRSO is primarily employed for reducing the risk of ovarian cancer. Early observational studies [57–59] investigating the association between BRRSO and breast cancer risk were confounded by selection bias, family relationships between patients and controls and inadequate information about hormone use; later prospective studies [52,60] showed breast cancer risk reduction in women undergoing BRRSO. Synthesis of evidence excluding the most recent studies [61–63] suggested that BRRSO reduces the risk of developing breast cancer by approximately 50%. The risk reduction appeared to be greater in *BRCA2* mutation carriers than in *BRCA1* carriers [60,64]. A systematic review [65] of evidence shows reduction in breast cancer risk and suggest (low certainty) reduction in breast cancer deaths or improvement in breast cancer-specific survival [65]. However, more robust recent studies correcting for biases, such as immortal-time bias [61–63], suggest the lack of overall benefit except in pre-menopausal *BRCA2* carriers. This is likely explained by the shortening of oestrogen exposure that would have an effect on the development of ER-positive cancers in *BRCA2* carriers. The lack of benefit in postmenopausal women is likely due to the absence of change in the length of oestrogen exposure, whereas the lack of benefit in *BRCA1* carriers could be due to a high proportion of ER-negative tumours in these women.

Therapeutic prevention

Selective oestrogen receptor modulators (SERMs), like tamoxifen, and AIs form the mainstay of endocrine treatment in breast cancer. Both these types of agents have shown efficacy as a preventive therapy [66]. Robust evidence involving more than 83000 participants from 9 major phase III trials shows that SERMs reduce breast cancer incidence by about 38% [67]. Two large phase III trials, IBIS-II [68] and NCIC-MAP.3 [69] evaluating anastrozole and exemestane, respectively, as breast cancer preventive therapy show that AIs reduce breast cancer incidence by at least 50% (Fig. 2). These benefits are restricted to the prevention of ER-positive breast cancers.

All major guidelines such as the UK-NICE [27], the American Society of Clinical Oncology (ASCO) [70], the US National Comprehensive Cancer Network (NCCN) [71] and expert panels like the International Society of Cancer Prevention (ISCaP) now known as the International Cancer Prevention Society (ICAPS) [72] recommend discussing preventive therapy with women at high risk of developing breast cancer.

Long carryover benefit

Long-term follow-up results (median 16 years) of IBIS-I trial [73] are worth noting. These show that tamoxifen continued to reduce breast cancer incidence in the post-treatment period and the reduction in breast cancer was similar between years 0 and 10 (HR = 0.72, 95% CI 0.59–0.88) and after 10 years (HR = 0.69, 95% CI 0.53–0.91). Such a long post-treatment benefit carryover period has important implications for the use of preventive therapy, especially when side effects are generally limited to the period of active treatment.

A greater benefit in women with high-risk lesions

The NSABP-P1 trial reported a larger preventive effect of tamoxifen for women with AH (86% reduction) as compared with those in the trial overall (49% reduction) [74]. A non-significantly greater reduction in breast cancer incidence was noted with tamoxifen in women with AH at entry as compared with those without benign disease in the IBIS-I trial as well [6,73]. Similarly, in the IBIS-II trial, women with LCIS, AH and hyperplasia derived greater preventive benefit (71%) with

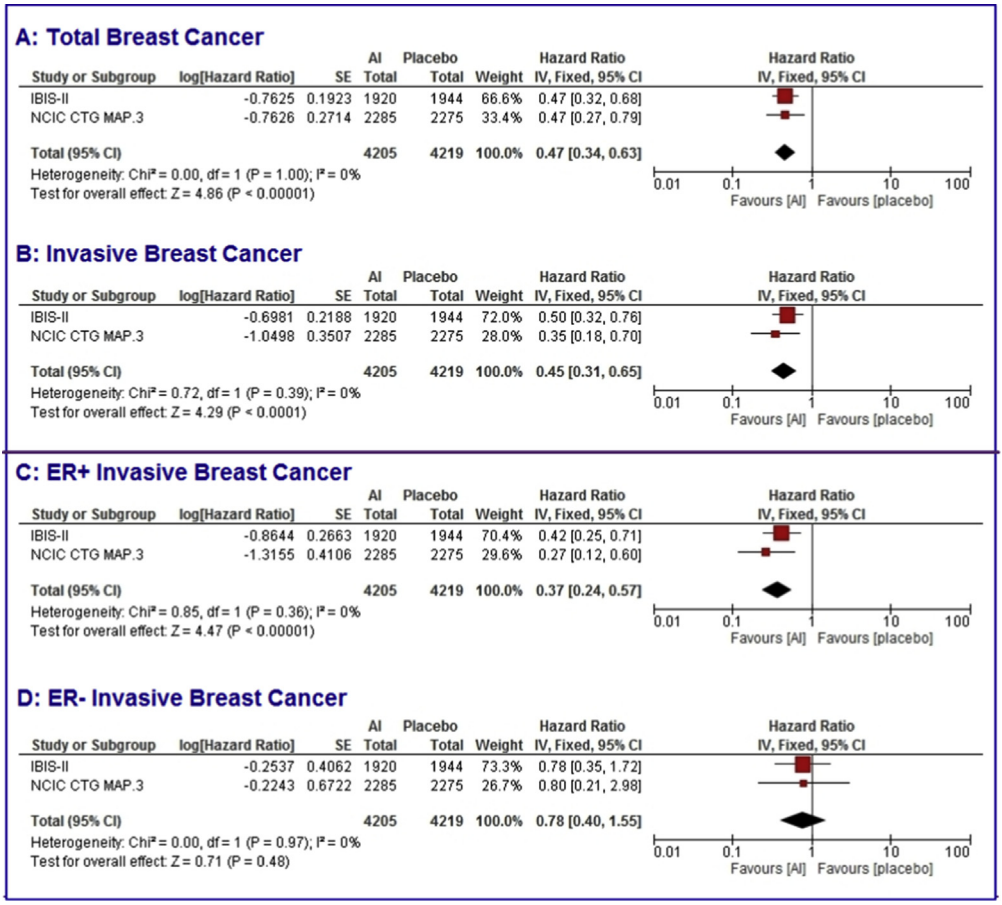

Fig. 2. Forest plots of pooled analyses (fixed effects model) of trials evaluating aromatase inhibitors for breast cancer prevention. Total breast cancer (A); Invasive breast cancer (B); ER-positive invasive breast cancer (C); ER-negative invasive breast cancer (D). Reprinted from Thorat MA, Cuzick J. Breast 2017. https://doi.org/10.1016/j.breast.2017.06.027 [66]. Copyright (2017), with permission from Elsevier.

anastrozole as compared with women without BBD (50%) [6,68]. In the NCIC-MAP.3 [69] trial, however, women with LCIS or AH derived non-significantly smaller preventive benefit with exemestane than those without; a much shorter median follow-up and resulting fewer events for subgroup analyses in this trial need to be taken into account. A greater effect in women with pre-cancerous lesions/BBD may underpin the long carryover effect seen with tamoxifen. Longer follow-up of AI trials will help explore this aspect.

Effect on mortality and tumour subtypes

None of the breast cancer therapeutic prevention trials was designed with either breast cancer-specific or all-cause mortality as an endpoint, and therefore, analyses with mortality endpoints are underpowered to derive any meaningful conclusion, which is discussed in detail by Thorat and Cuzick [2,66]. Briefly, the number of breast cancer events is still small in these trials. As breast cancer survival rates are high, the number of breast cancer deaths is even smaller. Furthermore, the length of follow-up after a breast cancer event is also inadequate, for example, only about 8 years in the IBIS-I trial, which

has the longest follow-up. For ER-positive breast cancer, a much longer follow-up is needed to see a meaningful survival difference [75].

A slight excess of ER-negative tumours (160 vs 131) has been observed in trials of SERMs [67]. Currently, no such excess has been observed in trials of AI. No significant differences or trends in effects of tamoxifen in subgroups by grade, nodal status and tumour size have been observed [73]. Lack of benefit in preventing ER-negative tumours, or a slight excess of such tumours remains an important concern in the use of tamoxifen as preventive therapy in *BRCA1* mutation carriers because almost two-thirds of breast cancers developing in such women are ER-negative (triple negative or basal phenotype) tumours [76,77]. This is much less of a concern in *BRCA2* mutation carriers in whom tumour phenotype is not substantially different than sporadic breast cancers [76,77]. Data from NSABP-P1 trial, based on a very small number of events show that tamoxifen benefit appears to be restricted to *BRCA2* carriers, with a lack of benefit in *BRCA1* carriers [78].

Barriers in the use of preventive therapy

Despite of a large body of supporting evidence and consistent guideline recommendations, the use of preventive therapy in high-risk women remains very low [2]. Several barriers (Table 4) have substantially curtailed the use of preventive therapy in high-risk women, which was reviewed in detail by DeCensi and colleagues [2].

Surgical prevention versus preventive therapy

Although this section heading appears to suggest that surgical prevention and therapeutic (drug-based) prevention are substitutes for each other; these really need to be considered as complementary strategies in offering personalised prevention to individual women. The important differences between these two approaches are the differences in effect sizes in terms of risk reduction and reversible/irreversible nature of intervention; while preventive therapy can be flexibly instituted or withdrawn in the event of adverse effects, surgical interventions are irreversible.

The group of women at a high risk of developing breast cancer essentially comprised of 2 separate subgroups – women with a known genetic mutation and women without any known high-risk mutation. The high-risk status in the former group is often known at a much earlier age, and their lifetime risk estimate is often much higher than the latter group.

Surgical risk-reduction at an appropriate age is often the intervention of choice in mutation carriers after a period of surveillance. This period of surveillance offers an opportunity to discuss and institute preventive therapy, although such an opportunity unfortunately is often not adequately utilised. Arguably, concerns regarding the use of SERMs in young *BRCA1* carriers exist, however, such concerns should not prevent personalised preventive therapy discussion in carriers of other mutations.

Table 4
Barriers to preventive therapy and strategies to overcome these barriers.

Barriers	Strategies to overcome barriers
Physicians' lack of knowledge/prejudices.	Increasing Physician awareness and countering prejudices.
Individual's lack of knowledge.	Improving physician-patient communication and information sharing; educational interventions.
Individual's fear of side effects.	Exploring re-purposing of commonly used agents with well-documented safety profile.
Underestimation of benefits and/or overestimation of harms.	• Acknowledging different needs of risk prediction for different diseases and agents. • Refining risk prediction and risk communication. • Development of biomarkers that can be frequently monitored by non-invasive means.
Adverse effects of agents.	Exploring strategies to reduce adverse effects, e.g. dosing modifications.
Lack of well-proven agents for several cancers.	Increased focus on preventive research, particularly in academia.
Licensing and off-label use issues.	Policy engagement.

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The benefit of BRRM in high-risk women without a known mutation has not been demonstrated and contralateral risk-reducing mastectomy (CRRM) has not been shown to offer risk reduction or survival benefit in high-risk women [52]. The absolute risk-reduction benefit of BRRM would not be substantially different from that of preventive therapy in such women due to a lower baseline risk. Many such women may get assigned to a high-risk category in their 40s, and may be near their menopausal age. This improves the availability of preventive therapy options including the possibility of instituting more efficacious AI-based preventive therapy soon after menopause. The selection of preventive therapy based on the tolerance of side effects/individual preferences may also be possible in these women [79]. Furthermore, a proportion of such women may have been assigned to a high-risk category due to a diagnosis of BBD, where preventive therapy may have even greater efficacy. Therefore, preventive therapy may be considered as the first choice of preventive intervention in high-risk women without a known mutation.

Research priorities

Risk models

Breast cancer prevention in high-risk women is highly dependent on the accuracy of risk stratification. More comprehensive models with the addition of MBD and genotyping information [26] have improved accuracy, however, further increments in accuracy are highly desirable. The accuracy of models is limited when used in ethnicities other than white women [24], and therefore, further research to develop population-specific models such as the Nigerian Breast Cancer Study (NBCS) model [80] is needed. Further research to improve risk prediction accuracy in women with high-risk lesions [28] and BBD is also needed.

Preventive therapy

Reduction in MBD appears to be a good surrogate marker to evaluate the benefit of tamoxifen as preventive therapy [66,81], however, further research is needed to identify surrogate biomarkers of response that are available at baseline. It was only through the long-term follow-up of IBIS-I trial that the long carryover effect of tamoxifen preventive therapy became apparent. The need to continue long-term follow-up of preventive therapy trials cannot be overemphasised. Preventive therapy intervention in the form of tamoxifen in *BRCA1* carriers, yet to reach appropriate age for surgical intervention is fraught with risks, or may not be possible at all while patient contemplates childbearing. Therefore, newer efficacious preventive agents that overcome these limitations are needed. Indeed, denosumab, a human monoclonal antibody that neutralises the receptor activator of nuclear factor κB ligand (RANKL) is being investigated in the BRCA-P trial [82] in *BRCA1* carriers.

Risk-reducing surgery

The psychosocial, psychosexual and cosmetic outcomes (where applicable) have not been robustly investigated in risk-reducing surgeries [52,65], and prospective studies evaluating these are an important area of research. The use of ADM in implant-based reconstructions in BRRM is also increasing, and prospective studies evaluating the use of such animal-source material and its impact on complications, such as capsular contracture as well as cosmetic outcomes, are urgently needed.

Comparison of surgical prevention versus preventive therapy

BRRM is often an intervention of choice in *BRCA* carriers, however, its impact on survival outcomes in *BRCA2* carriers is uncertain. Similarly, BRRM in high-risk women has not been shown to improve survival outcomes. The absolute benefit of risk-reducing mastectomy in *BRCA2* carriers who have undergone BRRSO may not be greater than AI-based preventive therapy. Therefore, scientific equipoise exists in these situations to evaluate the role of risk-reducing mastectomy as compared to preventive

therapy, and further research is urgently needed to evaluate if such a randomised trial is feasible and acceptable to high-risk women.

Practice points

- Women at a high-risk of breast cancer comprise of two subgroups of women - those with and those without high-risk genetic mutation.
- Preventive therapy with SERMs like tamoxifen and AIs substantially reduces breast cancer risk, well beyond the active treatment period, and the effect may be greater in those with BBD.
- Risk management of high-risk women should be undertaken by a multidisciplinary team and preventive interventions should be personalised as per individual's risk profile.
- BRRM reduces the risk of developing breast cancer by 90% in high-risk women, such as carriers of *BRCA* mutations. It also improves breast cancer-specific survival in *BRCA1* carriers. BRRSO may also reduce the risk of breast cancer, particularly ER-positive breast cancer.

Research agenda

- Improvement in accuracy of risk models and risk models for different ethnicities.
- Surrogate biomarkers of preventive therapy benefit.
- Newer preventive agents.
- Evaluation of psychosocial, psychosexual and cosmetic outcomes in risk-reducing surgery.
- Comparison of risk-reducing surgery with preventive therapy in a select subgroup of high-risk women.

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Declaration of Competing Interest

None.

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