Key steps for effective breast cancer prevention

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Abstract | Despite decades of laboratory, epidemiological and clinical research, breast cancer incidence continues to rise. Breast cancer remains the leading cancer-related cause of disease burden for women, affecting one in 20 globally and as many as one in eight in high-income countries. Reducing breast cancer incidence will likely require both a population-based approach of reducing exposure to modifiable risk factors and a precision-prevention approach of identifying women at increased risk and targeting them for specific interventions, such as risk-reducing medication. We already have the capacity to estimate an individual woman's breast cancer risk using validated risk assessment models, and the accuracy of these models is likely to continue to improve over time, particularly with inclusion of newer risk factors, such as polygenic risk and mammographic density. Evidence-based risk-reducing medications are cheap, widely available and recommended by professional health bodies; however, widespread implementation of these has proven challenging. The barriers to uptake of, and adherence to, current medications will need to be considered as we deepen our understanding of breast cancer initiation and begin developing and testing novel preventives.

In high-income countries, breast cancer mortality is decreasing, largely owing to improved treatments[1]. Conversely, breast cancer incidence has been steadily increasing[2–7] owing, in part, to an increase in diagnosis as a result of the implementation of mammographic screening, but also perhaps implying a failure of existing breast cancer prevention strategies[1]. Breast cancer will affect as many as one in eight women in high-income countries by age 85 years and remains the leading cancer-related cause of disease burden for women[8]. Prevention potentially offers the most cost-effective strategy for cancer control and would reduce the social impact of breast cancer.

Clinically, specific subtypes of breast cancer are defined by their histopathological appearance and expression of hormone receptors and growth factors (namely, the oestrogen receptor (ER), the progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2; also known as ERBB2)). Yet it is mostly ER-positive breast cancer that is increasing in incidence[4,5,9].

Both genetic and non-genetic risk factors influence breast cancer development. Genetic factors include pathogenic mutations in high and moderate-risk cancer predisposition genes (for example, *BRCA1* or *BRCA2* and checkpoint kinase 2 (*CHEK2*), respectively) and breast cancer-associated common single-nucleotide polymorphisms (SNPs)[10]. Non-genetic risk factors include increasing age, personal history of breast pathologies (such as atypical hyperplasia and lobular carcinoma in situ), high mammographic density (MD), exposure to therapeutic chest radiation (for example, for treatment of Hodgkin disease), high body mass index (BMI), exogenous female hormone use (for example, menopausal hormone therapy (MHT) and hormonal contraceptives; BOX 1), alcohol, inadequate physical activity and reproductive factors (early menarche, low parity, shorter breastfeeding periods and late menopause). The population frequency of some of these genetic and non-genetic factors, and their associations with breast cancer risk, is shown in FIG. 1. The distinction between genetic and non-genetic risk factors is not absolute, as many of the 'non-genetic' risk factors may have a genetic component that is yet to be fully elucidated[11–13].

This Review discusses the evidence for the role of risk factors in driving breast cancer incidence and their integration into tools to estimate the breast cancer risk for an individual woman — the first essential step towards precision prevention. Furthermore, it evaluates existing medications to reduce breast cancer risk and their associated challenges, as well as outlines the search to find better alternatives. Lastly, learning from the uptake and adherence issues of available medications, the Review also discusses the priorities that need to be considered when developing and implementing alternatives.

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Box 1 | **Role of exogenous hormones in breast cancer risk**

A major change in reproductive behaviours in the last century has been the introduction and widespread use of exogenous oestrogens in the form of hormonal contraceptives and menopausal hormone therapy (MHT)[33,264,278–280], which increase the oestrogen receptor (ER)-positive breast cancer risk[33,265,278,279,281]. The oral contraceptive pill (OCP) is now the most popular form of contraception, with a quarter of women of childbearing age in high-income countries using it at any one time[282].

In the late 1990s, a meta-analysis of individual data from over 150,000 women demonstrated that current users of OCPs had a 24% increased relative risk (RR) of breast cancer. The increased risk attenuates after cessation and is no longer evident 10 years post cessation[264]. A more recent, large Danish study supports these findings and also showed an increased risk associated with use of progestogen-containing intrauterine devices[265]. For OCPs, the RR of breast cancer is higher in current users who commenced use prior to 20 years of age, but because the baseline risk of breast cancer at such a young age is very low, for any given duration of use, early commencement of OCP does not contribute to more breast cancer being diagnosed in younger women than in those who start later in life[264]. Duration of use also impacts on risk; 5 years of use is associated with at least a 5% increased RR, whereas 10 and 13 years is associated with a 12% and 18% increase, respectively[264,265].

A key point is that the increase in absolute risk of breast cancer associated with hormonal contraception is low when the underlying risk is low (for example, in young women at average lifetime risk of the disease), but when the underlying risk is higher (for example, older premenopausal women with a strong family history of the disease) the increase in absolute risk is likely to be of more importance. In fact, it has been estimated that 7% of the breast cancer burden for premenopausal women is due to the use of hormonal contraceptives for 5 years or more[136]. US statistics indicate that as much as 5% of OCP users are older premenopausal women aged 40–49 years[283]. Therefore, when estimating the risk–benefit ratio for an individual woman, her underlying breast cancer risk at her current age is an important consideration.

The Collaborative Group on Hormonal Factors in Breast Cancer recently published their individual participant meta-analysis of the worldwide epidemiological evidence related to MHT and breast cancer risk[33]. They estimated that about 1 million of the approximately 20 million breast cancer cases diagnosed in western countries since 1990 were due to MHT use[33]. Every MHT type, except vaginal oestrogens, increased the breast cancer risk (compared with non-users), which steadily rose with duration of use and was greater for oestrogen and progestogen preparations (combined MHT) than oestrogen-only ones. Specifically, for combined MHT use (1–4 years) there was a 60% increase in risk of breast cancer (RR 1.60), and for oestrogen-only MHT there was a 17% increase (RR 1.17). Risk was greater for longer durations of use: for example, for 5–14 years of combined MHT use, the risk was more than doubled (RR 2.08) and was 33% higher for oestrogen-only MHT (RR 1.33). Furthermore, the RRs during years 5–14 were much greater for ER-positive tumours than for ER-negative tumours. After ceasing MHT, some excess risk persisted for more than 10 years but its magnitude was dependent on the duration of previous use[33]. These findings are consistent with other large studies[281,284–286], although the Women's Health Initiative (WHI) randomized trial showed a protective effect of oestrogen-only MHT for breast cancer, resulting in ongoing controversy over the risks and benefits of oestrogen-only MHT[287].

The relationship between oestrogen and breast cancer risk is complex and it is hoped that preclinical work assessing the effects of oestrogen alone and oestrogen–progestogen therapies on breast tissue may reveal how these therapies alter the breast to impact on cancer risk.

Genetic risk factors

A high incidence of breast cancer in certain families was first noted in 1866 (REF.[14]); however, the most common breast cancer susceptibility genes, *BRCA1* and *BRCA2*, were not discovered until the mid 1990s (REFS[15,16]). *BRCA1* and *BRCA2* are involved in the repair of DNA double-strand breaks through homologous recombination. Inherited mutations in these genes account for about 2.5% of all breast cancer, are responsible for only a minority of breast cancer in women with a strong family history of the disease[17] and result, on average, in about a 70% risk of breast cancer by age 80 years[18]. This average high risk is modified up or down for an individual mutation carrier by her family history of breast cancer, site of mutation and other genetic and non-genetic factors[18]. Other high and moderate-penetrance breast cancer predisposition genes include cadherin 1 (*CDH1*; which encodes E-cadherin), *PTEN*, serine/threonine protein kinase 11 (*STK11*; also known as *LKB1*), *TP53*, *CHEK2*, ataxia telangiectasia mutated (*ATM*), nibrin (*NBN*) and partner and localizer of BRCA2 (*PALB2*), but germline mutations in all of these are rare[19]. However, they are still included in many genetic risk gene testing panels, and additional screening, preventive options and genetic counselling are offered to mutation carriers[20].

Other, much more common, low-penetrance SNPs also affect the breast cancer risk. Although they confer small risks individually, their combined effect, when summarized as a polygenic risk score (PRS), can be substantial[21–23]. An SNP-based PRS can also be combined with other risk factors in risk prediction models, such as the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) and the International Breast Cancer Intervention Study (IBIS), which incorporate family history, age, genetic and other risk factors[24]. An SNP-based PRS also improves risk prediction in women with pathogenic mutations in rare high and moderate-penetrance genes[25,26]. Despite the PRS not being routinely used in clinics, there are large cohorts currently being assessed to see how an SNP-based PRS might affect breast cancer risk management in various settings, including the WISDOM (Women Informed to Screen Depending On Measures of risk) study[27–29]. Additionally, studies to assess chromatin organization are ongoing to identify the actual genes affected by the breast cancer-associated SNPs, which are often not located (in the nucleotide sequence) close to the genes they most strongly influence[30].

Non-genetic risk factors

Although obesity and alcohol use both contribute, the increased incidence of ER-positive breast cancer is driven to a large extent by changes in reproductive patterns[31–35].

Age of menarche and menopause. Since the mid nineteenth century, the average menarcheal age has decreased from 17 to 12 years of age[32,36,37]. The relative risk (RR) of breast cancer increases by 5% for each year younger a woman is at menarche[38]. Factors known to affect age at menarche include gestational exposure to cigarette smoke, diet, psychological state, maternal weight gain and BMI[39–45]. Moreover, the inverse association between BMI and menarche timing is particularly strong[34]. In one sequencing study, 30 new genetic loci encoding proteins involved in lipid metabolism and cell growth were shown to be associated with menarche timing[46]. Additionally, separate studies have shown that increased gestational weight gain is associated with a greater chance of obesity in adolescent offspring, and excessive maternal weight gain has been shown to lower the age at menarche in daughters[34,47,48].

Older age at menopause is associated with an increased RR of breast cancer of 2.9% per year of delay when compared with the mean age of natural

Mammographic density (MD). The extent of white or radio-opaque tissue (dense area) shown on a mammogram. Per cent MD is used to represent this dense area as a proportion of the total tissue area of the breast on a mammogram.

menopause[32,38,49–51]. The average age of menopause has increased from approximately 49 years in 1908 (REF.[52]) to 51.4 years now[53,54]. This 2-year increase in age at menopause would instil a moderate 6% increased RR of breast cancer. Menopause timing is affected by socio-economic status, parity, use of the oral contraceptive pill (OCP) and smoking[55]. In addition, through mother–daughter and twin studies, it has been demonstrated that 44–63% of the timing can be accounted for by heritability[34]. Polymorphisms within the ER signalling pathway have also been found, but more work is required to determine what this means for the level of ER signalling[56,57]. Further implicating hormones in menopause timing, women with a later menopause have longer menstrual cycles, and the latter are suggested to be related to hormone levels in the follicular phase[58]. Research in preclinical models and women should, where possible, focus on determining why the breast is particularly sensitive to cancer risk if there are changes in hormonal exposure at both the beginning and the end of reproductive cycling[34].

Childbearing. Women are having fewer children (and often later in life), which also increases the breast cancer risk, an association identified in the eighteenth century when nuns were found to have an increased risk of breast cancer[59]. Childbearing prior to 35 years of age provides longer-term protection against breast cancer, with the age of first birth being particularly important. If aged <20 years, the longer-term RR is reduced by 70% compared with nulliparous women. As the age at first full-term birth increases, the longer-term protection from parity is progressively lost[35], and for those women who begin childbearing after age 35 years, the risk of breast cancer is higher than for nulliparous women[35,60]. This parity-associated protection has been shown to be specific for ER-positive breast cancer[61–63] but the data related to molecular subtypes of breast cancer are mixed[64,65].

In Australia, as in other high-income countries[66–68], fertility rates have dropped to an average of 1.7 children per woman (compared with 3.5 children in 1960 and 5 children earlier in the twentieth century), almost a quarter of women will remain nulliparous[69,70] and over 60% of parous women delay childbearing until after age 30 years, which provides little or no breast cancer protection[71]. Older age at first birth is most common among highly educated women[70] (average age of first birth in the United States in 2017 was 3.5 years older for college-educated women[72]). These changes in

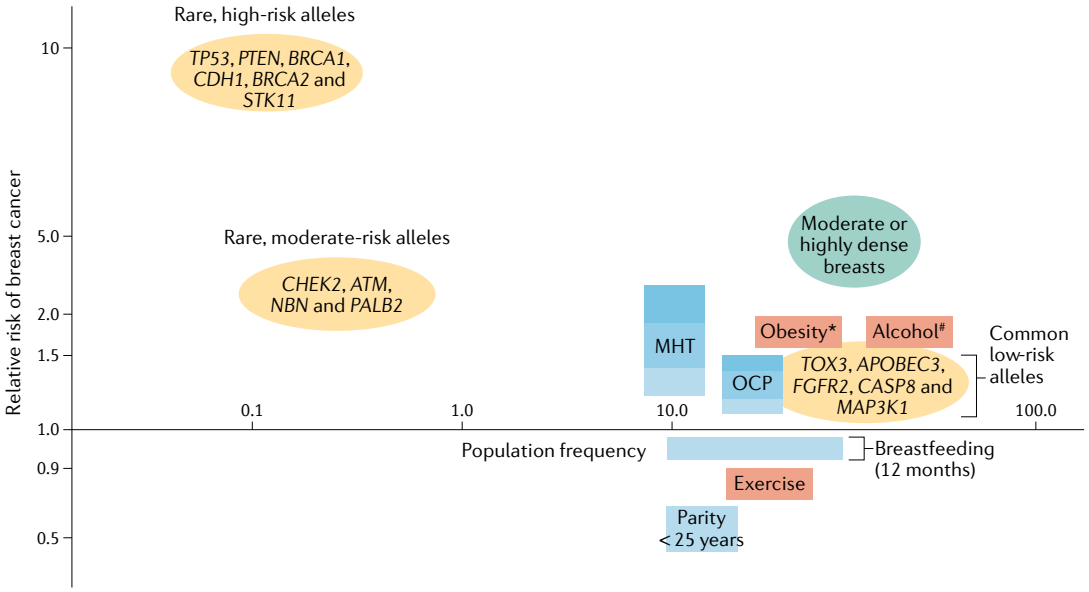

Fig. 1 | **Breast cancer risk modifiers and population frequency.** The population frequency (*x* axis) of genetic and non-genetic breast cancer risk modifiers is shown with their effects on, or associations with, the relative risk (RR) of breast cancer (*y* axis). Rare, high-risk alleles are shown, as are rare, moderate-risk alleles considered to have sufficient evidence to support their association. Examples of common low-penetrance variants, of which there are now several hundred, are also listed[18,19,21–23]. For menopausal hormone therapy (MHT) and oral contraceptive pill (OCP) use, combined oestrogen and progestogen therapy is assumed; dark blue denotes risk for current, long-term users, mid blue denotes shorter periods of use and light blue denotes past users[33,264,265]. *Refers only to postmenopausal obesity[266]. #Refers to 2 glasses of alcohol per day, which is the average consumption level in the 72% of the high socio-demographic index population who are drinkers[134,144]. Exercise refers to most active compared with least physically active[124]. The RR reduction associated with breastfeeding is for 12 months of cumulative breastfeeding[31]. Parity refers to a first full-term childbirth prior to 25 years of age[35]. The RR of breast cancer in women with moderate to high mammographic density (>25% to >75% density) is 1.8–6.0 compared with women with low mammographic density[104]. Currently, 50% of the female population in high-income countries are considered to have moderate (25–50%) to high (>75%) breast density[107]. Orange shapes refer to genetic risk factors, blue shapes to reproductive risk factors and pink shapes to lifestyle factors. *APOBEC3*, apolipoprotein B mRNA editing enzyme catalytic polypeptide-like; *ATM*, ataxia telangiectasia mutated; *CASP8*, caspase 8; *CDH1*, cadherin 1; *CHEK2*, checkpoint kinase 2; *FGFR2*, fibroblast growth factor receptor 2; *NBN*, nibrin; *PALB2*, partner and localizer of BRCA2; *STK11*, serine/threonine protein kinase 11.

Menopausal hormone therapy
(MHT). Sex hormones given to treat symptoms or prevent long-term morbidities associated with female menopause. Also known as hormone replacement therapy.

Menarche
The time in a girl's life when her first menstrual bleeding or period begins.

Parity
The state of having borne offspring (liveborn or stillborn). Also used to indicate the number of pregnancies reaching viable gestational age (liveborn or stillborn — pregnancies resulting in multiple births, such as twins, count as one).

Homologous recombination
The exchange of nucleotide sequences between two similar or identical molecules of DNA. It is used by cells to accurately repair damage that occurs on both strands of DNA, such as double-strand breaks or inter-strand DNA cross-links.

Relative risk
(RR). The ratio of the probability of an event occurring in the group exposed to the modifier of interest versus the probability of the event occurring in the non-exposed group. A relative risk of 1.5 means people exposed to the risk modifier, on average, have a 50% higher risk than those not exposed.

Oral contraceptive pill
(OCP). A birth control pill taken orally. Most contain oestrogen and progesterone, which when given at certain times in the menstrual cycle at defined doses can prevent the ovary from releasing the egg for fertilization.

Post-partum involution process
A cell death-mediated process by which the lactating breast returns to the pre-pregnant state after weaning (or after childbirth if lactation is not initiated). It is characterized by robust tissue remodelling.

Mammary stem cells
(MaSCs). Cells within the mammary gland that have the capacity to form a new mammary tree when transplanted into a cleared mammary fat pad. MaSCs reside within the basal/myoepithelial compartment and can be identified with CD24/EpCAM and either CD29 or CD49f.

reproductive behaviours and increases in breast cancer risk are observed globally[49,73,74].

The protection afforded by pregnancy is not immediate; first, there is a period of increased risk as the breast undergoes a post-partum involution process to return to its pre-pregnant state. This takes, on average, 10 years[75]. Older age of first-time childbearing means that this transient increased RR of breast cancer after birth is more important because the baseline breast cancer risk increases with age and also the transient increase is more prolonged in older first-time mothers[75].

The mechanisms that underlie the protection from breast cancer following childbirth have not been defined. A reduction in the number of mammary stem cells (MaSCs)[76] and reduced sensitivity to oestrogens[77] have been postulated. MaSCs are thought to be the cells of origin for carcinogenic transformation[78,79], and therefore reduced levels of them would leave the breast less susceptible to tumorigenesis[80]. In support of this, the RR of breast cancer owing to radiation exposure (environmental exposure or following treatment of other cancer types) is highest in young women, whom, it is proposed, acquire radiation-induced mutations in long-lived MaSCs[81,82]. Moreover, rat mammary glands are most sensitive to dimethybenz-(a)-anthracene (DMBA)-induced carcinogenesis in puberty, when terminal end buds (believed to serve as niches for MaSCs) are most abundant[79]. However, mouse studies directly assessing the role of MaSCs in parity protection have provided conflicting results[83–85], with one study in particular showing that MaSCs are not in fact localized in terminal end buds[86]. Our group has recently provided some insight into this controversy by demonstrating that whereas cellular repopulating activity is reduced by parity, this is not due to the classically defined MaSCs (K.L.B. and colleagues, unpublished data). Additionally, we have also shown that the number of ER-positive epithelial cells are decreased by parity, leaving the breast less sensitive to the pro-proliferative effects of oestrogen[77]. In line with this, Jindal et al.[87] have also shown that breast tissue of parous women has reduced proliferation.

The immune microenvironment may also contribute to parity-induced protection. However, the relationship is complicated by the fact that protection occurs only after women pass through an increased risk period immediately following the pregnancy as the breast undergoes post-partum involution. During the involution process (assessed during the first 5 years post pregnancy in women and the first weeks in mice) there is a transient period where there are increased numbers of myeloid cells, which can dampen the adaptive immune response and lead to a pro-tumorigenic environment[75,88,89]. However, once involution is completed, parous women are afforded long-term protection against breast cancer. The immune changes that occur at this time are now long-term changes and may mediate the decreased breast cancer risk in parous women. These changes include an enrichment of genes involved in immune surveillance (*SARM1*, T cell receptor β (*TCRB*), human leukocyte antigen-A24 (*HLA-A24*) and interleukin-22 receptor subunit α2 (*IL22RA2*)) when compared with nulliparous postmenopausal glands[89,90]. These genes are instrumental in triggering innate immune responses, activating T cells, eliciting cytotoxic T cell antitumour immunity and promoting apoptosis of tumour cells. Further work is needed to align these gene expression changes to the specific protective changes in the immune microenvironment. Understanding these may allow us to begin assessing the potential of therapeutically instilling a protective immune microenvironment.

Breastfeeding. For every 12 months of breastfeeding, there is a RR reduction for breast cancer of ~4% (REFS[31,73,91,92]). Importantly, the protection conferred by breastfeeding is not limited to ER-positive breast cancer[61,93,94]. The mechanisms of breastfeeding-induced protection are largely unknown; however, glycoproteins stanniocalcin 1 (STC1) and STC2 are increased during lactation and these in turn inhibit protease pappalysin 1 (also known as PAPP-A), an oncogene that is increased during pregnancy, which along with insulin-like growth factor-binding protein 5 (IGFBP5) stimulates tumour formation[95].

Current breastfeeding rates are much lower than the recommendation of the World Health Organization (WHO), which calls for breastfeeding alone for the first 6 months of life, with continued breastfeeding and complementary foods up until 2 years of age or beyond[96]. In Australia and the UK, respectively, 90% and 69% of women initiate exclusive breastfeeding; however, 50% and 23% of these have ceased by 6–8 weeks[97–99]. Moreover, Victora et al.[100] found that, in low-income and middle-income countries, only 37% of children younger than 6 months of age were exclusively breastfed. Breastfeeding rates and duration could potentially be rapidly increased by scaling up known interventions, policies and programmes, such as lactation support programmes, reinforcing a breastfeeding culture (for example, by removing actual and perceived restrictions on breastfeeding in public), adequate paid parental leave, flexible working arrangements and prohibition of aggressive and inappropriate marketing of breastmilk substitutes[101].

Mammographic density. There are multiple ways to measure MD, and controversy exists over the measure that best correlates with breast cancer risk. The Breast Imaging Reporting and Data System (BI-RADS) is the most commonly used tool clinically and includes four categories (almost entirely fat, scattered density, heterogeneously dense and extremely dense)[102]. Limitations of the BI-RADS assessment include that it provides crude categorical estimates of density (rather than a continuous measure) and is reader dependent. There have been five BI-RADS editions, with the 2017 release including clarification of previous terms to assist with risk stratification[103].

Many studies have demonstrated that, after adjustment for age and BMI, MD is an independent risk factor for breast cancer, with a RR ranging from 1.8 to 6.0 in women with high MD (HMD) when compared with those with low MD (LMD)[104]. A systematic review

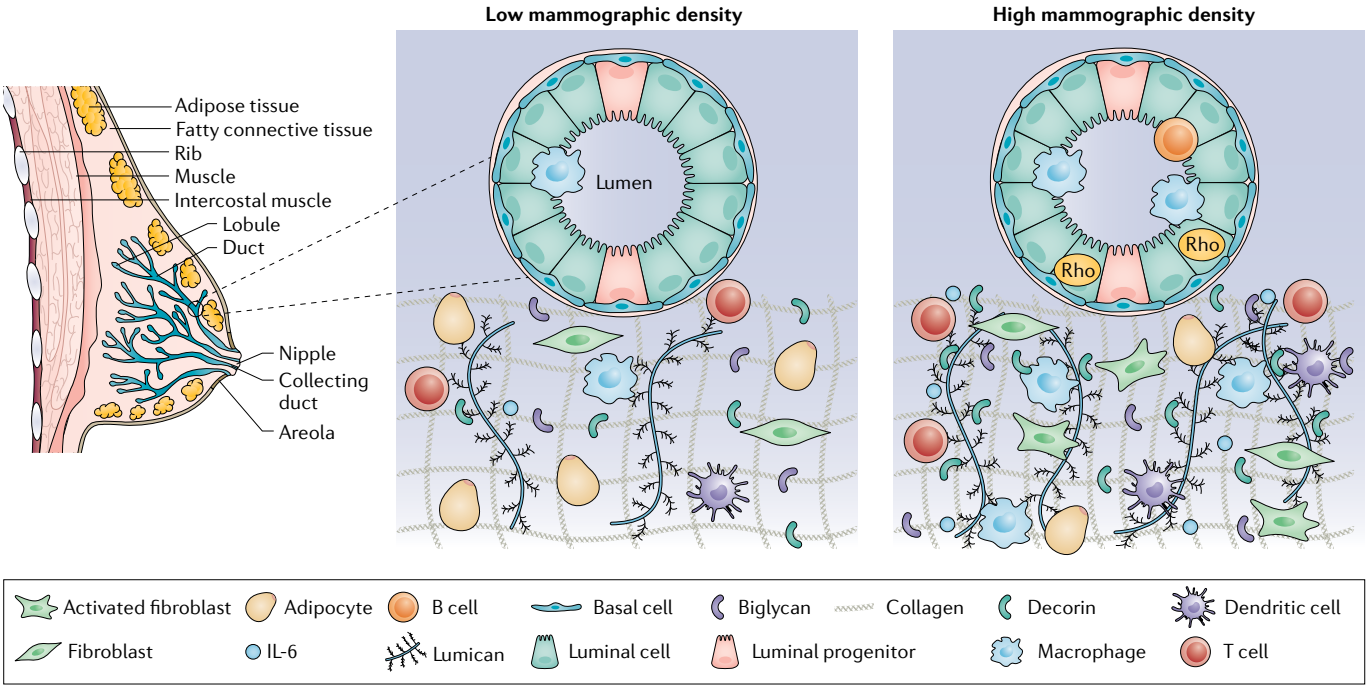

Fig. 2 | **Biological differences between high and low mammographic density.** Breast tissue with high mammographic density (HMD) has been shown to have increased levels of stroma and epithelium compared with areas with low mammographic density (LMD)[108]. Note that within the epithelium, however, an increase in stem or progenitor cells has not yet been shown. Tissue with HMD also has an increased amount of structured collagen. Breast cancer is often localized in areas of dense collagen or is stimulated to grow when the breast has increased stromal collagen[267]. Additionally, the collagen-binding proteoglycans lumican, decorin, fibromodulin and biglycan are also associated with HMD[268]. Lumican can induce initiation and progression of breast cancer by increasing angiogenesis, epithelial cell growth, migration and invasion[269]. The increased stiffness resulting from these extracellular matrix (ECM) changes may drive cancer formation through higher mechanical force and resistance to contractility on the epithelial cells (via focal adhesions and the Rho GTPase signalling pathway) driving proliferation[270]. Stromal fibroblasts in areas of HMD have also been shown to exhibit gene expression signatures associated with cancer-stimulating pathways, such as stress response, inflammation, stemness and signal transduction[271]. Breast cancer with immune infiltration is known to have better prognosis and may respond to chemotherapeutic drugs and be responsive to immune-based therapies[272,273]. However, less is known about immune infiltration in the normal breast and early, pre-invasive lesions. Tissue with HMD has been shown to have a pro-tumorigenic immune microenvironment, including increased innate cells (macrophages and dendritic cells), adaptive cells (T and B cells) and increased levels of interleukin-6 (IL-6), which may aid escape from immune regulation for early tumour cell variants[109]. Furthermore, the ECM has been shown to modulate activation, fate determination and chemotaxis of immune cells[274–276], indicating that the changes may be interrelated.

and meta-analysis of 42 studies found that the RR for breast cancer was 2.92 and 4.64 for women with heterogeneously dense or extremely dense breasts, respectively, compared with women with almost entirely fatty breasts[104]. Hopper and colleagues showed that measures of MD may explain more variation in risk across the population than known genetic variants, when adjusted for other risk factors, in particular age and BMI[105,106].

HMD is an important breast cancer risk factor, not only because of the magnitude of the risk with which it is associated but because it is highly prevalent; 43% of women in high-income countries aged 40–74 years have extremely or heterogeneously dense breasts[107]. In the United States, this corresponds to more than 27.6 million women. The United States and the state of Western Australia are the only places where standardized mammographic reporting includes a MD measure, largely resulting from consumer advocacy campaigns. The lack of routine MD reporting globally may be owing to controversy over which density measure best correlates with risk and a lack of clear clinical pathways for management of women with HMD.

Although generally considered a non-genetic risk factor, twin studies have demonstrated that about 60% of the variation in MD is explained by genetic factors[13]. The pathobiology underlying HMD is not well understood but recently has been correlated with increased levels of stroma and epithelium[108] as well as immune cells[109] compared with LMD (FIG. 2).

Lastly, MD is also emerging as a potential biomarker for prevention. A reduction of MD greater than 10% following treatment with the selective ER modulator (SERM) tamoxifen has been associated with a 63% breast cancer risk reduction (odds ratio (OR) 0.37)[110]. However, the case for aromatase inhibitors (which reduce postmenopausal oestrogen synthesis) is not as strong[111]. The reasons why MD is appealing as a predictive biomarker are that it is strongly associated with endocrine exposure, is non-invasively measured and can be incorporated into routine patient management. Nevertheless, before it is

Odds ratio
(OR). A statistic that quantifies the strength of the association between an exposure and an outcome. OR = 1 means that the exposure does not affect the odds of outcome, OR > 1 means that the exposure is associated with higher odds of outcome, and OR < 1 means that the exposure is associated with lower odds of outcome.

introduced we need to determine the change threshold in MD that best predicts improved outcome, the most accurate predictive parameter of MD (that is, per cent density versus absolute measures or categorical density (BI-RADS, Boyd or Wolfe[112,113])) and how we should interpret MD (that is, visual versus computer-assisted versus fully automated methods).

Overweight and obesity. High BMI in the postmenopausal years is associated with a significant increase in breast cancer risk, although it appears protective in premenopausal women. Specifically, in an international meta-analysis of ten studies from nine prospective cohorts and 22 case–control studies, postmenopausal women in the highest body weight categories had an 82% increased RR for ER-positive breast cancer compared with those in the lowest body weight categories; there was no association with the other breast cancer subtypes[114]. Conversely, premenopausal women in the highest body weight category had a 20% lower risk of developing ER-positive breast cancer (similarly, there was no association with the other breast cancer subtypes). Several mechanisms have been proposed to explain the link between increased BMI and cancer risk, including increased conversion of androgens to oestrogens, insulin and insulin-like growth factor (IGF) signalling, adipokine pathophysiology and chronic inflammation[115]. For breast cancer specifically, the case for hormonal stimulation is supported by in vitro and in vivo experimental data[116] and the fact that male breast cancer risk factors (obesity, Klinefelter syndrome and gynaecomastia) are associated with increased oestrogen levels[117].

The Iowa Women's Health Study and the Nurses' Health Study showed that women who maintained or lost weight as they got older had a reduced RR of postmenopausal breast cancer[118,119]. This is supported by earlier epidemiological studies showing that weight loss of >10 kg between 22 and 44 years of age was associated with an OR of 0.6 (REF.[120]). Meta-analyses have also confirmed that adult weight gain is associated with increased postmenopausal, but not premenopausal, breast cancer risk[121]. However, it is only those women with BMI <23.4 kg/m^2 at age 20 years who had their breast cancer risk influenced by adult weight gain[122]. It is not clear why BMI at age 20 years impacts postmenopausal breast cancer risk but it is postulated to be due to hormonal differences in adolescent girls with high BMI[122].

Physical inactivity. Independent of BMI-mediated risk reduction, moderate to vigorous physical activity is associated with about a 20% reduced RR of breast cancer when comparing the most with the least physically active women[123–126]. Informed by these findings, the World Cancer Research Fund has concluded that physical activity probably protects against breast cancer[127]. Independent of changes in adiposity, mechanisms that may account for this protection include physical activity effects on oestrogen metabolism, insulin sensitivity, chronic low-level inflammation, oxidative stress and immune function[124,126]. Physical activity-induced transcriptional changes are also possible[128,129]. Experimental studies have also directly addressed why exercise is beneficial. For example, the colony-forming ability of non-small-cell lung cancer (NSCLC) cells is reduced by 80% after pre-incubation with conditioned serum from exercised individuals[130], and the tumour incidence in mice is halved[131,132]. Work is underway to define the molecular signals underlying this. Although the optimal level of physical activity necessary for breast cancer prevention is not clear, as more than half of the population in high-income countries (including Australia, the UK and the United States) do not meet the recommended physical activity guidelines[133] there are opportunities for improvement.

Alcohol. Data from the Nurses' Health Study showed that women consuming 5–10 g of alcohol per day (that is, 3–6 glasses of wine per week) were 15% more likely (RR 1.15) to develop breast cancer than non-drinkers, and those consuming at least 30 g per day (that is, at least 2 drinks per day) were 50% (RR 1.50) more likely[134]. Similar results were found in the Million Women Study[135]. Using a large prospective pooled Australian cohort, Arriaga et al.[136] have recently shown that regular alcohol consumption is the leading modifiable cause of breast cancer burden for premenopausal women, explaining 12.6% of breast cancer.

The mechanism by which alcohol (now considered a class I carcinogen by the International Agency for Research on Cancer (IARC)) increases breast cancer risk is an active area of study. Ethanol is known to stimulate cell proliferation and the transcriptional activity of ligand-activated ER, which in turn increases levels of circulating oestrogen levels[137,138]. Ethanol metabolism takes place mainly in the liver, where it is oxidized to acetaldehyde by the alcohol dehydrogenase (ADH) enzymes; however, ADH enzymes are also expressed in the breast[139]. Acetaldehyde can induce DNA strand deletions, chromosome aberrations and DNA adducts, and is considered mutagenic and carcinogenic[140]. Furthermore, some experimental work has been performed in mice looking at the effects of alcohol on the immune response to cancer[141]. It was found that CD8$^+$ cytotoxic T cells (which are capable of killing tumour cells) were decreased, in particular CD8$^+$ memory T cells, which enable an efficient antitumour response should relapse occur. Myeloid-derived suppressor cells (MDSCs) were also increased, which suppress T cell responses, as well as CD3$^+$ invariant natural killer T (NKT) cells, which had a pro-tumorigenic expression profile[141]. Overall, this suggests that alcohol suppresses the ability of the immune system to respond to cancer.

The World Cancer Research Fund and the American Institute for Cancer Research (AICR) report recommends that if alcoholic drinks are to be consumed, this is limited to no more than two drinks a day for men and one drink a day for women[142]. Although earlier research supported potential health benefits for low to moderate alcohol intake[143], more recent, methodologically robust research has concluded that the safest level of alcohol intake is none[144]. Alcohol is an ingrained aspect of the culture in many parts of the world. Reducing population intake of alcohol will require government commitments

Adipokine
A cell signalling protein secreted by adipose (fat) cells.

Klinefelter syndrome
A genetic condition, affecting about 1 in every 550 men, in which a male is born with an extra copy of the X chromosome. This results in higher levels of female hormones.

Gynaecomastia
Excessive enlargement of the male breast. May be unilateral (one side) or bilateral (both sides).

Absolute risk
The risk of developing a disease over a time period, for example, a person may have a one in ten risk (that is, a 10% risk) of a certain disease in their life. Absolute risk is one of the most easily understood ways of communicating health risks to the general public.

Hazards ratio
(HR). A measure of how often a particular event happens in one group compared with another group, over time. HR = 1.0 means that there is no difference in survival between the two groups. HR >1.0 or HR <1.0 means that survival was better in one of the groups.

Basal-like breast cancer
A breast cancer subtype that is more prevalent in African-American women, characterized by high histological grade, high mitotic indices and lack of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) protein overexpression.

Polygenic disease
A genetic disorder that is caused by the combined action of more than one gene.

Breast cancer risk estimation models
Tools that estimate a person's likelihood of developing breast cancer within a specific time frame.

Discriminatory accuracy
The ability of a risk model to separate individuals who will get breast cancer from those who will not. A value of 1.0 represents perfect discrimination, a value of 0.5 means that the model performance is no better than chance alone, values of 0.6–0.7 are considered good and values of 0.5–0.6 are considered sufficient.

Calibration
The ratio of the observed number of breast cancer cases to the expected number; values of one indicate optimal calibration.

to developing and implementing policies similar to those that have reduced smoking rates in many jurisdictions, such as increased alcohol taxation, control of the physical availability of alcohol and hours of sale, banning alcohol advertising and implementing plain packaging.

Lifestyle. It is important to note that the benefits of a healthy lifestyle in terms of reducing breast cancer risk are particularly important, in absolute terms, in women at high familial risk of the disease. We have shown that the RR for associations between breast cancer risk factors such as BMI and physical activity are similar regardless of the underlying familial risk[145,146]; this means that the absolute risk associated with higher BMI or lower physical activity is much greater for women at high familial risk compared with those at population risk. Therefore, it is crucial that the larger potential benefits for lifestyle changes are explained to women at increased risk who may otherwise feel that the familial factors are so overwhelming that there is little to be gained by lifestyle adjustment. Unfortunately, there is limited interventional trial data on lifestyle changes. However, the Women's Health Initiative (WHI) dietary modification trial showed that reduced fat intake and increased consumption of vegetables, fruits and grains led to a 5% relative reduction in breast cancer risk (hazards ratio (HR) 0.95) at the long-term follow-up (19.6 years)[147]. Further well-designed lifestyle intervention trials assessing impacts on breast cancer risk are needed and will surely help to convince those at risk of the impact these changes could have on their personal risk.

Breast cancer risk in diverse populations

The National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program showed that, in the United States, the age-adjusted breast cancer incidence for ethnic minorities was lower than that for white women, with 141 cases per 100,000 in white women, 122 cases per 100,000 in African American women, 97 cases per 100,000 in Asian and Pacific Islander women, 90 cases per 100,000 in Hispanic women and 58 cases per 100,000 in American Indian and Alaskan Native women[148]. This difference of breast cancer incidence with respect to ethnicity is also seen in global breast cancer statistics[8,149]. The difference in risk factors across the ethnicities and the use of screening mammography could explain some of the differences, but the breast cancer incidence was still significantly lower in African American women than in white women when adjusted for these differences[148]. Despite the lower overall incidence, African American women are more likely to be diagnosed with advanced and largely ER-negative breast cancer compared with white women[150]. Although the reason for these differences is not fully understood, it may involve the known associations between certain risk factors and disease subtypes. For example, multiparity and early first pregnancy protects against ER-positive luminal breast cancer, but does not protect against the development of basal-like breast cancer[62,151].

Heritability analyses show that breast cancer is a highly polygenic disease[152]. In addition to the rare, high-risk alleles, there are common variants with a small effect on risk (FIG. 1). The use of a PRS assessing the effects of these variants on risk has only been thoroughly validated in European populations. Only the Breast Cancer Risk Assessment Tool (BCRAT) from the National Institutes of Health (NIH) has been validated for use in black or African American women, Hispanic women and Asian and Pacific Islander women[153–155]. Genome-wide association studies (GWAS) in multiple ethnicities, such as the NCI-led Confluence project (300,000 breast cancer cases and 300,000 controls), will drive a better understanding of the aetiology of breast cancer and allow us to improve risk stratification across ancestry groups.

Predicting breast cancer risk

A key component of optimal precision prevention is the capacity to accurately estimate a woman's breast cancer risk. This facilitates the use of evidence-based prevention interventions appropriate to the woman's personal risk level. It also enables calculation of the absolute risk reduction from preventive interventions, thus assisting informed decision-making.

Breast cancer risk estimation models now exist that attempt to quantify the combined effect of many of the breast cancer risk factors discussed above[156]. Many of these models have not undergone independent validation in study populations other than those used in their development and will not be considered further here. The independently validated models vary regarding the risk factors they utilize. The risk factor inputs for some of the main models are shown in TABLE 1 (REFS[157–165]).

Most of the validated models[160,162,164–170], but not all[157–159,161,171], incorporate non-familial risk factors to varying degrees. The IBIS model encompasses the most comprehensive list of risk factors and performs well in comparative validation studies[163,172–175]. Polygenic risk owing to SNPs has been shown to predict breast cancer risk almost independently of other factors, including MD[175], and the IBIS model is the only validated, widely available model that currently incorporates polygenic risk[175,176].

The performance of risk prediction models is often measured based on their discriminatory accuracy and calibration. The performance of the various breast cancer risk prediction models varies, with discriminatory accuracy ranging from 0.56 to 0.71 (poor to good)[177] and calibration ranging from 0.85 to 1.52 according to a recent systematic review[178]. Work is ongoing to improve the accuracy of these risk prediction models. For example, common risk prediction models do not currently include some modifiable risk factors, such as alcohol, hormonal contraception use, physical activity or time since last pregnancy. It will also be important to determine whether additional, more novel risk factors, such as steroid hormone levels (for example, oestradiol and testosterone)[179], epigenetic markers[180] and double-strand DNA repair phenotype[181], will give maximal improvement to the models. Incorporation of new risk factors into existing models will require consideration of potential interactions with existing risk factors and extensive validation, preferably using prospective data.

Table 1 | **Comparison of model inputs for major breast cancer risk estimation models**

Model input	Risk estimation model				
	BCRAT[160,162]	IBIS[163,165]	BRCAPRO[a159,161,259]	BCSC[164]	BOADICEA[157,158]
Individual factors					
Age	≥35	+	+	+	+
Race or ethnicity	+	+	+	+	+
Age at menarche	+	+	NA	NA	NA
Age at menopause	NA	+	NA	NA	NA
Age at first birth	+	+	NA	NA	NA
Parity	NA	+	NA	NA	NA
BMI	NA	+	NA	NA	NA
Hormonal contraception use	NA	NA	NA	NA	NA
MHT use	NA	+	NA	NA	NA
Alcohol use	NA	NA	NA	NA	NA
Breast-related factors					
Number of prior breast biopsies	+	+	NA	+	NA
Atypical hyperplasia	+	+	NA	NA	NA
LCIS	NA	+	NA	NA	NA
Other benign pathology	NA	+	NA	NA	NA
Mammographic density	NA	+	NA	+	NA
Therapeutic irradiation[b]	NA	NA	NA	NA	NA
Genetic testing					
BRCA1 or *BRCA2*	NA	+	+	NA	+
Other high-risk genes	NA	NA	NA	NA	+
SNPs or polygenic risk score	NA	+	NA	NA	–[c]
FHx factors[d]					
Cancer status of first-degree relatives	+	+	+	+	+
Cancer status of second-degree relatives	NA	+	+	NA	+[d]
Age at breast cancer diagnosis	NA	+	+	NA	+
Pathology of breast cancer	NA	NA	+	NA	+
Bilateral breast cancer	NA	+	+	NA	+
Male breast cancer	NA	+	+	NA	+
Ovarian cancer	NA	+	+	NA	+
Pancreatic and prostate cancer	NA	NA	NA	NA	+
Genetic testing	NA	+	+	NA	+
Mastectomy status	NA	NA	+	NA	NA
Oophorectomy status	NA	NA	+	NA	NA

Web links to the online risk estimation models can be found in Related Links box. +, input possible; BCRAT, Breast Cancer Risk Assessment Tool; BCSC, Breast Cancer Surveillance Consortium; BMI, body mass index; BOADICEA, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; FHx, family history; IBIS, International Breast Cancer Intervention Study; LCIS, lobular carcinoma in situ; MHT, menopausal hormone therapy; NA, not applicable; SNP, single-nucleotide polymorphism. [a]BRCAPRO is a statistical model, with associated software, for assessing the probability that an individual carries a germline deleterious mutation of the *BRCA1* and *BRCA2* genes. [b]For example, mantle field radiation for Hodgkin disease. [c]Newest version of BOADICEA, version 5, includes SNPs. [d]Includes family history of breast, ovarian, pancreatic or prostate cancers in first-degree, second-degree and/or third-degree relatives.

The current models have other limitations besides their limited discriminatory accuracy. Firstly, the models tend to have different performance characteristics depending on the subset of women they are applied to, but many clinicians are not skilled in choosing the most appropriate risk model and neither do clear guidelines exist[182]. A related issue is that the models have been developed and validated largely in populations of European descent, so their accuracy in estimating breast cancer risk for women of other ethnicities is uncertain. Importantly, none of the major validated risk estimation models couples the risk estimation to comprehensive, personalized breast cancer prevention and screening advice, nor estimation of the absolute risk reduction

that can be achieved. Lastly, most of the models have user interfaces that are difficult for women and less experienced clinicians to use. We have recently developed iPrevent[183] to overcome these issues and to facilitate collaborative decision-making about breast cancer risk management, between women and their clinicians. Women can complete the tool online at home and print the output for discussion with their clinician. iPrevent has been independently validated, is well calibrated and has good discriminatory accuracy (0.70 overall and 0.74 for women under age 50 years)[184]. It has good acceptability and usability for both women and clinicians and seems to improve the accuracy of risk perception without adversely affecting anxiety[185].

To date, all of these breast cancer risk models have generally been used on an ad hoc basis and, to our knowledge, there has been little consideration of population-based risk assessment followed by targeted risk reduction, despite the potential of precision prevention to reduce breast cancer incidence.

Targeted risk reduction might include modifying the specific risk factors (such as alcohol intake, use of MHT and hormonal contraceptives, physical inactivity and obesity) contributing to each woman's personal risk and, for some women at higher risk, consideration of risk-reducing medication. It is known that consumers find the constant information about breast cancer risk factors in the media and other sources confusing and are often uncertain how it pertains to them as individuals, with many having expressed a preference for more targeted information[186]. In Australia, formally assessing breast cancer risk at the time of (free, government-funded) breast screening in order to risk stratify women for different screening approaches is currently being considered. However, given that breast screening usually starts at age 50 years, such an approach would provide no opportunity to prevent the approximately 20% of breast cancer that occurs before that age[187]. We suggest that consideration should be given to routine risk assessment of women in the general population in early adulthood (and at regular intervals thereafter, given that risk factors change over time). Nevertheless, it will be important to identify a risk assessment tool that is accurate and easy to use; shows that such risk assessment results in behavioural change and uptake of risk-reducing medication that will reduce breast cancer risk without increasing anxiety beyond acceptable thresholds; and determines the cost, suitability and feasibility of such an approach in different health-care systems and among different subgroups (for example, by ethnicity, age and socio-economic status).

Currently available preventive options

Women at increased risk of breast cancer have several options to reduce their risk, including surgery, medication and lifestyle options (the latter is also relevant to women at moderate risk). TABLE 2 summarizes the major US and UK guidelines[188–190].

Table 2 | **UK and US breast cancer prevention guidelines for women at increased risk**

Professional body	Intervention			
	RRBM	RRSO	Medication[a]	Lifestyle factors
NCCN[188]	Consider for: high-risk breast cancer gene mutation; compelling FHx; prior thoracic RT below the age of 30 years	Controversy over whether RRSO reduces breast cancer risk for BRCA mutation carriers but, based on the OC risk, recommend for: *BRCA1* between age 35 and 40 years; *BRCA2* between age 40 and 45 years. Exercise caution in prescribing HRT post RRSO	Offer if: ≥35 years old with 5-year breast cancer risk ≥1.7%; have LCIS. Premenopausal: tamoxifen; postmenopausal: tamoxifen, raloxifene, exemestane or anastrozole	MHT (consider associated breast cancer risk); alcohol (limit consumption); exercise (premenopausal: vigorous; postmenopausal: moderate to vigorous); healthy weight; breastfeeding
NICE[189]	Consider for: lifetime risk ≥30%	Consider for: lifetime risk ≥30%; offer MHT up until age of natural menopause — oestrogen alone if prior hysterectomy, combined MHT otherwise	Consider if: lifetime risk ≥17%. Premenopausal: tamoxifen; postmenopausal: anastrozole (unless severe osteoporosis), tamoxifen (if severe osteoporosis or if the individual does not want to take anastrozole) or raloxifene (if the individual does not want to take tamoxifen)	OCP (if >35 years old inform of increased risk of breast cancer; for *BRCA1* mutation carriers, discuss potential increased risk of breast cancer before age 40 years); breastfeeding; MHT (advise of increased breast cancer risk; tailor use to individual circumstances; use lowest dose for shortest time possible (generally not after age 50 years); prescribe oestrogen without progesterone if hysterectomy); alcohol (advise of increased breast cancer risk); smoking (advise cessation); healthy weight; exercise
ASCO[190]	NA	NA	Consider if: ≥35 years old with 5-year risk ≥1.66 or have LCIS. Premenopausal: tamoxifen; postmenopausal: raloxifene, exemestane or anastrozole	NA

ACSO, American Society of Clinical Oncology; FHx, family history; HRT, hormone replacement therapy; LCIS, lobular carcinoma in situ; MHT, menopausal hormone therapy; NA, not applicable; NCCN, (US) National Comprehensive Cancer Network; NICE, (UK) National Institute for Health and Care Excellence; OC, ovarian cancer; OCP, oral contraceptive pill; RRBM, risk-reducing bilateral mastectomy; RRSO, risk-reducing bilateral salpingo-oophorectomy; RT, radiotherapy. [a]A 5-year course; no guideline currently recommends a 3-year lower-dose course as tested by DeCensi et al.[224], although ASCO guidelines suggest that women who stop tamoxifen after 3 years will likely still derive benefit and that for women with intraepithelial neoplasia the low dose of tamoxifen (5 mg per day) may be an alternative if there are concerns over adverse events with the higher dose.

Bilateral mastectomy
The removal of as much breast tissue as possible to reduce the breast cancer risk.

Bilateral salpingo-oophorectomy
A surgical procedure to remove both ovaries and fallopian tubes.

Risk-reducing bilateral mastectomy. The most effective measure for reducing breast cancer risk is bilateral mastectomy, although guidelines recommend limiting this to women at substantially increased risk. There are no randomized trials of this intervention, but observational studies show that it is associated with a 90% reduction in risk[191,192]. Immediate breast reconstruction is usually offered, although it is associated with much higher rates of unanticipated reoperations. Most women are satisfied with their decision to have bilateral risk-reducing mastectomy and have a significant reduction in worry associated with getting breast cancer, but there is less satisfaction with cosmetic results, body image and sexual feelings[193]. Risk-reducing mastectomy that spares the nipple has better cosmetic outcomes than simple or skin-sparing mastectomy, and limited data suggest that it confers similar risk reduction[194]. Uptake of risk-reducing bilateral mastectomy in high-risk women is highly variable, with high uptake rates in the United States, the UK, the Netherlands and Norway and low rates in Poland and France[195].

Bilateral salpingo-oophorectomy. Bilateral salpingo-oophorectomy is effective at reducing the risk of cancers of the ovary and fallopian tube. *BRCA1* and *BRCA2* mutation carriers are generally counselled to consider this procedure by the age at which their ovarian and fallopian tube cancer risk increases above that of the general population, that is by their late 30s (for *BRCA1* carriers) and late 40s (for *BRCA2* carriers)[18]. Historically, these women have also been counselled to consider the procedure at an earlier age (after childbearing) in order to reduce their breast cancer risk. Randomized trial data on the efficacy of bilateral salpingo-oophorectomy in reducing breast cancer risk are not available. Earlier studies suggested halving of the breast cancer risk for mutation carriers who underwent risk-reducing salpingo-oophorectomy (RRSO)[196]; however, issues related to the methodology used in this study have been raised[197]. Furthermore, recent prospective cohort studies have found no convincing overall association between RRSO and breast cancer risk in *BRCA1* or *BRCA2* mutation carriers[198–200].

Lifestyle modification. Modification of non-genetic risk factors, such as obesity, alcohol use and lack of physical activity, is an important component of breast cancer prevention. In general, these non-genetic risk factors confer similar RRs of breast cancer in high-risk women as for those in the general population[201]. Unfortunately, lifestyle modification can be difficult to achieve and sustain. Therefore, focus on the development of efficacious interventions for behavioural change as well as government policies, as already discussed, to support healthy lifestyles will be essential.

Clinically available risk-reducing medication. Risk-reducing medication is an important prevention option for women at increased risk of breast cancer who do not wish to undergo (or who wish to postpone) risk-reducing mastectomy or whose risk is increased but not elevated enough for surgery to be considered appropriate. The risk-reducing medications recommended in international guidelines are the SERMs tamoxifen and raloxifene, and the aromatase inhibitors exemestane and anastrozole (see TABLE 2). None of these has been shown to reduce breast cancer mortality, and all of them are only able to reduce the risk of ER-positive breast cancer. Nevertheless, ER-positive breast cancer is the most common type, and avoiding a breast cancer diagnosis and subsequent treatment, even if that breast cancer was not going to result in premature mortality, seems a worthwhile goal in terms of reducing the burden on the health-care system, women and their families.

Tamoxifen is the best-studied risk-reducing medication and is the only preventive agent that has been demonstrated to be effective in premenopausal and postmenopausal women. It reduces the ER-positive breast cancer risk by 33% (REF.[202]), with the risk reduction seen not only during the 5 years of taking the medication but also for at least 15 years after cessation[203]. Reductions in MD in tamoxifen users correlate with its preventive efficacy[110]. However, side effects of tamoxifen can include menopausal symptoms, such as hot flushes, and a doubling of the risk of thrombosis, although the absolute risk remains low, particularly in younger women[204]. Tamoxifen also doubles the risk of endometrial cancer in postmenopausal women, although again the absolute risk is small[204]. Another major impediment to uptake of tamoxifen by premenopausal women for a 5-year period is the inability to prescribe it safely in women who are trying to conceive, who are pregnant or who are lactating and the fact that women need to use a non-hormonal form of contraception[205].

Raloxifene, another SERM, has only undergone trials in postmenopausal women. Raloxifene (60 mg daily for 5 years) was compared directly with tamoxifen (20 mg daily for 5 years) in the STAR trial, and at the 81-month median follow-up raloxifene was only 76% as effective at reducing ER-positive breast cancer compared with tamoxifen, but without the increased endometrial cancer risk seen with tamoxifen and with fewer thromboembolic events[206]. Risks and benefits of treatment with raloxifene or tamoxifen in postmenopausal women depend on age, ethnicity, breast cancer risk and hysterectomy status. Risk–benefit tables have been published for both tamoxifen and raloxifene that can help identify groups of women for whom the benefits of these risk-reducing medications outweigh the risks[207]. Aromatase inhibitors are more effective than either of these agents but can only be used in postmenopausal women, where in most cases they should be the agent of first choice, with tamoxifen or raloxifene reserved for those who cannot tolerate them. Tamoxifen remains the clear treatment of choice for premenopausal women, with continued benefits up to at least 20 years after initiation[203]. Long-term follow-up is highly desirable for raloxifene as prevention is a long-term issue.

Randomized controlled trials of the aromatase inhibitors exemestane and anastrozole have also shown that these medications can reduce the breast cancer risk by 60% at a median 2.5 years of follow-up and by 49% at a median 10.9 years of follow-up, respectively[208–210]. These medications can only be used in postmenopausal

women as they are ineffective in women with functioning ovaries.

Despite the clear benefits of risk-reducing medication, uptake is low among women at increased risk[211,212]. The reasons for this are complex and both clinician and patient related. There is a lack of clarity over the most appropriate type of clinician to initiate discussions about risk-reducing medications[182,211], in addition to clinicians having difficulty using the existing risk assessment models[211,213] and preferring to have a tool that links risk assessment with risk management[213]. Furthermore, clinicians often lack deep knowledge about prevention medications[214–216] and are concerned over the lack of surrogate markers for the effectiveness of preventive medications as well as the overall lack of commercial interest in prevention[211]. The latter concern comes about because all current prevention medications were off-patent by the time their role in prevention was proven. Thus, unlike newer patented drugs, where companies have a commercial incentive and spend considerable proportions of their budget educating clinicians about their drug, there is no investment to educate clinicians about implementing these older, generic prevention medicines into their practice. Additionally, in some countries/regions in Europe and in Australia, there is a lack of a clear pathway for regulatory approval of repurposed, off-patent drugs. Tamoxifen was shown to reduce breast cancer risk in 1998 (REF.[217]) and was promptly approved by the US Food and Drug Administration (FDA) for primary prevention, but in Australia regulatory approval was not sought until 2016 and only then after substantial advocacy by clinicians and consumer groups. Lack of regulatory approval in Australia before 2016 was a factor in the low rate of tamoxifen prescriptions[214].

The major patient factor contributing to low uptake of risk-reducing medications is said to be fear of side effects[218,219]. However, in the main prevention trials, which included over 13,000 women who took preventive medication, 5-year adherence to the study drug or placebo was approximately 70%. Importantly, there was only at most a 5% difference between the intervention and placebo arms with regard to the proportion of women who ceased the study drug or placebo because of side effects[209,210,217,220]. This demonstrates that much of the symptomatology experienced by women taking preventive medicines is background symptomatology rather than due to the medicines themselves. Clinician recommendation and the way clinicians frame information about side effects are important. For example, regarding the risk for endometrial cancer for postmenopausal women, it may be better to frame the risk as 'approximately 996 in every thousand women can take tamoxifen for 5 years without getting endometrial cancer', rather than 'your risk is doubled'. Few online tools are available currently to help clinicians balance absolute benefits against absolute risks for individual women[183]. Clinicians should also be sure to convey not only potentially adverse side effects but also beneficial ones, such as, for example, the potential for decreased breast tenderness, lighter menstrual periods, better bone density and lower cholesterol for women considering tamoxifen use. Clinicians should also consider offering women a short trial of 6–8 weeks of risk-reducing medication to assess their tolerance and so that women do not feel they are committing to a 5-year course with no knowledge of how well they, as an individual, will tolerate the drug. If such a short trial also had a biomarker of effectiveness, it may assist women in drug adherence.

Other patient factors that limit uptake of tamoxifen for ER-positive breast cancer risk reduction include the fact that it is a cancer drug, the experience of others (usually those with cancer) and the tablet being a daily reminder of their increased cancer risk; although the latter can presumably also work in reverse, with some women reassured by the daily tablet that they are actively reducing their breast cancer risk[218]. Importantly, it has also been shown that women often confuse tamoxifen with chemotherapy, and this has led to recommendations that the word 'chemoprevention' should be avoided[218,221] with 'risk-reducing medication' seemingly a more appropriate term.

Developing novel preventive agents

The 'perfect' risk-reducing medication would be highly efficacious, have minimal adverse side effects, but potentially several beneficial ones, and be able to be used even if on hormonal contraception, during pregnancy or when lactating. It could potentially be a long-acting depot preparation, avoiding the need for a daily tablet, and would not be associated in the public mind with a cancer drug. It would be inexpensive and preferably developed in a way that facilitated rapid regulatory approval and engagement of the pharmaceutical industry in implementation. Ongoing trials of breast cancer prevention medications are summarized in TABLE 3.

One tactic to provide a new approach to risk-reducing medication that has fewer adverse side effects than current agents is to modify the dose and delivery system of available agents. Tamoxifen is largely a pro-drug that is metabolized to its active metabolites, including endoxifen, by hepatic enzymes (for example, cytochrome P450 2D6 (CYP2D6))[222]. Biomarker studies have suggested that 5 mg per day is equivalent to the usual dose of 20 mg per day in inhibiting breast cancer proliferation[223], suggesting that low-dose tamoxifen might be efficacious for prevention. Furthermore, a recent multicentre, randomized trial suggested that a lower dose and duration of tamoxifen (5 mg daily for 3 years) might have similar breast cancer prevention efficacy as the usual dose of 20 mg daily for 5 years, with fewer side effects. Unfortunately, these two tamoxifen regimens were not compared with one another; however, based on this trial[224], 5 mg of daily tamoxifen for 3 years is now a reasonable breast cancer prevention option for women who do not tolerate dosing at 20 mg. It will be important to assess whether this smaller dose for a shorter duration provides the same long-term risk reduction as 20 mg daily for 5 years and whether the CYP2D6 status affects the efficacy of the smaller dose. Another approach to potentially reduce the side effects of tamoxifen is transdermal therapy, which can result in high drug concentrations in the breast but low systemic exposure. A window of opportunity trial in patients with ER-positive ductal carcinoma in situ (DCIS) (NCT00952731)[225]

Transdermal therapy
A route of drug administration wherein the drug is delivered across the skin, via patches or creams, for systemic distribution.

Table 3 | **Ongoing registered clinical trials of pharmacological interventions for breast cancer prevention**

Clinical trial identifier	Short study name	Sponsor	Phase	Intervention	Study design	Study population	Primary outcome	Secondary outcomes
Endocrine agents								
NCT02408770 (REF.[248])	BC-APPS1	Manchester University	II	Ulipristal acetate (5 mg oral daily for 3 months)	Single-arm	Premenopausal >17% lifetime breast cancer risk	Change in Ki67 staining of breast epithelium	Percentage of luminal, basal and mixed colonies; MRI background parenchyma enhancement; side effects
NCT00078832 (REF.[260])	IBIS-II	Queen Mary University of London	III	Anastrozole (1 mg oral daily for 5 years); placebo	Randomized, double-blind, placebo-controlled	Postmenopausal; 40–70 years old; increased risk of breast cancer	Breast cancer incidence (invasive and non-invasive)	Breast cancer mortality
NCT03063619 (REF.[261])	Afimoxifene in reducing the risk of breast cancer in women with mammographically dense breasts	M.D. Anderson Cancer Center	II	Afimoxifene gel (4 mg topically to each breast daily for up to 52 weeks); placebo	Randomized, double-blind, placebo-controlled	40–69 years old, or less than 40 years old if 5-year BCRAT risk is ≥1.66%; BI-RADS score 3 or 4	Percentage change in mammographic density (using Cumulus software)	Other breast density measures and measurement methods; breast tissue biomarkers; hormone-mediated cellular activity; inflammatory response; markers of tamoxifen exposure; toxicity; pharmacogenomics
EudraCT Number 2016-001087-11 (REF.[262])	CIBRAC	Belfast Health and Social Care Trust	NA	Tamoxifen (20 mg oral daily); Anastrazole (1 mg oral daily with goserelin 3.6 mg s/c every 28 days)	Randomized, open-label, crossover	*BRCA1* mutation; premenopausal >18 years old	Feasibility — recruitment and compliance	Tolerability — QOL, AEs
Retinoids								
NCT03323658 (REF.[238])	Bexarotene in preventing breast cancer in patients at high risk for breast cancer	NCI	I	Bexarotene (topically to one breast)	Single-arm, dose escalation	Hx of breast cancer and ≥5 years since diagnosis; or Hx of LCIS, ADH or ALH; or *BRCA1* or *BRCA2* mutation carrier; or breast cancer risk ≥1.7% in 5 years; or lifetime risk ≥20% ≥18 years old	Incidence of AEs	Systemic toxicity; bexarotene concentration; tissue markers
EudraCT Number 2009-010260-41 (REF.[239])	Breast cancer prevention with fenretinide in young women at genetic and familial risk	Istituto Europeo Di Oncologia	III	Retinamide (200 mg daily oral for 5 years); placebo	Double-blind, randomized, placebo-controlled	*BRCA1* or *BRCA2* mutation or 20% chance of mutation; 25–44 years old	Breast cancer incidence (invasive and DCIS)	Incidence of LCIS, ADH or ALH, ovarian cancer and other cancers
Bisphosphonates								
NCT02781805 (REF.[237])	Pilot study of bisphosphonates for breast cancer	University of Wisconsin	I	Alendronate (10 mg daily for 1–3 weeks before breast surgery)	Single-arm, window study	Women ≥18 years old; referred for risk-reducing mastectomy; premenopausal	Percentage change in γδ T cells in breast tissue	Percentage change in mammary epithelial basal cells; percentage change in mammary luminal cells

Table 3 (cont.) | **Ongoing registered clinical trials of pharmacological interventions for breast cancer prevention**

Clinical trial identifier	Short study name	Sponsor	Phase	Intervention	Study design	Study population	Primary outcome	Secondary outcomes
RANKL inhibitors								
ACTRN12614000694617 (REF.[263])	BRCA-D	Melbourne Health	NA	Denosumab (120 mg s/c monthly for 3 months)	Single-arm, window study	*BRCA1* or *BRCA2* mutation carrier; premenopausal; 18–50 years old	Change in Ki67 expression in breast epithelium	Safety and tolerability; change in RANK and RANKL expression in epithelial and stromal breast cells; change in ER and PR levels; change in c-KIT, ALDH1 and RANK immunostaining; change in luminal cell expression; change in MRI breast parenchymal enhancement
EudraCT Number 2017-002505-35 (REF.[246])	BRCA-P	ABCSG	III	Denosumab (70 mg s/c 6-monthly for 5 years); placebo	Double-blind, randomized, placebo-controlled	*BRCA1* mutation; age ≥25 years and ≤55 years	Breast cancer incidence (invasive or DCIS)	Incidence of invasive breast cancer, invasive TNBC, ovarian, fallopian and peritoneal cancers, other cancers, breast biopsies and benign lesions, and clinical fractures
Metformin								
EudraCT Number 2009-009921-28 (REF.[228])	PLOTINA	Istituti Fisioterapici Ospitalieri	III	Metformin (850 mg oral, twice daily); placebo	Double-blind, randomized, placebo-controlled	Postmenopausal; central obesity; another component of metabolic syndrome	Breast cancer incidence	CVD incidence

ABCSG, Austrian Breast & Colorectal Cancer Study Group; ADH, atypical ductal hyperplasia; AE, adverse event; ALDH1, aldehyde dehydrogenase 1; ALH, atypical lobular hyperplasia; BCRAT, Breast Cancer Risk Assessment Tool; BI-RADS, Breast Imaging Reporting and Data System; CVD, cardiovascular disease; DCIS, ductal carcinoma in situ; ER, oestrogen receptor; Hx, personal history; IBIS, International Breast Cancer Intervention Study; LCIS, lobular carcinoma in situ; MRI, magnetic resonance imaging; NA, not applicable; NCI, National Cancer Institute; PR, progesterone receptor; QOL, quality of life; RANK, receptor activator of nuclear factor-κB; RANKL, RANK ligand; s/c, subcutaneous; TNBC, triple-negative breast cancer.

showed that oral and transdermal delivery both decreased (by 50–60%) expression of the proliferation marker Ki67. Atossa Genetics recently announced the results of a phase II study of daily topical endoxifen applied to the breasts, which showed reductions in MD in women using the transdermal medication, with no difference in menopausal side effects between the topical endoxifen and placebo groups, although the duration of treatment was limited by skin rash.

Metformin is a drug that is commonly used to treat type 2 diabetes[226]. Metformin users have a decreased incidence of cancer, and long-term use (≥5 years) is associated with a reduced, adjusted OR of 0.63 for developing breast cancer[227]. This knowledge and promising preclinical work has led to a phase III randomized control trial (the PLOTINA study, EudraCT Number 2009-009921-28)[228] comparing metformin with placebo in postmenopausal women at high risk of type 2 diabetes.

Bisphosphonates, originally used as a treatment for osteoporosis, have been shown in preclinical studies to inhibit breast cancer proliferation and metastasis and have been proposed as breast cancer preventives[229–232]. They are currently used in patients with metastatic breast cancer to reduce skeletal-related events, and their use in the adjuvant setting in postmenopausal women reduces mortality[233] and is recommended in North American and European guidelines[234,235]. Women who take bisphosphonates for bone density have reduced breast cancer incidence (20–47% lower depending on the study)[230,236], suggesting a possible role in breast cancer prevention. Conversely, they do not reduce the contralateral breast cancer risk when given as an adjuvant[233]. An interventional prevention trial is underway (NCT02781805)[237] assessing the effects of the bisphosphonate alendronate on mammary epithelial cell differentiation and immune cells in high-risk women.

Retinoids are another class of drugs that are currently in breast cancer prevention trials (EudraCT Number 2009-010260-41 and NCT03323658)[238,239]. Retinoids are anti-proliferative, cyto-differentiating and apoptotic through their activation of the nuclear hormone retinoic acid receptor α (RARα), RARβ and RARγ. Strong data in preclinical models using the retinoid fenretinide[240] led to a phase III prevention trial in the late 1980s.

Luminal progenitors
A type of luminal epithelial cell within the mammary epithelium that has both luminal differentiation markers and progenitor activity (colony-forming and repopulating activity in vivo).

Fenretinide showed a trend for reducing the incidence of second primary breast cancer in premenopausal women (HR 0.66 and HR 0.65 for contralateral and ipsilateral breast cancer, respectively), which was maintained at a 15-year follow-up[241]. This drug has a low toxicity profile (mainly reversible skin dryness and rashes as well as difficulties adapting to darkness) that is often overcome by a monthly weekend suspension of the drug. However, it is not safe for pregnant women and so has similar reproductive contraindications in premenopausal women to tamoxifen. Yet the results of these novel breast cancer-preventive trials are eagerly awaited.

Medical prevention of breast cancer in *BRCA1* mutation carriers has been controversial. These women usually develop ER-negative breast cancer, and existing prevention agents have not reduced ER-negative breast cancer in clinical trials, although observational data in the secondary prevention setting[242,243] show that tamoxifen is associated with reduced contralateral breast cancer risk. There is growing evidence suggesting that receptor activator of nuclear factor-κB (RANK; also known as TNFRSF11A) and its ligand (RANKL) play a pivotal role in the development of *BRCA1* mutant-associated tumours. RANK$^+$ luminal progenitors are increased in pre-neoplastic tissue of *BRCA1* mutation carriers compared with non-mutation carriers[244]. Moreover, these cells have been identified as the cell of origin for the basal-like breast cancer that develops in *BRCA1* mutation carriers. Preclinical studies in *Brca1*-deficient mice targeting these cells with the RANKL inhibitor (and osteoporosis drug) denosumab successfully inhibited tumour development[245]. Preliminary data from a preclinical window study to evaluate the biological effects of denosumab on breast tissue biopsies from *BRCA1* mutation carriers showed that proliferation was markedly reduced[244]. An international phase III randomized trial of denosumab is testing whether administering denosumab once every 6 months for 5 years will reduce breast cancer incidence in *BRCA1* mutation carriers (EudraCT Number 2017-002505-35)[246].

There is also interest in anti-progestins (synthetic progestogens) for breast cancer prevention. Treatment of *Brca1*-deficient mice with the progesterone antagonist mifepristone inhibits tumorigenesis[247]. Mifepristone is considered too toxic to move into the prevention setting, but other less toxic PR modulators are under investigation (NCT02408770)[248]. Aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs) and statins are inexpensive, widely available and relatively safe drugs, making their potential repurposing for breast cancer prevention an attractive strategy. Although mature, randomized trial data are not available for any of these agents in the breast cancer primary prevention setting, aspirin use at a dose of ≥2 times per week for 5 years was associated with reduced breast cancer risk (RR 0.86), with decreasing risk for longer duration (RR 0.73 for 10 years and RR 0.54 for 20 years)[249]. Similar results are observed with another type of NSAID, the cyclooxygenase 2 (COX2) inhibitors[250]. Recent work assessing these associations in a cohort enriched in women with a strong family history showed that regular aspirin was associated with a 37–39% reduction in breast cancer risk, whereas for COX2 inhibitors this was 61–71% (REF.[251]). Some studies have found that aspirin and COX2 inhibitors reduce both ER-positive breast cancer and ER-negative breast cancer[251], whereas in others only ER-positive breast cancer was reduced[252–254]. Large-scale, randomized controlled trials with both population-risk women and those at higher risk are needed to define the true benefits of long-term aspirin use in the preventive setting.

For all of these preventives, a major task will be determining the best timing of preventive therapy. With a future improved ability to estimate not only overall risk but also age of onset of increased breast cancer risk for individuals, it may be possible to deliver preventive therapy immediately prior to the age-dependent increase in risk of hormonal breast cancer. This would drive high protection levels during the most crucial time. Additionally, as the time between puberty and first pregnancy is known to be a window that affects risk[34], ongoing work should determine why this period is so important and whether it is also the most effective time to deliver long-lasting preventive therapy. Prevention trials are, by their very nature, quite lengthy, and thus clinical trials assessing the impact of new therapies on early breast lesions (such as hyperplasia and in situ carcinoma) can be informative when assessing efficacy.

A deeper understanding of the earliest steps in breast cancer development will aid in our quest to develop novel preventives. The normal breast epithelium contains numerous cell types and is imbedded within a dense stromal and immune microenvironment[255,256]. Epithelial changes occur in *BRCA1* mutation carriers at risk of breast cancer[244], and it is possible that other epithelial cell subtypes may be increased under alternative risk conditions (FIG. 3). Additionally, the stromal and immune microenvironments play a significant role in the growth and progression of pre-invasive and invasive breast cancer[255,257] and can stimulate tumour development in the normal post-partum breast[88]. The microenvironment of early lesions and breasts at risk of cancer should be studied in order to determine whether cells can be targeted for breast cancer prevention (FIG. 3).

Conclusions and perspective

To date, breast cancer prevention in most parts of the world has largely focused on untargeted, population-based educational interventions (such as increasing physical activity and reducing BMI and alcohol intake). These will remain an appropriate component of breast cancer prevention, as these interventions also reduce the risk of other important causes of morbidity. However, we are moving towards the ability to augment this approach with systematic targeting, or precision prevention. Precision breast cancer prevention will mean delivering the right risk-reducing intervention, at the right time, to the right woman. A vital starting point will be a systematic and accurate method of assessing each individual woman's breast cancer risk. Risk assessment models currently exist, and their accuracy will continue to improve. Developing better risk assessment algorithms for specific breast cancer subtypes that are validated in ethnically diverse populations is a high priority. Having a user-friendly interface that enables

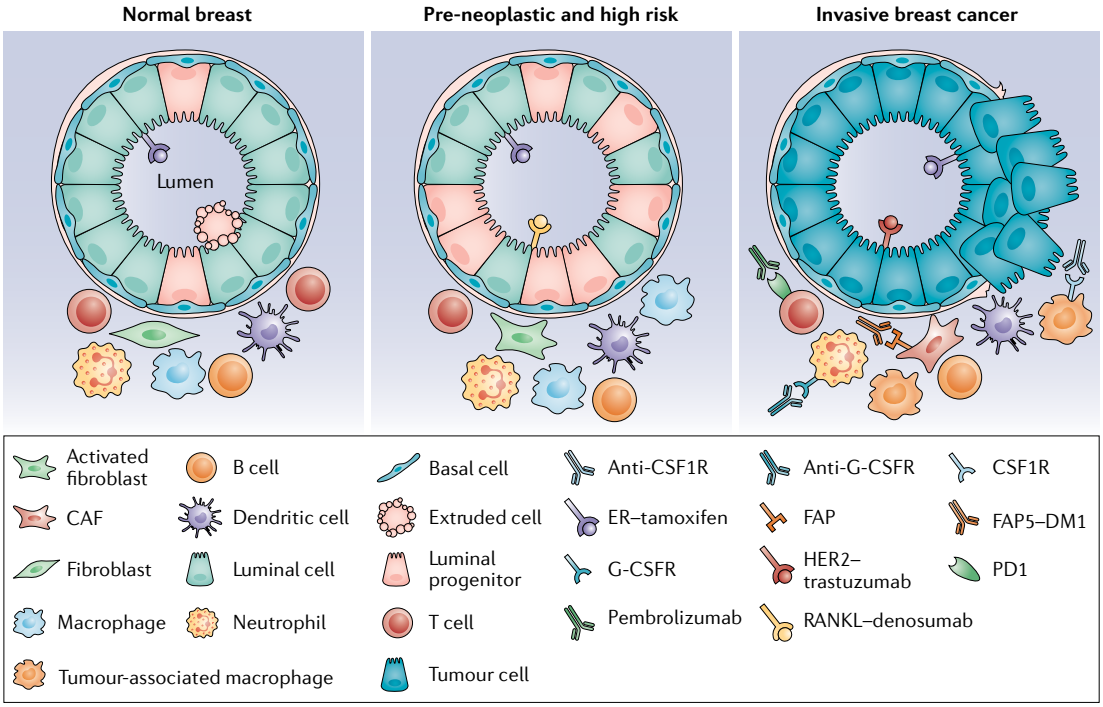

Fig. 3 | **Developing novel preventives based on a deeper understanding of the early events in breast cancer development.** Schematic of the normal breast, pre-neoplastic changes and invasive breast cancer showing the alterations that occur and the drugs currently used in prevention and treatment. One of the earliest stages of cancer development is the transformation of a single cell within the epithelial layer. In the normal breast, the oncogene-expressing cells are ejected from the epithelium by surrounding normal cells in a process called oncogenic extrusion[277]. Work is undergoing to assess oncogenic extrusion in early tumour development and the factors that control it. The selective oestrogen receptor (ER) modulator tamoxifen is used to prevent breast cancer in women with normal breast tissue and also in those women at high risk of breast cancer owing to pathogenic mutations. Recently, denosumab, a receptor activator of nuclear factor-κB ligand (RANKL) inhibitor, has shown promising results in breast cancer prevention in *BRCA1* mutation carriers by targeting the $RANK^+$ luminal progenitor population that is increased in these women. Future work should determine whether a *BRCA2* mutation status also alters the breast epithelial hierarchy and how this can be exploited to develop therapies for *BRCA2* mutation carriers. In terms of the non-genetic risk factors, it is important that we define how body mass index, age and reproductive factors alter the breast epithelial cells. The epithelial cells sit embedded in a stromal and immune microenvironment, which is emerging as having a significant role in the growth and progression of pre-invasive and invasive breast cancer[255,257]. In the stroma of pre-neoplastic lesions, fibroblasts become activated and the macrophage and T cell populations are altered. Currently, immune-modulating therapies are not used this early in tumour development. In invasive breast cancer, the luminal epithelial cells have transformed, extrusion does not occur and the basement membrane is breached. The epithelial cells can be targeted in invasive breast cancer with tamoxifen (for ER-positive breast cancer) and trastuzumab (for human epidermal growth factor receptor 2 (HER2)-positive breast cancer). There are also additional changes to the stromal fibroblasts and immune cells (for example, fewer T cells and repolarization of macrophages), which can further stimulate cancer growth. Immune-based therapies, such as pembrolizumab, the programmed cell death protein 1 (PD1) inhibitor, inhibitors of granulocyte colony-stimulating factor receptor (G-CSFR) and colony-stimulating factor 1 receptor (CSF1R), are currently being explored in cancer treatment. Similarly, cancer-associated fibroblast (CAF)-targeting therapies, such as fibroblast activation protein (FAP) antibodies conjugated to cytotoxic drugs (FAP5–DM1), are being investigated. As we begin to understand more about the changes occurring in the pre-neoplastic breast, it can be envisioned that the use of additional epithelial and stromal or immune-targeted therapies will be explored also at this early time point.

women and clinicians to identify and manage risk will be important in implementing risk management. Implementation researchers and policy-makers should consider how models can be applied to populations in order to ensure that women at increased risk are identified at an early age when there is still time to effectively reduce their risk with existing proven interventions. To effectively deliver these interventions we will need to define which treatments can be given at which ages for maximal protection. Preclinical studies will be informative in determining such dosing regimens. The treatments will also need to be well tolerated as they are being used in otherwise healthy individuals. Ultimately, it is hoped that risk assessment models might one day predict not only whether a woman will or will not develop breast cancer but at what age, so that risk-reducing interventions can be applied in the most appropriate time frame. The perfect intervention may target all molecular subtypes of breast cancer, but this is unlikely given their different aetiologies, so models that predict subtypes and thus enable the application of future medications that target particular subtypes would be optimal.

As we move to find preventive therapies that do not rely on disrupting oestrogen activity, we need to

understand more about what drives increased breast cancer risk. Assessing the pre-neoplastic breast tissue of women at increased risk of basal-like breast cancer (*BRCA1* mutation carriers) led to the identification of the cell of origin and the first cell-specific potential breast cancer preventive (FIG. 3). Now we need to ask how *BRCA2* mutation status alters the breast epithelial hierarchy and whether this can be targeted for preventive therapies. Furthermore, how do BMI, age and reproductive factors alter breast epithelial cells. If we find that aberrant control of distinct populations of breast epithelial cells are responsible for the generation of the different breast cancer subtypes (such as for $RANK^+$ luminal progenitors and basal-like breast cancer), the development of new preventives may need to be subtype-specific.

In the twentieth century, the eradication or control of many deadly communicable diseases transformed human health[258]. It is not impossible to imagine that, with the augmentation of our existing breast cancer prevention toolbox with future discoveries, we could achieve the same for breast cancer in the twenty-first century. By focusing on the risk factors for breast cancer and their incorporation into effective risk estimation tools, we will identify those women at increased risk. Research into the mechanisms underlying risks will be instrumental in driving the development of therapies to effectively counter or manage those risks and prevent breast cancer where we can. It is unlikely that we can reverse the reproductive choices that are driving hormonally responsive breast cancer; however, public health awareness and preventive therapies will be important, as will a focus on the development of improved hormonal therapies (MHT and OCP) that deliver symptom control and contraceptive benefits without increasing the breast cancer risk. Although this may begin in high-income countries, a global move to prioritize women's health is required.

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1. Narod, S. A., Iqbal, J. & Miller, A. B. Why have breast cancer mortality rates declined? *J. Cancer Policy* **5**, 8–17 (2015).
2. Althuis, M. D., Dozier, J. M., Anderson, W. F., Devesa, S. S. & Brinton, L. A. Global trends in breast cancer incidence and mortality 1973–1997. *Int. J. Epidemiol.* **34**, 405–412 (2005).
3. Boffetta, P. & Parkin, D. M. Cancer in developing countries. *CA Cancer J. Clin.* **44**, 81–90 (1994).
4. Glass, A. G. & Hoover, R. N. Rising incidence of breast cancer: relationship to stage and receptor status. *J. Natl Cancer Inst.* **82**, 693–696 (1990).
5. Li, C. I., Daling, J. R. & Malone, K. E. Incidence of invasive breast cancer by hormone receptor status from 1992 to 1998. *J. Clin. Oncol.* **21**, 28–34 (2003). **This paper uses data from the NCI SEER Program to show that the proportion of hormone receptor-positive tumours rose in the 1990s**.
6. Parkin, D. M. & Fernandez, L. M. Use of statistics to assess the global burden of breast cancer. *Breast J.* **12** (Suppl. 1), S70–S80 (2006).
7. Ries, L. A. G., Melbert, D. & Krapcho, M. *SEER Cancer Statistics Review*, 1975–2004 (NIH, 2006).
8. Global Burden of Disease Cancer Collaboration. et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: a systematic analysis for the Global Burden of Disease study. *JAMA Oncol.* **4**, 1553–1568 (2018).
9. Bigaard, J., Stahlberg, C., Jensen, M. B., Ewertz, M. & Kroman, N. Breast cancer incidence by estrogen receptor status in Denmark from 1996 to 2007. *Breast Cancer Res. Treat.* **136**, 559–564 (2012).
10. Coughlin, S. S. *Epidemiology of Breast Cancer in Women* Vol. 1152 (ed. Ahmad, A.) (Springer, 2019).
11. He, C. et al. A large-scale candidate gene association study of age at menarche and age at natural menopause. *Hum. Genet.* **128**, 515–527 (2010).
12. Stolk, L. et al. Meta-analyses identify 13 loci associated with age at menopause and highlight DNA repair and immune pathways. *Nat. Genet.* **44**, 260–268 (2012).
13. Stone, J. et al. The heritability of mammographically dense and nondense breast tissue. *Cancer Epidemiol. Biomarkers Prev.* **15**, 612–617 (2006).
14. Broca, P. *Taite des tumeurs* Vol. 13 (Libraire De La Faculte De Medecine, 1866).
15. Miki, Y. et al. A strong candidate for the breast and ovarian cancer susceptibility gene *BRCA1*. *Science* **266**, 66–71 (1994). **This study uses positional cloning to identify the chromosome 17q-linked *BRCA1* gene as a tumour suppressor, which if mutated predisposes individuals to both breast cancer and ovarian cancer**.
16. Wooster, R. et al. Identification of the breast cancer susceptibility gene *BRCA2*. *Nature* **378**, 789–792 (1995). **This study identifies the breast cancer susceptibility gene *BRCA2* on chromosome 13q12-q13 with mutations detected in this gene in families with breast cancer**.
17. Ligtenberg, M. J. et al. Characteristics of small breast and/or ovarian cancer families with germline mutations in BRCA1 and BRCA2. *Br. J. Cancer* **79**, 1475–1478 (1999).
18. Kuchenbaecker, K. B. et al. Risks of breast, ovarian, and contralateral breast cancer for *BRCA1* and *BRCA2* mutation carriers. *JAMA* **317**, 2402–2416 (2017). **This prospective cohort study of *BRCA1* and *BRCA2* female carriers shows that the risk of breast cancer by 80 years of age was 72% and 69%, respectively**.
19. Easton, D. F. et al. Gene-panel sequencing and the prediction of breast-cancer risk. *N. Engl. J. Med.* **372**, 2243–2257 (2015). **This special report on multigene or panel testing looks for the presence of genetic variants that may be associated with a risk of breast cancer**.
20. National Comprehensive Cancer Network. *Genetic/ Familial High-risk Assessment: Breast and Ovarian* (National Comprehensive Cancer Network, 2019).
21. Michailidou, K. et al. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. *Nat. Genet.* **47**, 373–380 (2015).
22. Mavaddat, N. et al. Prediction of breast cancer risk based on profiling with common genetic variants. *J. Natl Cancer Inst.* **107**, djv036 (2015).
23. Mavaddat, N. et al. Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. *Am. J. Hum. Genet.* **104**, 21–34 (2019). **This paper develops a PRS for predicting breast cancer using the largest available genome-wide association data set**.
24. Rudolph, A. et al. Joint associations of a polygenic risk score and environmental risk factors for breast cancer in the Breast Cancer Association Consortium. *Int. J. Epidemiol.* **47**, 526–536 (2018).
25. Muranen, T. A. et al. Genetic modifiers of CHEK2*1100delC-associated breast cancer risk. *Genet. Med.* **19**, 599–603 (2017).
26. Kuchenbaecker, K. B. et al. Associations of common breast cancer susceptibility alleles with risk of breast cancer subtypes in *BRCA1* and *BRCA2* mutation carriers. *Breast Cancer Res.* **16**, 3416 (2014).
27. Esserman, L. J., Study, W. & Athena, I. The WISDOM study: breaking the deadlock in the breast cancer screening debate. *NPJ Breast Cancer* **3**, 34 (2017).
28. Evans, D. G. R. et al. Breast cancer pathology and stage are better predicted by risk stratification models that include mammographic density and common genetic variants. *Breast Cancer Res. Treat.* **176**, 141–148 (2019).
29. Gabrielson, M. et al. Cohort profile: The Karolinska Mammography Project for Risk Prediction of Breast Cancer (KARMA). *Int. J. Epidemiol.* **46**, 1740–1741g (2017).
30. French, J. D. et al. Functional variants at the 11q13 risk locus for breast cancer regulate cyclin D1 expression through long-range enhancers. *Am. J. Hum. Genet.* **92**, 489–503 (2013).
31. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50 302 women with breast cancer and 96 973 women without the disease. *Lancet* **360**, 187–195 (2002). **This reanalysis of 47 epidemiological studies shows that the RR of breast cancer is reduced by 4.3% for each year a woman breastfeeds, in addition to a reduction of 7% for each birth**.
32. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol.* **13**, 1141–1151 (2012). **This meta-analysis of data from 117 epidemiological studies shows that each year younger at menarche or older at menopause is associated with a 5% and 2.9% increased risk of breast cancer, respectively**.
33. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet* **394**, 1159–1168 (2019). **This meta-analysis of MHT use shows that all therapy types except vaginal oestrogens are associated with increased breast cancer risk**.
34. Dall, G. V. & Britt, K. L. Estrogen effects on the mammary gland in early and late life and breast cancer risk. *Front. Oncol.* **7**, 110 (2017).
35. MacMahon, B. et al. Age at first birth and breast cancer risk. *Bull. World Health Organ.* **43**, 209–221 (1970). **This landmark international collaborative study shows that a young age at first childbirth significantly decreases breast cancer risk**.
36. Morris, D. H., Jones, M. E., Schoemaker, M. J., Ashworth, A. & Swerdlow, A. J. Secular trends in age at menarche in women in the UK born 1908–93: results from the breakthrough generations study. *Paediatr. Perinat. Epidemiol.* **25**, 394–400 (2011).
37. Braithwaite, D. et al. Socioeconomic status in relation to early menarche among black and white girls. *Cancer Causes Control.* **20**, 713–720 (2009).
38. Sisti, J. S. et al. Reproductive risk factors in relation to molecular subtypes of breast cancer: results from the Nurses' Health Studies. *Int. J. Cancer* **138**, 2346–2356 (2016).
39. Silva, C. A. et al. Gonadal function in adolescents and young women with juvenile systemic lupus erythematosus. *Lupus* **11**, 419–425 (2002).
40. Harris, M. A., Prior, J. C. & Koehoorn, M. Age at menarche in the Canadian population: secular trends and relationship to adulthood BMI. *J. Adolesc. Health* **43**, 548–554 (2008).
41. Fernandez-Rhodes, L. et al. Association of adiposity genetic variants with menarche timing in 92,105 women of European descent. *Am. J. Epidemiol.* **178**, 451–460 (2013).

42. Chisholm, J. S., Quinlivan, J. A., Petersen, R. W. & Coall, D. A. Early stress predicts age at menarche and first birth, adult attachment, and expected lifespan. *Hum. Nat.* **16**, 233–265 (2005).
43. Carwile, J. L. et al. Sugar-sweetened beverage consumption and age at menarche in a prospective study of US girls. *Hum. Reprod.* **30**, 675–683 (2015).
44. Belsky, J., Steinberg, L. & Draper, P. Childhood experience, interpersonal development, and reproductive strategy: and evolutionary theory of socialization. *Child. Dev.* **62**, 647–670 (1991).
45. Behie, A. M. & O'Donnell, M. H. Prenatal smoking and age at menarche: influence of the prenatal environment on the timing of puberty. *Hum. Reprod.* **30**, 957–962 (2015).
46. Elks, C. E. et al. Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies. *Nat. Genet.* **42**, 1077–1085 (2010).
47. Boynton-Jarrett, R. et al. Gestational weight gain and daughter's age at menarche. *J. Womens Health* **20**, 1193–1200 (2011).
48. Deardorff, J. et al. Maternal pre-pregnancy BMI, gestational weight gain, and age at menarche in daughters. *Matern. Child. Health J.* **17**, 1391–1398 (2013).
49. Gao, Y. T. et al. Association of menstrual and reproductive factors with breast cancer risk: results from the Shanghai Breast Cancer Study. *Int. J. Cancer* **87**, 295–300 (2000).
50. O'Brien, K. M., Sun, J., Sandler, D. P., DeRoo, L. A. & Weinberg, C. R. Risk factors for young-onset invasive and in situ breast cancer. *Cancer Causes Control.* **26**, 1771–1778 (2015).
51. Reeves, G. K. et al. Reproductive factors and specific histological types of breast cancer: prospective study and meta-analysis. *Br. J. Cancer* **100**, 538–544 (2009).
52. Rodstrom, K. et al. Evidence for a secular trend in menopausal age: a population study of women in Gothenburg. *Menopause* **10**, 538–543 (2003).
53. Gold, E. B. et al. Factors related to age at natural menopause: longitudinal analyses from SWAN. *Am. J. Epidemiol.* **178**, 70–83 (2013).
54. Gold, E. B. et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. *Am. J. Epidemiol.* **153**, 865–874 (2001).
55. Gold, E. B. The timing of the age at which natural menopause occurs. *Obstet. Gynecol. Clin. North. Am.* **38**, 425–440 (2011).
56. He, L. N. et al. Association study of the oestrogen signalling pathway genes in relation to age at natural menopause. *J. Genet.* **86**, 269–276 (2007).
57. Weel, A. E. et al. Estrogen receptor polymorphism predicts the onset of natural and surgical menopause. *J. Clin. Endocrinol. Metab.* **84**, 3146–3150 (1999).
58. den Tonkelaar, I., te Velde, E. R. & Looman, C. W. Menstrual cycle length preceding menopause in relation to age at menopause. *Maturitas* **29**, 115–123 (1998).
59. Ramazzini, B. *De Morbis Artificum (Diseases of Workers)* (University of Chicago Press, 1940).
60. Albrektsen, G., Heuch, I., Hansen, S. & Kvale, G. Breast cancer risk by age at birth, time since birth and time intervals between births: exploring interaction effects. *Br. J. Cancer* **92**, 167–175 (2005).
61. Ursin, G. et al. Reproductive factors and subtypes of breast cancer defined by hormone receptor and histology. *Br. J. Cancer* **93**, 364–371 (2005).
62. Ma, H., Bernstein, L., Pike, M. C. & Ursin, G. Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: a meta-analysis of epidemiological studies. *Breast Cancer Res.* **8**, R43 (2006).
This meta-analysis of epidemiological studies investigates parity, age at first birth, breastfeeding and age at menarche in relation to ER^+PR^+ and ER^-PR^- breast cancer risk.
63. Anderson, K. N., Schwab, R. B. & Martinez, M. E. Reproductive risk factors and breast cancer subtypes: a review of the literature. *Breast Cancer Res. Treat.* **144**, 1–10 (2014).
64. Tamimi, R. M. et al. Traditional breast cancer risk factors in relation to molecular subtypes of breast cancer. *Breast Cancer Res. Treat.* **131**, 159–167 (2012).
65. Gaudet, M. M. et al. Risk factors by molecular subtypes of breast cancer across a population-based study of women 56 years or younger. *Breast Cancer Res. Treat.* **130**, 587–597 (2011).
66. Australian Birth Statistics. *Births, Australia, 2017* Cat. No. 3301.0 (Australian Bureau of Statistics, 2018).
67. Hamilton, B. E., Martin, J. A., Osterman, M. J. K. & Rossen, L. M. *Births: Provisional data for 2018* (NCHS, 2019).
68. Office for National Statistics. *Births in England and Wales 2018, Statistical Bulletin* (2019).
69. Australian Institute of Health and Welfare. *Reproductive Health Indicators Australia 2002* Cat. No. PER 20 (Pew Research Center, 2003).
70. Livingstone, G. & Cohn, D. *Childlessness Up Among all Women; Down Among Women with Advanced Degrees* (Pew Research Center, 2010).
71. Australian Institute of Health and Welfare. *Cancer in Australia 2017* Cat. No. CAN 100 (Australian Institute of Health and Welfare, 2017).
72. Martin, J. A., Hamilton, B. E., Osterman, M. J. K., Driscoll, A. K. & Drake, P. *Final data for 2017* National Vital Statistics Reports Vol. 67 No. 8 Report No. 1568–7856 (Electronic) 1568–7856 (Linking), 844–855 (National Center for Health Statistics, 2018).
73. Huo, D. et al. Parity and breastfeeding are protective against breast cancer in Nigerian women. *Br. J. Cancer* **98**, 992–996 (2008).
74. Khalis, M. et al. Menstrual and reproductive factors and risk of breast cancer: a case–control study in the Fez region, Morocco. *PLoS One* **13**, e0191333 (2018).
75. Schedin, P. Pregnancy-associated breast cancer and metastasis. *Nat. Rev. Cancer* **6**, 281–291 (2006).
This comprehensive Review discusses the role of the pro-inflammatory immune microenvironment of the post-partum breast in the development of pregnancy-associated breast cancer.
76. Britt, K., Ashworth, A. & Smalley, M. Pregnancy and the risk of breast cancer. *Endocr. Relat. Cancer* **14**, 907–933 (2007).
77. Dall, G. V. et al. Estrogen receptor subtypes dictate the proliferative nature of the mammary gland. *J. Endocrinol.* **237**, 323–336 (2018).
78. Chang, C. C. et al. A human breast epithelial cell type with stem cell characteristics as target cells for carcinogenesis. *Radiat. Res.* **155**, 201–207 (2001).
79. Russo, J., Tay, L. K. & Russo, I. H. Differentiation of the mammary gland and susceptibility to carcinogenesis. *Breast Cancer Res. Treat.* **2**, 5–73 (1982).
80. Russo, I. H. & Russo, J. Developmental stage of the rat mammary gland as determinant of its susceptibility to 7,12-dimethylbenz[a]anthracene. *J. Natl Cancer Inst.* **61**, 1439–1449 (1978).
81. Land, C. E. et al. Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1990. *Radiat. Res.* **160**, 707–717 (2003).
82. Tokunaga, M. et al. Incidence of female breast cancer among atomic bomb survivors, 1950–1985. *Radiat. Res.* **138**, 209–223 (1994).
83. Britt, K. L. et al. Pregnancy in the mature adult mouse does not alter the proportion of mammary epithelial stem/progenitor cells. *Breast Cancer Res.* **11**, R20 (2009).
84. Meier-Abt, F. et al. Parity induces differentiation and reduces Wnt/Notch signaling ratio and proliferation potential of basal stem/progenitor cells isolated from mouse mammary epithelium. *Breast Cancer Res.* **15**, R36 (2013).
85. Siwko, S. K. et al. Evidence that an early pregnancy causes a persistent decrease in the number of functional mammary epithelial stem cells—implications for pregnancy-induced protection against breast cancer. *Stem Cell* **26**, 3205–3209 (2008).
86. Dall, G. V. et al. SCA-1 labels a subset of estrogen-responsive bipotential repopulating cells within the $CD24^+CD49f^{hi}$ mammary stem cell-enriched compartment. *Stem Cell Rep.* **8**, 417–431 (2017).
87. Jindal, S. et al. Postpartum breast involution reveals regression of secretory lobules mediated by tissue-remodeling. *Breast Cancer Res.* **16**, R31 (2014).
88. Martinson, H. A., Jindal, S., Durand-Rougely, C., Borges, V. F. & Schedin, P. Wound healing-like immune program facilitates postpartum mammary gland involution and tumor progression. *Int. J. Cancer* **136**, 1803–1813 (2015).
This study finds that the post-partum mammary gland of mice is in an immunosuppressed state immediately after pregnancy, which can drive tumour formation.
89. Santucci-Pereira, J. et al. Genomic signature of parity in the breast of premenopausal women. *Breast Cancer Res.* **21**, 46 (2019).
90. Balogh, G. A. et al. Genomic signature induced by pregnancy in the human breast. *Int. J. Oncol.* **28**, 399–410 (2006).
91. Lambertini, M. et al. Reproductive behaviors and risk of developing breast cancer according to tumor subtype: a systematic review and meta-analysis of epidemiological studies. *Cancer Treat. Rev.* **49**, 65–76 (2016).
92. Hadjisavvas, A. et al. An investigation of breast cancer risk factors in Cyprus: a case control study. *BMC Cancer* **10**, 447 (2010).
93. Fortner, R. T. et al. Parity, breastfeeding, and breast cancer risk by hormone receptor status and molecular phenotype: results from the Nurses' Health Studies. *Breast Cancer Res.* **21**, 40 (2019).
94. Islami, F. et al. Breastfeeding and breast cancer risk by receptor status — a systematic review and meta-analysis. *Ann. Oncol.* **26**, 2398–2407 (2015).
95. Takabatake, Y. et al. Lactation opposes pappalysin-1-driven pregnancy-associated breast cancer. *EMBO Mol. Med.* **8**, 388–406 (2016).
96. World Heath Organization. *Global Strategy on Infant and Young Child Feeding: Infant and Young Child Nutrition* (WHO, 2002).
97. Australian Institute of Health and Welfare. *2010 Australian National Infant Feeding Survey: Indicator Results* (AIHW, 2011).
98. Ayton, J., van der Mei, I., Wills, K., Hansen, E. & Nelson, M. Cumulative risks and cessation of exclusive breast feeding: Australian cross-sectional survey. *Arch. Dis. Child.* **100**, 863–868 (2015).
99. McAndrew, F. et al. *Infant Feeding Survey 2010* (Health and Social Care Information Centre, IFF Research, 2012).
100. Victora, C. G. et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet* **387**, 475–490 (2016).
101. Rollins, N. C. et al. Why invest, and what it will take to improve breastfeeding practices? *Lancet* **387**, 491–504 (2016).
102. Sickles, E. A., D'Orsi, C. J., Bassett, L. W. *ACR BI-RADS Mammography* Vol. 5 134–136 (American College of Radiology, 2013).
103. Spak, D. A., Plaxco, J. S., Santiago, L., Dryden, M. J. & Dogan, B. E. BI-RADS® fifth edition: a summary of changes. *Diagn. Interv. Imaging* **98**, 179–190 (2017).
104. McCormack, V. A. & dos Santos Silva, I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol. Biomarkers Prev.* **15**, 1159–1169 (2006).
This meta-analysis shows that increasing breast density is associated with an increased risk of breast cancer.
105. Krishnan, K. et al. Mammographic density and risk of breast cancer by mode of detection and tumor size: a case–control study. *Breast Cancer Res.* **18**, 63 (2016).
106. Hopper, J. L. Odds per adjusted standard deviation: comparing strengths of associations for risk factors measured on different scales and across diseases and populations. *Am. J. Epidemiol.* **182**, 863–867 (2015).
107. Sprague, B. L. et al. Prevalence of mammographically dense breasts in the United States. *J. Natl Cancer Inst.* **106**, dju255 (2014).
108. Huo, C. W. et al. High mammographic density is associated with an increase in stromal collagen and immune cells within the mammary epithelium. *Breast Cancer Res.* **17**, 79 (2015).
109. Huo, C. W. et al. High mammographic density in women is associated with protumor inflammation. *Breast Cancer Res.* **20**, 92 (2018).
110. Cuzick, J. et al. Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case–control study. *J. Natl Cancer Inst.* **103**, 744–752 (2011).
This nested case–control study within the IBIS-1 prevention trial shows that women in the tamoxifen group who experienced a 10% or greater reduction in breast density had a 63% reduction in breast cancer risk.
111. Shawky, M. S. et al. Mammographic density: a potential monitoring biomarker for adjuvant and preventative breast cancer endocrine therapies. *Oncotarget* **8**, 5578–5591 (2017).
112. Wolfe, J. N. Risk for breast cancer development determined by mammographic parenchymal pattern. *Cancer* **37**, 2486–2492 (1976).
113. Boyd, N. F. et al. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. *J. Natl Cancer Inst.* **87**, 670–675 (1995).
114. Suzuki, R., Orsini, N., Saji, S., Key, T. J. & Wolk, A. Body weight and incidence of breast cancer defined

by estrogen and progesterone receptor status-a meta-analysis. *Int. J. Cancer* **124**, 698–712 (2009). **This meta-analysis shows that postmenopausal women in the highest body weight categories had an 80% increased RR for breast cancer compared with those in the lowest weight categories**.
115. Renehan, A. G., Zwahlen, M. & Egger, M. Adiposity and cancer risk: new mechanistic insights from epidemiology. *Nat. Rev. Cancer* **15**, 484–498 (2015).
116. Travis, R. C. & Key, T. J. Oestrogen exposure and breast cancer risk. *Breast Cancer Res.* **5**, 239–247 (2003).
117. Brinton, L. A. et al. Anthropometric and hormonal risk factors for male breast cancer: male breast cancer pooling project results. *J. Natl Cancer Inst.* **106**, djt465 (2014).
118. Eliassen, A. H., Colditz, G. A., Rosner, B., Willett, W. C. & Hankinson, S. E. Adult weight change and risk of postmenopausal breast cancer. *JAMA* **296**, 193–201 (2006). **This study uses data from the Nurses' Health Study to show that women who maintained or lost weight as they got older had a reduced RR of postmenopausal breast cancer compared with those who gained weight**.
119. Harvie, M. et al. Association of gain and loss of weight before and after menopause with risk of postmenopausal breast cancer in the Iowa Women's Health Study. *Cancer Epidemiol. Biomarkers Prev.* **14**, 656–661 (2005).
120. Mannisto, S. et al. Body-size indicators and risk of breast cancer according to menopause and estrogen-receptor status. *Int. J. Cancer* **68**, 8–13 (1996).
121. Keum, N. et al. Adult weight gain and adiposity-related cancers: a dose–response meta-analysis of prospective observational studies. *J. Natl Cancer Inst.* **107**, djv088 (2015).
122. Renehan, A. G. et al. Young adulthood body mass index, adult weight gain and breast cancer risk: the PROCAS study (United Kingdom). *Br. J. Cancer* **122**, 1552–1561 (2020).
123. Lynch, B. M., Neilson, H. K. & Friedenreich, C. M. Physical activity and breast cancer prevention. *Recent. Results Cancer Res.* **186**, 13–42 (2011).
124. Neilson, H. K. et al. Moderate–vigorous recreational physical activity and breast cancer risk, stratified by menopause status: a systematic review and meta-analysis. *Menopause* **24**, 322–344 (2017).
125. World Cancer Research Fund/American Institute for Cancer Research. *Physical Activity and the Risk of Cancer* Report No. 0022-2623 (Print) 0022-2623 (Linking) https://www.wcrf.org/sites/default/files/Physical-activity.pdf (2018).
126. Wu, Y., Zhang, D. & Kang, S. Physical activity and risk of breast cancer: a meta-analysis of prospective studies. *Breast Cancer Res. Treat.* **137**, 869–882 (2013).
127. World Cancer Research Fund/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Breast Cancer* https://www.wcrf.org/sites/default/files/Summary-of-Third-Expert-Report-2018.pdf (2018).
128. Lammert, J. et al. Physical activity during adolescence and young adulthood and the risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers. *Breast Cancer Res. Treat.* **169**, 561–571 (2018).
129. Wang, M. et al. Prepubertal physical activity up-regulates estrogen receptor β, *BRCA1* and p53 mRNA expression in the rat mammary gland. *Breast Cancer Res. Treat.* **115**, 213–220 (2009).
130. Kurgan, N. et al. Inhibition of human lung cancer cell proliferation and survival by post-exercise serum is associated with the inhibition of Akt, mTOR, p70 S6K, and Erk1/2. *Cancers (Basel)* **9**, 46 (2017).
131. Rundqvist, H. et al. Effect of acute exercise on prostate cancer cell growth. *PLoS One* **8**, e67579 (2013).
132. Dethlefsen, C. et al. Exercise-induced catecholamines activate the hippo tumor suppressor pathway to reduce risks of breast cancer development. *Cancer Res.* **77**, 4894–4904 (2017).
133. National Statistics NHS. *Health Survey for England 2012* (NHS, 2013).
134. Chen, W. Y., Rosner, B., Hankinson, S. E., Colditz, G. A. & Willett, W. C. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. *JAMA* **306**, 1884–1890 (2011). **This paper uses data from the Nurses' Health Study to show that women consuming 3–6 glasses of wine per week or two drinks per day were 15% or 50% more likely, respectively, to develop breast cancer than non-drinkers**.
135. Allen, N. E. et al. Moderate alcohol intake and cancer incidence in women. *J. Natl Cancer Inst.* **101**, 296–305 (2009).
136. Arriaga, M. E. et al. The preventable burden of breast cancers for premenopausal and postmenopausal women in Australia: a pooled cohort study. *Int. J. Cancer* **145**, 2383–2394 (2019).
137. Singletary, K. W. & Gapstur, S. M. Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. *JAMA* **286**, 2143–2151 (2001).
138. Dorgan, J. F. et al. Serum hormones and the alcohol–breast cancer association in postmenopausal women. *J. Natl Cancer Inst.* **93**, 710–715 (2001).
139. Triano, E. A. et al. Class I alcohol dehydrogenase is highly expressed in normal human mammary epithelium but not in invasive breast cancer: implications for breast carcinogenesis. *Cancer Res.* **63**, 3092–3100 (2003).
140. Seitz, H. K. & Stickel, F. Acetaldehyde as an underestimated risk factor for cancer development: role of genetics in ethanol metabolism. *Genes Nutr.* **5**, 121–128 (2010).
141. Meadows, G. G. & Zhang, H. Effects of alcohol on tumor growth, metastasis, immune response, and host survival. *Alcohol. Res.* **37**, 311–322 (2015).
142. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective* (American Institute for Cancer Research, 2007).
143. Ronksley, P. E., Brien, S. E., Turner, B. J., Mukamal, K. J. & Ghali, W. A. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. *BMJ* **342**, d671 (2011).
144. GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* **392**, 1015–1035 (2018).
145. Hopper, J. L. et al. Age-specific breast cancer risk by body mass index and familial risk: prospective family study cohort (ProF-SC). *Breast Cancer Res.* **20**, 132 (2018).
146. Kehm, R. et al. Recreational physical activity and breast cancer risk: a cohort study of women selected for familial and genetic risk. *Cancer Res.* **80**, 116–125 (2020).
147. Chlebowski, R. T. et al. Dietary modification and breast cancer mortality: long-term follow-up of the women's health initiative randomized trial. *J. Clin. Oncol.* **38**, 1419–1428 (2020).
148. Chlebowski, R. T. et al. Ethnicity and breast cancer: factors influencing differences in incidence and outcome. *J. Natl Cancer Inst.* **97**, 439–448 (2005).
149. Li, N. et al. Global burden of breast cancer and attributable risk factors in 195 countries and territories, from 1990 to 2017: results from the Global Burden of Disease Study 2017. *J. Hematol. Oncol.* **12**, 140 (2019).
150. Li, C. I., Malone, K. E. & Daling, J. R. Differences in breast cancer hormone receptor status and histology by race and ethnicity among women 50 years of age and older. *Cancer Epidemiol. Biomarkers Prev.* **11**, 601–607 (2002).
151. Millikan, R. C. et al. Epidemiology of basal-like breast cancer. *Breast Cancer Res. Treat.* **109**, 123–139 (2008).
152. Pharoah, P. & Ponder, B. in *Genes and Common Diseases: Genetics in Modern Medicine* (eds A. Wright & N. Hastie) 224–232 (Cambridge Univ. Press, 2007).
153. Banegas, M. P. et al. Projecting individualized absolute invasive breast cancer risk in US Hispanic women. *J. Natl Cancer Inst.* **109**, djw215 (2017).
154. Gail, M. H. et al. Projecting individualized absolute invasive breast cancer risk in African American women. *J. Natl Cancer Inst.* **99**, 1782–1792 (2007).
155. Matsuno, R. K. et al. Projecting individualized absolute invasive breast cancer risk in Asian and Pacific Islander American women. *J. Natl Cancer Inst.* **103**, 951–961 (2011).
156. Cintolo-Gonzalez, J. A. et al. Breast cancer risk models: a comprehensive overview of existing models, validation, and clinical applications. *Breast Cancer Res. Treat.* **164**, 263–284 (2017).
157. Antoniou, A. C. et al. A comprehensive model for familial breast cancer incorporating *BRCA1*, *BRCA2* and other genes. *Br. J. Cancer* **86**, 76–83 (2002).
158. Antoniou, A. C., Pharoah, P. P., Smith, P. & Easton, D. F. The BOADICEA model of genetic susceptibility to breast and ovarian cancer. *Br. J. Cancer* **91**, 1580–1590 (2004).
159. Berry, D. A., Parmigiani, G., Sanchez, J., Schildkraut, J. & Winer, E. Probability of carrying a mutation of breast-ovarian cancer gene *BRCA1* based on family history. *J. Natl Cancer Inst.* **89**, 227–238 (1997).
160. Gail, M. H. et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J. Natl Cancer Inst.* **81**, 1879–1886 (1989).
161. Parmigiani, G., Berry, D. & Aguilar, O. Determining carrier probabilities for breast cancer-susceptibility genes *BRCA1* and *BRCA2*. *Am. J. Hum. Genet.* **62**, 145–158 (1998).
162. Rosner, B. & Colditz, G. A. Nurses' Health Study: log-incidence mathematical model of breast cancer incidence. *J. Natl Cancer Inst.* **88**, 359–364 (1996).
163. Terry, M. B. et al. 10-Year performance of four models of breast cancer risk: a validation study. *Lancet Oncol.* **20**, 504–517 (2019). **This study uses data from a large international prospective cohort study to validate commonly used breast cancer risk prediction models and shows that models that include multigenerational family cancer history, such as IBIS and BOADICEA, perform best, even for women at average risk**.
164. Tice, J. A. et al. Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. *Ann. Intern. Med.* **148**, 337–347 (2008).
165. Tyrer, J., Duffy, S. W. & Cuzick, J. A breast cancer prediction model incorporating familial and personal risk factors. *Stat. Med.* **23**, 1111–1130 (2004).
166. Petracci, E. et al. Risk factor modification and projections of absolute breast cancer risk. *J. Natl Cancer Inst.* **103**, 1037–1048 (2011).
167. Gail, M. H., Anderson, W. F., Garcia-Closas, M. & Sherman, M. E. Absolute risk models for subtypes of breast cancer. *J. Natl Cancer Inst.* **99**, 1657–1659 (2007).
168. Colditz, G. A. & Rosner, B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. *Am. J. Epidemiol.* **152**, 950–964 (2000).
169. Brentnall, A. R., Cuzick, J., Buist, D. S. M. & Bowles, E. J. A. Long-term accuracy of breast cancer risk assessment combining classic risk factors and breast density. *JAMA Oncol.* **4**, e180174 (2018).
170. Bodian, C. A., Perzin, K. H. & Lattes, R. Lobular neoplasia. Long term risk of breast cancer and relation to other factors. *Cancer* **78**, 1024–1034 (1996).
171. Claus, E. B., Risch, N. & Thompson, W. D. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer* **73**, 643–651 (1994).
172. Amir, E. et al. Evaluation of breast cancer risk assessment packages in the family history evaluation and screening programme. *J. Med. Genet.* **40**, 807–814 (2003).
173. Brentnall, A. R. et al. A case–control evaluation of 143 single nucleotide polymorphisms for breast cancer risk stratification with classical factors and mammographic density. *Int. J. Cancer* **146**, 2122–2129 (2020).
174. Quante, A. S., Whittemore, A. S., Shriver, T., Strauch, K. & Terry, M. B. Breast cancer risk assessment across the risk continuum: genetic and nongenetic risk factors contributing to differential model performance. *Breast Cancer Res.* **14**, R144 (2012).
175. van Veen, E. M. et al. Use of single-nucleotide polymorphisms and mammographic density plus classic risk factors for breast cancer risk prediction. *JAMA Oncol.* **4**, 476–482 (2018).
176. Cuzick, J. et al. Impact of a panel of 88 single nucleotide polymorphisms on the risk of breast cancer in high-risk women: results from two randomized tamoxifen prevention trials. *J. Clin. Oncol.* **35**, 743–750 (2017).
177. Steyerberg, E. W. et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* **21**, 128–138 (2010).
178. Louro, J. et al. A systematic review and quality assessment of individualised breast cancer risk prediction models. *Br. J. Cancer* **121**, 76–85 (2019).
179. Endogenous Hormones and Breast Cancer Collaborative Group. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. *Lancet Oncol.* **14**, 1009–1019 (2013).
180. Terry, M. B., McDonald, J. A., Wu, H. C., Eng, S. & Santella, R. M. Epigenetic biomarkers of breast cancer risk: across the breast cancer prevention continuum. *Adv. Exp. Med. Biol.* **882**, 33–68 (2016).
181. Machella, N. et al. Double-strand breaks repair in lymphoblastoid cell lines from sisters discordant for

breast cancer from the New York site of the BCFR. *Carcinogenesis* **29**, 1367–1372 (2008).
182. Phillips, K. A. et al. Transitioning to routine breast cancer risk assessment and management in primary care: what can we learn from cardiovascular disease? *Aust. J. Prim. Health* **22**, 255–261 (2016).
183. Collins, I. M. et al. iPrevent®: a tailored, web-based, decision support tool for breast cancer risk assessment and management. *Breast Cancer Res. Treat.* **156**, 171–182 (2016).
184. Phillips, K. A. et al. Accuracy of estimates from the iPrevent breast cancer risk assessment and risk management tool. *JNCI – Cancer Spec.* **3**, pkz066 (2019).
185. Lo, L. L. et al. The iPrevent online breast cancer risk assessment and risk management tool: usability and acceptability testing. *JMIR Form. Res.* **2**, e24 (2018).
186. Keogh, L. A. et al. Consumer and clinician perspectives on personalising breast cancer prevention information. *Breast* **43**, 39–47 (2019).
187. DeSantis, C. E. et al. Breast cancer statistics, 2019. *CA Cancer J. Clin.* **69**, 438–451 (2019).
188. National Comprehensive Cancer Network. Breast cancer risk reduction. *NCCN* https://www2.tri-kobe.org/nccn/guideline/breast/english/breast_risk.pdf (2019).
189. National Institute for Health and Care Excellence. Familial breast cancer: Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer. *NICE* https://www.nice.org.uk/guidance/cg164 (2020).
190. Visvanathan, K. et al. Use of endocrine therapy for breast cancer risk reduction: ASCO clinical practice guideline update. *J. Clin. Oncol.* **37**, 3152–3165 (2019).
191. Li, X. et al. Effectiveness of prophylactic surgeries in *BRCA1* or *BRCA2* mutation carriers: a meta-analysis and systematic review. *Clin. Cancer Res.* **22**, 3971–3981 (2016).
192. Hartmann, L. C. et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N. Engl. J. Med.* **340**, 77–84 (1999).
193. Carbine, N. E., Lostumbo, L., Wallace, J. & Ko, H. Risk-reducing mastectomy for the prevention of primary breast cancer. *Cochrane Database Syst. Rev.* **4**, CD002748 (2018).
194. Jakub, J. W. et al. Oncologic safety of prophylactic nipple-sparing mastectomy in a population with *BRCA* mutations: a multi-institutional study. *JAMA Surg.* **153**, 123–129 (2018).
195. Metcalfe, K. et al. International trends in the uptake of cancer risk reduction strategies in women with a *BRCA1* or *BRCA2* mutation. *Br. J. Cancer* **121**, 15–21 (2019).
196. Rebbeck, T. R., Kauff, N. D. & Domchek, S. M. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in *BRCA1* or *BRCA2* mutation carriers. *J. Natl Cancer Inst.* **101**, 80–87 (2009).
197. Heemskerk-Gerritsen, B. A. et al. Breast cancer risk after salpingo-oophorectomy in healthy *BRCA1/2* mutation carriers: revisiting the evidence for risk reduction. *J. Natl Cancer Inst.* **107**, djv033 (2015).
198. Terry, M. B. et al. Risk-reducing oophorectomy and breast cancer risk across the spectrum of familial risk. *J. Natl Cancer Inst.* **111**, 331–334 (2019).
199. Kotsopoulos, J. et al. Bilateral oophorectomy and breast cancer risk in BRCA1 and BRCA2 mutation carriers. *J. Natl Cancer Inst.* **109**, djw177 (2017).
200. Mai, P. L. et al. Risk-reducing salpingo-oophorectomy and breast cancer risk reduction in the Gynecologic Oncology Group Protocol-0199 (GOG-0199). *JNCI Cancer Spectr.* **4**, pkz075 (2019).
201. Milne, R. L. & Antoniou, A. C. Modifiers of breast and ovarian cancer risks for *BRCA1* and *BRCA2* mutation carriers. *Endocr. Relat. Cancer* **23**, T69–T84 (2016).
202. Cuzick, J. et al. Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. *Lancet* **381**, 1827–1834 (2013).
203. Cuzick, J. et al. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. *Lancet Oncol.* **16**, 67–75 (2015).
This paper describes the long-term follow-up of the IBIS-I trial participants who received 5 years of preventive tamoxifen and shows that the protection against breast cancer is maintained for at least 20 years.
204. Nelson, H. D., Smith, M. E., Griffin, J. C. & Fu, R. Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventive Services Task Force. *Ann. Intern. Med.* **158**, 604–614 (2013).
205. Skandarajah, A. R. et al. Patient and medical barriers preclude uptake of tamoxifen preventative therapy in women with a strong family history. *Breast* **32**, 93–97 (2017).
206. Vogel, V. G. et al. Update of the national surgical adjuvant breast and bowel project study of tamoxifen and raloxifene (STAR) P-2 trial: preventing breast cancer. *Cancer Prev. Res.* **3**, 696–706 (2010).
207. Freedman, A. N. et al. Benefit/risk assessment for breast cancer chemoprevention with raloxifene or tamoxifen for women age 50 years or older. *J. Clin. Oncol.* **29**, 2327–2333 (2011).
208. Cuzick, J. et al. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. *Lancet* **395**, 117–122 (2020).
This paper describes the long-term follow-up of a randomized controlled trial of anastrozole or placebo for breast cancer prevention and shows that 5 years of anastrozole confers at least 10 years of preventive benefit.
209. Cuzick, J. et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. *Lancet* **383**, 1041–1048 (2014).
210. Goss, P. E. et al. Exemestane for breast-cancer prevention in postmenopausal women. *N. Engl. J. Med.* **364**, 2381–2391 (2011).
211. Noonan, S. et al. A survey among breast cancer specialists on the low uptake of therapeutic prevention with tamoxifen or raloxifene. *Cancer Prev. Res.* **11**, 38–43 (2018).
212. Collins, I. M. et al. Preventing breast and ovarian cancers in high-risk *BRCA1* and *BRCA2* mutation carriers. *Med. J. Aust.* **199**, 680–683 (2013).
213. Collins, I. M. et al. Assessing and managing breast cancer risk: clinicians' current practice and future needs. *Breast* **23**, 644–650 (2014).
214. Keogh, L. A., Hopper, J. L., Rosenthal, D. & Phillips, K. A. Australian clinicians and chemoprevention for women at high familial risk for breast cancer. *Hered. Cancer Clin. Pract.* **7**, 9 (2009).
215. Smith, S. G. et al. Prescribing tamoxifen in primary care for the prevention of breast cancer: a national online survey of GPs' attitudes. *Br. J. Gen. Pract.* **67**, e414–e427 (2017).
216. Smith, S. G. et al. Factors affecting uptake and adherence to breast cancer chemoprevention: a systematic review and meta-analysis. *Ann. Oncol.* **27**, 575–590 (2016).
This meta-analysis shows that uptake of therapeutic agents for the prevention of breast cancer is low and persistent long-term use is often insufficient, meaning that women do not experience the full preventive effect.
217. Fisher, B. et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J. Natl Cancer Inst.* **90**, 1371–1388 (1998).
218. Donnelly, L. S. et al. Uptake of tamoxifen in consecutive premenopausal women under surveillance in a high-risk breast cancer clinic. *Br. J. Cancer* **110**, 1681–1687 (2014).
219. Bober, S. L., Hoke, L. A., Duda, R. B., Regan, M. M. & Tung, N. M. Decision-making about tamoxifen in women at high risk for breast cancer: clinical and psychological factors. *J. Clin. Oncol.* **22**, 4951–4957 (2004).
220. Cuzick, J. et al. First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial. *Lancet* **360**, 817–824 (2002).
221. Heisey, R., Pimlott, N., Clemons, M., Cummings, S. & Drummond, N. Women's views on chemoprevention of breast cancer: qualitative study. *Can. Fam. Physician* **52**, 624–625 (2006).
222. Kuderer, N. M. & Peppercorn, J. CYP2D6 testing in breast cancer: ready for prime time? *Oncology* **23**, 1223–1232 (2009).
223. DeCensi, A. et al. A randomized trial of low-dose tamoxifen on breast cancer proliferation and blood estrogenic biomarkers. *J. Natl Cancer Inst.* **95**, 779–790 (2003).
224. DeCensi, A. et al. Randomized placebo controlled trial of low-dose tamoxifen to prevent local and contralateral recurrence in breast intraepithelial neoplasia. *J. Clin. Oncol.* **37**, 1629–1637 (2019).
225. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT00952731 (2009).
226. Rojas, L. B. & Gomes, M. B. Metformin: an old but still the best treatment for type 2 diabetes. *Diabetol. Metab. Syndr.* **5**, 6 (2013).
227. Bodmer, M., Meier, C., Krahenbuhl, S., Jick, S. S. & Meier, C. R. Long-term metformin use is associated with decreased risk of breast cancer. *Diabetes Care* **33**, 1304–1308 (2010).
228. EU Clinical Trials Register. *ClinicalTrialsRegister.eu* https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-009921-28 (2010).
229. Boissier, S. et al. Bisphosphonates inhibit breast and prostate carcinoma cell invasion, an early event in the formation of bone metastases. *Cancer Res.* **60**, 2949–2954 (2000).
230. Chlebowski, R. T. et al. Oral bisphosphonate use and breast cancer incidence in postmenopausal women. *J. Clin. Oncol.* **28**, 3582–3590 (2010).
231. Daubine, F., Le Gall, C., Gasser, J., Green, J. & Clezardin, P. Antitumor effects of clinical dosing regimens of bisphosphonates in experimental breast cancer bone metastasis. *J. Natl Cancer Inst.* **99**, 322–330 (2007).
232. van der Pluijm, G. et al. Bisphosphonates inhibit the adhesion of breast cancer cells to bone matrices in vitro. *J. Clin. Invest.* **98**, 698–705 (1996).
233. Early Breast Cancer Trialists' Collaborative Group. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet* **386**, 1353–1361 (2015).
234. Dhesy-Thind, S. et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a Cancer Care Ontario and American Society of Clinical Oncology clinical practice guideline. *J. Clin. Oncol.* **35**, 2062–2081 (2017).
235. Gnant, M., Harbeck, N. & St. Thomssen, C. Gallen/Vienna 2017: a brief summary of the consensus discussion about escalation and de-escalation of primary breast cancer treatment. *Breast Care (Basel)* **12**, 102–107 (2017).
236. Vestergaard, P., Fischer, L., Mele, M., Mosekilde, L. & Christiansen, P. Use of bisphosphonates and risk of breast cancer. *Calcif. Tissue Int.* **88**, 255–262 (2011).
237. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02781805 (2016).
238. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03323658 (2017).
239. EU Clinical Trials Register. *ClinicalTrialsRegister.eu* https://www.clinicaltrialsregister.eu/ctr-search/search?query=2009-010260-41 (2009).
240. Moon, R. C. et al. *N*-(4-Hydroxyphenyl)retinamide, a new retinoid for prevention of breast cancer in the rat. *Cancer Res.* **39**, 1339–1346 (1979).
241. Veronesi, U. et al. Randomized trial of fenretinide to prevent second breast malignancy in women with early breast cancer. *J. Natl Cancer Inst.* **91**, 1847–1856 (1999).
242. Xu, L. et al. Tamoxifen and risk of contralateral breast cancer among women with inherited mutations in *BRCA1* and *BRCA2*: a meta-analysis. *Breast Cancer* **22**, 327–334 (2015).
243. Phillips, K. A. et al. Tamoxifen and risk of contralateral breast cancer for *BRCA1* and *BRCA2* mutation carriers. *J. Clin. Oncol.* **31**, 3091–3099 (2013).
This large international study of pooled cohort data shows that tamoxifen use for first breast cancer is associated with a marked reduction in contralateral breast cancer risk in both *BRCA1* and *BRCA2* mutation carriers.
244. Nolan, E. et al. RANK ligand as a potential target for breast cancer prevention in *BRCA1*-mutation carriers. *Nat. Med.* **22**, 933–939 (2016).
This study identifies RANK$^+$ luminal progenitors as the cancer cell of origin for breast cancer that develops in *BRCA1* mutation carriers and shows that inhibition of RANKL signalling can reduce proliferation in patient-derived organoids and tumour development in transgenic mice.
245. Nolan, E., Lindeman, G. J. & Visvader, J. E. Out-RANKing BRCA1 in mutation carriers. *Cancer Res.* **77**, 595–600 (2017).
246. EU Clinical Trials Register. *ClinicalTrialsRegister.eu* https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-002505-35/AT (2018).
247. Poole, A. J. et al. Prevention of *Brca1*-mediated mammary tumorigenesis in mice by a progesterone antagonist. *Science* **314**, 1467–1470 (2006).
248. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02408770 (2015).

249. Lu, L., Shi, L., Zeng, J. & Wen, Z. Aspirin as a potential modality for the chemoprevention of breast cancer: a dose–response meta-analysis of cohort studies from 857,831 participants. *Oncotarget* **8**, 40389–40401 (2017).
250. de Pedro, M. et al. Effect of COX-2 inhibitors and other non-steroidal inflammatory drugs on breast cancer risk: a meta-analysis. *Breast Cancer Res. Treat.* **149**, 525–536 (2015).
251. Kehm, R. D. et al. Regular use of aspirin and other non-steroidal anti-inflammatory drugs and breast cancer risk for women at familial or genetic risk: a cohort study. *Breast Cancer Res.* **21**, 52 (2019).
252. Gierach, G. L. et al. Nonsteroidal anti-inflammatory drugs and breast cancer risk in the National Institutes of Health–AARP Diet and Health Study. *Breast Cancer Res.* **10**, R38 (2008).
253. Marshall, S. F. et al. Nonsteroidal anti-inflammatory drug use and breast cancer risk by stage and hormone receptor status. *J. Natl Cancer Inst.* **97**, 805–812 (2005).
254. Terry, M. B. et al. Association of frequency and duration of aspirin use and hormone receptor status with breast cancer risk. *JAMA* **291**, 2433–2440 (2004).
255. Unsworth, A., Anderson, R. & Britt, K. Stromal fibroblasts and the immune microenvironment: partners in mammary gland biology and pathology? *J. Mammary Gland. Biol. Neoplasia* **19**, 169–182 (2014).
256. Visvader, J. E. & Stingl, J. Mammary stem cells and the differentiation hierarchy: current status and perspectives. *Genes Dev.* **28**, 1143–1158 (2014).
257. Gil Del Alcazar, C. R. et al. Immune escape in breast cancer during in situ to invasive carcinoma transition. *Cancer Discov.* **7**, 1098–1115 (2017).
This paper assesses normal breast, DCIS and invasive ductal carcinomas to reveal co-evolution of cancer cells and the immune microenvironment.
258. Cossart, Y. E. The rise and fall of infectious diseases: Australian perspectives, 1914–2014. *Med. J. Aust.* **201**, S11–S14 (2014).
259. Harvard University. *BayesMendel R Package* https://projects.iq.harvard.edu/bayesmendel/brcapro (2020).
260. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT00078832 (2004).
261. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03063619 (2017).
262. EU Clinical Trials Register. *ClinicalTrialsRegister.eu* https://www.clinicaltrialsregister.eu/ctr-search/search?query=2016-001087-11 (2016).
263. Australia NewZealand Clinical Trials registry. *ANZCTR* https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12614000694617 (2014).
264. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* **347**, 1713–1727 (1996).
This study uses a large data set of epidemiological data spanning 25 countries to show that women who are currently taking the OCP (or those still within 10 years of stopping) are at an increased risk of breast cancer.
265. Morch, L. S. et al. Contemporary hormonal contraception and the risk of breast cancer. *N. Engl. J. Med.* **377**, 2228–2239 (2017).
266. Australia Institute of Health and Welfare. *AIHW* https://www.aihw.gov.au/reports/overweight-obesity/overweight-and-obesity-an-interactive-insight/contents/prevalence (2019).
267. Provenzano, P. P. et al. Collagen density promotes mammary tumor initiation and progression. *BMC Med.* **6**, 11 (2008).
268. Alowami, S., Troup, S., Al-Haddad, S., Kirkpatrick, I. & Watson, P. H. Mammographic density is related to stroma and stromal proteoglycan expression. *Breast Cancer Res.* **5**, R129–R135 (2003).
269. Cho, A., Howell, V. M. & Colvin, E. K. The extracellular matrix in epithelial ovarian cancer—a piece of a puzzle. *Front. Oncol.* **5**, 245 (2015).
270. Provenzano, P. P. & Keely, P. J. Mechanical signaling through the cytoskeleton regulates cell proliferation by coordinated focal adhesion and Rho GTPase signaling. *J. Cell Sci.* **124**, 1195–1205 (2011).
271. Lisanti, M. P. et al. JNK1 stress signaling is hyper-activated in high breast density and the tumor stroma: connecting fibrosis, inflammation, and stemness for cancer prevention. *Cell Cycle* **13**, 580–599 (2014).
272. Dushyanthen, S. et al. Relevance of tumor-infiltrating lymphocytes in breast cancer. *BMC Med.* **13**, 202 (2015).
273. Tower, H., Ruppert, M. & Britt, K. The immune microenvironment of breast cancer progression. *Cancers* **11**, 1375 (2019).
274. Simon, T. & Bromberg, J. S. Regulation of the immune system by laminins. *Trends Immunol.* **38**, 858–871 (2017).
275. Lu, P., Takai, K., Weaver, V. M. & Werb, Z. Extracellular matrix degradation and remodeling in development and disease. *Cold Spring Harb. Perspect. Biol.* **3**, a005058 (2011).
276. Hallmann, R. et al. The regulation of immune cell trafficking by the extracellular matrix. *Curr. Opin. Cell Biol.* **36**, 54–61 (2015).
277. Kajita, M. & Fujita, Y. EDAC: epithelial defence against cancer-cell competition between normal and transformed epithelial cells in mammals. *J. Biochem.* **158**, 15–23 (2015).
278. Hunter, D. J. et al. Oral contraceptive use and breast cancer: a prospective study of young women. *Cancer Epidemiol. Biomarkers Prev.* **19**, 2496–2502 (2010).
279. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet* **350**, 1047–1059 (1997).
280. Althuis, M. D. et al. Hormonal content and potency of oral contraceptives and breast cancer risk among young women. *Br. J. Cancer* **88**, 50–57 (2003).
281. Beral, V., Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* **362**, 419–427 (2003).
282. Jones, J., Mosher, W. & Daniels, K. Current contraceptive use in the United States, 2006–2010, and changes in patterns of use since 1995. *Natl Health Stat Report* **60**, 1–25 (2012).
283. Daniels, K. & Abma, J. C. Current contraceptive status among women aged 15–49: United States, 2015–2017 *CDC* https://www.cdc.gov/nchs/data/databriefs/db327-h.pdf (2018).
US statistics indicate that as much as 5% of OCP users are older premenopausal women aged 40–49 years.
284. Rossouw, J. E. et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* **288**, 321–333 (2002).
285. Chlebowski, R. T. et al. Breast cancer after use of estrogen plus progestin and estrogen alone: analyses of data from 2 Women's Health Initiative randomized clinical trials. *JAMA Oncol.* **1**, 296–305 (2015).
286. Chlebowski, R. T. et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* **289**, 3243–3253 (2003).
287. Chlebowski, R. T. et al. Long-term influence of estrogen plus progestin and estrogen alone use on breast cancer incidence: The Women's Health Initiative randomized trials [abstract]. *Cancer Res.* **80**, GS5-00 (2020).

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Competing interests
The authors wish to disclose that Cancer Research UK (CRUK) licences the International Breast Cancer Intervention Study (IBIS; also known as Tyrer–Cuzick) model for commercial use and J.C. receives some benefit. K.A.-P has a patent, System and Process of Cancer Risk Estimation (Australian Innovation Patent), issued regarding iPrevent. K.L.B has no competing interests.

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