

Review

Oestrogen exposure and breast cancer risk

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Abstract

Epidemiological and experimental evidence implicates oestrogens in the aetiology of breast cancer. Most established risk factors for breast cancer in humans probably act through hormone-related pathways, and increased concentrations of circulating oestrogens have been found to be strongly associated with increased risk for breast cancer in postmenopausal women. This article explores the evidence for the hypothesis that oestrogen exposure is a major determinant of risk for breast cancer. We review recent data on oestrogens and breast cancer risk, consider oestrogen-related risk factors and examine possible mechanisms that might account for the effects of oestrogen. Finally, we discuss how these advances might influence strategies for reducing the incidence of breast cancer.

Keywords: breast cancer, epidemiology, oestrogen, prevention, risk factors

Introduction

Epidemiological and experimental evidence implicates oestrogens in the aetiology of breast cancer. Most established risk factors for breast cancer in humans are thought to influence risk through hormone-related pathways [1], increased concentrations of endogenous oestrogens are strongly associated with increased risk for breast cancer in postmenopausal women [2], and trials have shown that the anti-oestrogens tamoxifen and raloxifene reduce the incidence of breast cancer [3]. Furthermore, experimental studies in animals have shown that oestrogens can promote mammary tumours, and a decrease in exposure to oestrogens, by performing an oophorectomy or giving an anti-oestrogenic drug, has the reverse effect [4]. However, the effects of oestrogen alone do not fully account for the relationships observed between breast cancer and hormone-related risk factors. Other hormones, such as progesterone [1], prolactin [5] and testosterone [6], may also be important.

This article explores the evidence for the hypothesis that exposure to oestrogen is a major determinant of risk for breast cancer. It is not intended to be a comprehensive review but rather focuses on recent epidemiological and experimental data relating to the role of oestrogen in the

aetiology of breast cancer and possible mechanisms that might account for the association. There are several forms of oestrogen, the principal form in humans being oestradiol, but for convenience in this article we refer generally to oestrogens except where it is necessary to be more specific.

Reproductive risk factors, oestrogen and breast cancer

Oestrogens have an essential role, together with other hormones, in the development of the female sex organs and secondary sex characteristics, the regulation of the menstrual cycle and reproduction. Thus, it has been proposed that the effects of many established reproductive risk factors for breast cancer are mediated by hormonal mechanisms, for the most part involving oestrogens [1].

Although risk for breast cancer increases with age, there is a marked decline in the rate of increase in risk with age following the loss of ovarian function, either as a result of a bilateral oophorectomy or due to the menopause [7,8], showing that hormone production by the ovaries is a crucial risk factor for breast cancer in humans. The duration of exposure to ovarian hormones seems to be closely related to breast cancer risk: a 1-year delay in the

onset of menarche is associated with a 5% reduction in risk for developing breast cancer in later life [9], and each 1-year delay in the onset of menopause is associated with a 3% increase in risk [7].

Epidemiological studies have also firmly established associations between risk for breast cancer and other reproductive factors, including nulliparity (having no children) or low parity, late age at first birth, and breast feeding [10]. After a transient increase in risk for breast cancer, peaking at about 5 years after giving birth [11], having at least one child is associated with a decrease in the long-term risk of developing breast cancer compared with risk among the nulliparous, and this protective effect increases with number of children [12]. Each birth reduces the relative risk of breast cancer by an average of 7% [12]. The reduction in risk per birth is greater for births at young ages than older ages, such that women who have their first birth before the age of 20 years have a 30% lower risk than women with a first birth after the age of 35 years [13].

A mechanism involving oestrogens, and probably other hormones, has been proposed to explain both the transient increase in risk and the reduced risk in the long term associated with pregnancy. The very high serum levels of oestrogens and progesterone during pregnancy stimulate growth of the mammary epithelium and also promote the differentiation of epithelial tissue, reducing the number of epithelial structures most vulnerable to malignant transformation [14]. Thus, the short-term effect of pregnancy may be to promote the growth of cancer if a malignant transformation is present in the breast, but in the longer term the risk for breast cancer is reduced. In contrast, malignant transformations are more likely to have accumulated in the breast tissue of older women, and there might therefore be a higher risk of cancer developing in these women when breast cells are stimulated to divide during pregnancy. The effect of age at first birth highlights the importance of timing of exposure as a critical determinant of the effects of steroid hormones such as oestrogen.

Breast feeding is associated with a modest decrease in risk for breast cancer, above and beyond that associated with multiple pregnancies (4% for every 12 months of breast feeding) [12]. This effect might be due to the suppression of ovulation, reducing exposure to ovarian hormones.

Diet-related and lifestyle factors in relation to breast cancer

Two diet-related factors, high alcohol intake [15] and obesity [16], are established risk factors for breast cancer. A moderate intake of alcohol (one unit a day) increases risk by 7%, and higher intakes of alcohol increase risk in an approximately linear fashion. The mechanism for this effect remains unknown but has been proposed to involve

increased concentrations of circulating oestrogens [15,17]. Breast cancer risk among postmenopausal women is also strongly associated with body mass index (BMI, an index of body weight independent of height, calculated as body weight in kilograms divided by the square of the height measured in metres). Risk for breast cancer is increased by 30% among obese postmenopausal women (with a BMI of more than 30 kg/m²) compared with those with a normal BMI (less than 25 kg/m²) [16]. This association is probably due to the relationship between BMI and endogenous oestrogen concentrations because, in postmenopausal women, circulating oestrogen concentrations are dependent on the extraglandular production of oestrogen in the adipose tissue.

For premenopausal women, the lack of a positive association of BMI with breast cancer risk [16] is consistent with the facts that most oestrogen is produced by the ovaries and that levels are homeostatically regulated by a negative feedback system involving gonadotrophins (follicle-stimulating hormone and luteinising hormone). Thus, oestrogen concentrations in premenopausal women are not directly affected by the levels of adipose tissue. Indeed, obesity in premenopausal women has been linked to a slight decrease in risk for breast cancer [16], possibly mediated through an increase in the occurrence of anovulatory cycles and a subsequent decrease in exposure to ovarian progesterone among these women (see below). It has been suggested that this decrease in breast cancer risk due to obesity in early adulthood may continue into later life, negating some of the increased risk of breast cancer among women who remain obese after the menopause [18]. Evidence for this comes from the finding that weight gain from adolescence to adulthood is most strongly and consistently associated with risk of postmenopausal breast cancer [16], with weight gains of over 20 kg associated with an increase in risk of 40% [19].

Physical activity has also been observed to be associated with a reduced risk for breast cancer in both premenopausal and postmenopausal women. Most studies have found a 20–40% decrease in risk of breast cancer among the most physically active [16]. The effects of physical activity on breast cancer risk may be mediated through alterations in endogenous hormones including oestrogens, energy balance, body mass and possibly immune function [20]. In postmenopausal women this low risk might be due in part to physical activity preventing weight gain and obesity [20], although there is some evidence to suggest that the effects of physical activity are independent of weight control [21]. In premenopausal women the effects of high levels of physical exercise may be mediated by other mechanisms [20]. For example, there is considerable evidence that intense physical activity can alter menstrual cycle characteristics, delay menarche and increase the probability of anovulatory cycles,

amenorrhoea or oligomenorrhoea, thus reducing exposure to ovarian hormones [20,22–24], and there is also some promising evidence that even moderate exercise may be beneficial [25–27].

Endogenous oestrogens and breast cancer in humans

Direct evidence for a relationship between oestrogens and risk of developing breast cancer comes from observational studies that have found circulating and excreted oestrogen levels to be associated with risk for the disease [28]. Because breast cancer itself might affect hormone production, it is necessary to conduct prospective studies of oestrogens and breast cancer risk in which samples are collected at the start of the study from healthy women, who are then followed up with respect to cancer diagnoses. Such investigations have considered premenopausal and postmenopausal women separately because the endogenous production of and exposure to endogenous oestrogen varies greatly during a woman's lifespan. In premenopausal women, the predominant form of circulating oestrogen is oestradiol secreted by the ovaries in cyclical monthly patterns. After the menopause, however, the production of oestrogens in the ovaries ceases and the major source of oestradiol is by conversion from oestrone, itself produced mostly through the peripheral conversion of androgen precursors, predominantly androstenedione, in extraglandular tissue such as adipose tissue [29].

A recent pooled analysis of nine prospective studies in postmenopausal women, including 663 breast cancer cases, found a highly significant increase in breast cancer risk with increasing concentrations of oestradiol, free oestradiol and oestrone in the blood [2]. Postmenopausal women with relatively high serum oestrogen concentrations had an approximately twofold risk of breast cancer compared with postmenopausal women with relatively low serum concentrations of sex hormones [2]. Studies have also evaluated the relationship between urinary endogenous oestrogens and breast cancer; recent results from the largest prospective study of oestrogens and breast cancer found women with a higher excretion of oestrone and oestradiol to have a significantly increased risk for breast cancer [30].

Data on oestrogen levels in premenopausal women and breast cancer risk are sparse, with only five small prospective studies published so far [31–35]. Of the three larger and more recent studies, two found a nonsignificant increase in mean oestradiol concentrations among cases in comparison with controls [33,34], and the third reported significantly elevated levels of bioavailable oestradiol and a nonsignificant increase in total oestradiol in cases [35]. These results are compatible with the oestrogen hypothesis, but the numbers studied are too

small, and the difficulties of appropriate adjustment for day of menstrual cycle too complex, to allow any firm conclusions.

A limitation with all these studies is that they rely on measurements made from just one sample, and whereas measurements in single samples from postmenopausal women have been found to be fairly representative of long-term circulating oestrogen concentrations, single sample measurements from premenopausal women are less representative of average circulating concentrations [36,37]. The reliable estimation of circulating oestrogen concentrations in premenopausal women is complicated by the fluctuating levels of oestrogen over the course of the menstrual cycle, such that the timing of the sample is a strong determinant of the oestrogen concentration measured.

Binding proteins and the bioavailability of oestrogens

The availability of oestrogen in tissues is determined not only by the production of the hormone and concentrations in circulation but also by the extent to which it is bound to a binding protein, sex-hormone-binding globulin (SHBG). Thus, high concentrations of SHBG decrease the proportion of oestradiol that is able to leave the circulation and enter the cells. SHBG might partly mediate the effects of obesity in postmenopausal women because obesity is associated with lower levels of SHBG [36] and an inverse association has been observed between concentrations of SHBG and breast cancer risk in postmenopausal women [2]. So far, however, the few studies that have investigated the relationship between SHBG and breast cancer risk in premenopausal women have failed to find an association [34,35,38].

Genetic determinants of endogenous hormones in relation to breast cancer risk

The genetic control of oestrogen levels has recently received much attention and with it the notion that susceptibility to breast cancer might in part be determined through germline polymorphisms in metabolic genes, specifically those encoding enzymes involved in the biosynthesis and metabolism of oestrogens [39]. Further, it has been suggested that small effects of individual polymorphisms in genes involved in steroid biosynthesis and catabolism might be cumulative [40]. Such polymorphisms might be particularly important among postmenopausal women, in whom oestrogen production is not homeostatically controlled by pituitary gonadotrophins. Several recent epidemiological studies have observed an association between risk for breast cancer and polymorphisms in genes involved in oestrogen synthesis, such as *CYP17* and *CYP19*, and in *HSD17B1*, which codes for an enzyme that converts oestrone to oestradiol [40,41]. However, other studies have not found an association between such polymorphisms and breast cancer, and a

biological relationship of these polymorphisms with circulating oestrogens and oestrogen metabolites has yet to be established (reviewed in [42,43]).

Variations in oestrogen catabolism may also influence risk for breast cancer by causing differences in the cumulative exposure to oestrogen, by influencing the balance between different forms of oestrogen and by altering exposure to the various metabolites, some of which might have carcinogenic properties. In humans, oestrogens are catabolised into hydroxy-oestrogens such as 16 α -hydroxylated oestrogens and 2-hydroxylated (catechol) oestrogens, which are then converted into methoxylated metabolites. Polymorphisms in genes such as *COMT*, which is involved in the methylation of oestrogens to harmless metabolites, have been the subject of epidemiological studies [44]. Several studies have found women with the low-activity *COMT* allele to be at higher risk for breast cancer [45–47]. However, other studies have failed to find a significant association [48,49] or have found *COMT* to be important only in certain histotypes or in conjunction with other exposures [49,50].

Exogenous oestrogens and breast cancer

In the past 50 years, exposure to exogenous oestrogens from a variety of sources has become increasingly common, particularly from hormonal preparations for use as contraceptives or to combat the symptoms of the menopause. Hormonal contraception, using oestrogens and progestins in various forms and doses, is now one of the most widely used forms of contraception, being taken by 200 million women worldwide in 1996 [51]. Similarly, the prescription of hormone replacement therapy (HRT) for older women, containing oestrogens with or without progestins, has become common. In Britain, for example, 33% of women aged 50–64 are current users [52]. Given the high prevalence of exposure to these exogenous oestrogens, even small associated increases in risk for breast cancer could have a substantial effect on the incidence of breast cancer.

Oral contraceptives and breast cancer

In 1996, data from 54 published studies on use of the combined contraceptive pill (containing an oestrogen and a progestogen) in relationship to breast cancer risk were brought together in a pooled analysis [53]. Women who were currently using combined oral contraceptives or who had used them in the past 10 years were found to be at slightly higher risk of having breast cancer diagnosed (relative risk [95% confidence interval] in current user, 1.24 [1.15–1.33]; 1–4 years after stopping, 1.16 [1.08–1.23]; 5–9 years after stopping, 1.07 [1.02–1.13]), although the associated cancers tended to be localised to the breast [53]. However, there was no evidence of a significant excess risk of having breast cancer diagnosed 10 or more years after ceasing to use the combined contraceptive pill

(relative risk 1.01 [0.96–1.05]) [53]. More recent results are broadly compatible with these findings, but inconsistencies remain and formulations are changing; further research is therefore crucial [54–59].

HRT and breast cancer

So far there have been more than 60 analytical studies investigating the relationship between menopausal HRT and breast cancer risk. Data from these studies were brought together in a pooled analysis [7], which found that current users of HRT, or those who ceased use 1–4 years previously, had a 2.3% excess risk of being diagnosed with breast cancer for each year of use, an increase in risk that is comparable with the effect of delaying menopause for a year [7]. The excess risk of breast cancer among women who had used HRT for 5 years or longer was 35%. This effect was reduced after ceasing use of HRT and had largely, if not wholly, disappeared after about 5 years. These results did not vary significantly by type of HRT, although the collaborative study had relatively little power to assess relationships with combined oestrogen–progestin therapy. More recent studies have reported that the long-term use of preparations containing progestins is more detrimental than the use of oestrogen alone [60,61]. Recent data from three randomised controlled trials have confirmed that exposure to oestrogens plus progestins for 5 years is associated with an approximate 26–30% increase in risk for breast cancer [62].

Phyto-oestrogens and breast cancer

The observation that breast cancer rates are lower in most Asian countries than in Western Europe and the USA [63] has given rise to hypotheses about the possible protective effects of foods rich in phyto-oestrogens, particularly soybeans, which form an important part of the diet in several Asian countries [64]. Phyto-oestrogens are naturally occurring plant compounds (or their metabolites) that are effectively weak exogenous oestrogens because they can mimic or modulate the actions of more potent endogenous oestrogens, usually by binding to oestrogen receptors (ERs) [65]. It has also been suggested that they might reduce risk by altering oestrogen metabolism away from the production of genotoxic metabolites [66] or through non-oestrogenic pathways [65].

Results from numerous animal studies suggest that high intake of soy may confer a protective effect against breast cancer [67], but the findings from studies in humans remain equivocal [68]. Two early case-control analyses suggested that high levels of dietary isoflavone intake may be protective against breast cancer in premenopausal women [69,70], but results from later analytical studies of adult exposure and breast cancer risk have been inconsistent [68]. Two recent case-control studies have suggested that a high intake of isoflavone-rich foods during adolescence may have a protective effect on risk for

breast cancer in adulthood [71,72]. These findings support the possibility that exposure to phyto-oestrogens at critical periods of development might be an important determinant of risk for breast cancer.

The proliferative effects of oestrogen

Oestrogens have a marked proliferative effect on breast epithelial tissue in model systems [73]. Both endogenous and exogenous oestrogens stimulate breast epithelial cell mitosis, increasing the number of cell divisions and thus the opportunity for random genetic errors [1,74]. Oestrogen concentrations may be important at all stages in the development of breast neoplasms because the hormonal stimulus to cell division continues all along the progression pathway [75]. The proliferative effects of oestrogens are brought about on entering target cells, where they bind with a receptor protein, which then binds to hormone response elements on the nuclear DNA, activating or suppressing specific sequences in the regulatory regions of genes responsive to oestrogen that control cell growth and differentiation [76].

The possible role of oestrogens as mutagens in the initiation of breast tumorigenesis has also received much scrutiny. Although early experimental data suggested that oestradiol did not have any mutagenic properties because no mutagenic activity was found in either bacterial or mammalian cell test systems, more recent research has suggested that oestrogens, and to a greater extent their metabolites including catechol oestrogens and reactive semiquinone/quinone intermediates, may act as weak pro-carcinogens. They might induce direct and indirect free-radical-mediated DNA damage, genetic instability, and mutations in cells in culture and *in vivo* [77]. However, even if oestrogens can induce genetic damage, the data overall suggest that proliferative effects are likely to be the most important mechanism by which this hormone acts to influence the development of breast cancer.

It has also been suggested that oestrogens might have an important influence on risk for developing breast cancer through effects before the initiation of the disease [78]. Raised oestrogen levels during fetal life have been shown to influence morphology of the mammary gland [79], and increased levels are also thought to be responsible for the persistence of epithelial structures (terminal end buds) that are known to be sites of malignant transformation [80]. Furthermore, results from animal models and indirect human evidence indicate that exposure to elevated oestrogen levels *in utero* may increase the risk for developing breast cancer in adulthood [79,81].

Epidemiological studies investigating the relationship between breast cancer risk and oestrogen exposure *in utero* have examined several perinatal factors, such as high birth weight [82,83]. In six out of seven epidemiologi-

cal studies, birth weight has been found to be positively associated with risk for breast cancer [82,84], although several studies have also found low birth weight (less than 2500 g) to be associated with a higher risk for breast cancer [84]. This intriguing field relates to the suggestion that certain perinatal factors are associated with high concentrations of maternal oestrogens in pregnancy [78] or high levels of oestrogens in the infant postnatally [85]. However, these associations remain to be confirmed [86].

Sensitivity to oestrogen

The sensitivity of breast tissue to oestrogen is dependent on the levels and types of ERs [76] and it is possible that variation in breast cancer risk is, in part, attributable to inter-individual variation in receptor levels in normal breast tissue [87]. ER levels have been found to vary by age, menopausal status and perhaps by ethnic group [88,89]. Sensitivity of breast tissue to oestrogens might also be determined by the balance between the two ER types, ER- α and ER- β . ER- β has a lower affinity for oestrogen than ER- α and may decrease the sensitivity of ER- α to oestrogen [90].

Other hormones and breast cancer risk

Whereas early hypotheses focused on oestrogens as important hormonal determinants of breast cancer risk [91], current epidemiological and experimental data indicate that other hormones, such as progesterone [1], prolactin [5] and testosterone [6], are also important in the aetiology of breast cancer.

It has been proposed that progesterone augments the effects of oestrogens on breast cancer development [1], and this hypothesis has gained support from several lines of evidence. Breast cell proliferation has been found to be greatest during the luteal phase of the menstrual cycle [1], when levels of progesterone are at their highest, and a cross-sectional study of women undergoing breast biopsies found that the mitotic activity in the terminal ductal lobular unit of the breast was greater in women taking combined hormone preparations than in women using oestrogen alone [92]. Furthermore, recent data indicate that hormone replacement therapies containing both oestrogens and progestogens have a greater detrimental effect on risk for breast cancer than preparations containing oestrogens alone [61]. Progestins, like oestrogens, are thought to exert their effects mainly through binding to nuclear receptor proteins.

Epidemiological studies of prolactin have found that circulating levels of the hormone are correlated with some established risk factors for breast cancer; for example, concentrations are higher in nulliparous than parous women [93] and higher among women using certain types of oral contraceptives than among those who were not [94,95]. High concentrations of prolactin have also been

found to be associated with increased risk for breast cancer in prospective studies in postmenopausal women [5]. In the largest prospective study so far, more than a doubling in risk for breast cancer was observed among women in the highest 25% of the prolactin distribution relative to those in the lowest 25%, independent of the effects of concentrations of circulating oestrogens, androgens and insulin-like growth factor-1 [96]. Prolactin, produced at the endocrine and autocrine/paracrine levels, acts to stimulate the proliferation, survival and motility of mammary epithelial cells through its interaction with receptors at the cell surface [5].

Testosterone might also have a role in the aetiology of breast cancer [6]. Results from a recent pooled analysis of prospective studies in postmenopausal women estimated that breast cancer risk among women in the top quintile of exposure to endogenous testosterone was more than double that of women in the lowest quintile [2]. However, the mechanisms by which testosterone might influence the risk for developing breast cancer remain unclear, as do the effects of the androgen on the risk for premenopausal breast cancer [6]. It may be that, in postmenopausal women at least, testosterone is converted to oestrogen in the breast.

Preventive strategies

The epidemiological evidence suggests that the risk of breast cancer might be reduced by lowering lifetime exposure to oestrogens through changes in lifestyle and reproductive behaviour. At present the only clear oestrogen-related risk factor for breast cancer that is amenable to change is obesity after the menopause. Thus, prudent advice is to maintain weight such that body mass is below 25 kg/m². Other lifestyle changes that may have protective effects mediated by oestrogens include minimising alcohol consumption and taking regular physical exercise. Recent data suggest, too, that long-term use of HRT should be avoided, unless there are strong clinical indications. Voluntary changes in most of the important reproductive risk factors such as parity and ages at menarche and menopause are not realistic, but extended breast feeding will produce a small decrease in breast cancer risk, in addition to its benefits for the child.

More radical measures including surgery, such as bilateral prophylactic oophorectomy and/or mastectomy, or chemoprophylaxis may be considered for particularly susceptible subgroups, such as those with a family history of breast cancer or characteristics predisposing them to exposure to high oestrogen levels. Bilateral oophorectomy has been found to result in a 50–70% reduction in breast cancer risk [97] although, in general, studies have focused only on women with mutations in *BRCA1/BRCA2*. Trial data show that the partial ER agonist tamoxifen and other ER modulators such as raloxifene [98] reduce the incidence

of primary ER-positive breast cancer [3,99]. Aromatase inhibitors [100], which suppress the peripheral conversion of androstenedione to oestradiol through inhibition of the aromatase enzyme, and agonists of gonadotrophin-releasing hormone, which suppress ovarian function in premenopausal women, have been shown to be effective in the treatment of early breast cancer [101] and may be developed for chemoprevention [1].

As these chemopreventatives may themselves be associated with detrimental effects, clinicians try to identify women at particularly high risk for breast cancer, for whom benefits of such interventions are likely to outweigh the risks [102,103]. One method of identifying women at high risk for the disease is to use mathematical models; one such tool is the Gail model, which uses data on risk factors to predict individualised risk for breast cancer [104].

Conclusion

Oestrogens have a key role in the aetiology of breast cancer, probably because of their proliferative effects. Current data suggest that these steroid hormones mediate the relationship between breast cancer and many established risk factors, such as age at menarche, age at menopause, and obesity in postmenopausal women. However, the effects of other risk factors, such as parity and breast feeding, may not be explained only by oestrogens; other hormones such as progesterone, prolactin and testosterone may also be important. More work is needed to clarify the effects of hormones on risk for breast cancer and the mechanisms involved, as well as to unravel the complex environmental and genetic determinants of endogenous hormone concentrations.

Competing interests

None declared.

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