Mechanisms of Disease

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ESTROGEN AND THE RISK OF BREAST CANCER

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The connection between breast cancer and estrogen has been recognized for more than 100 years, since George Beatson demonstrated that bilateral oophorectomy resulted in the remission of breast cancer in premenopausal women. Subsequent evidence has implicated both endogenous and exogenous estrogen in the pathogenesis of breast cancer. In this article, we review the relation between estrogen and the risk of breast cancer.

ESTROGEN AND BREAST CARCINOGENESIS

Experimental data strongly suggest that estrogens have a role in the development and growth of breast cancer. Although the exact mechanisms remain to be fully elucidated, the alkylation of cellular molecules and the generation of active radicals that can damage DNA, together with the potential genotoxicity of estrogen and some of its metabolites (e.g., the catechol estrogens), have been implicated. Estrogens promote the development of mammary cancer in rodents and exert both direct and indirect proliferative effects on cultured breast-cancer cells from humans. Direct tumor-initiating effects may occur through the induction of enzymes and proteins involved in nucleic acid synthesis and through the activation of oncogenes. Indirect effects may occur through the stimulation of prolactin secretion and the production of growth factors (e.g., transforming growth factor α and epidermal growth factor) and non–growth-factor peptides (e.g., plasminogen activators).

Tumor formation may also result from excessive hormonal stimulation of an organ in which normal growth and function are under endocrine control. The response of an organ to the proliferative effects of a hormone may be a progression from normal growth to hyperplasia to neoplasia. In this model, the risk of breast cancer could be determined by the cumulative exposure of breast tissue to estrogen. Indirect evidence of this sequence includes the increased risk of breast cancer associated with early menarche, late first full-term pregnancy, and late menopause as well as the reduced risk associated with early menopause (Table 1). The predictive value of these factors in assessing the risk of breast cancer is increased by combining them. For example, the combination of current age, age at first delivery of a child, and time since childbirth provides a more accurate assessment of risk than each factor provides independently. This may be because the age at first delivery reflects not only the total exposure to estrogen but also the effect of estrogen on terminal-duct epithelium that has not undergone the final differentiation induced by pregnancy and lactation.

Other factors may contribute to individual variation in exposure to estrogen. Obese postmenopausal women have lower serum concentrations of sex hormone–binding globulin and therefore higher serum concentrations of bioavailable estrogen than do thin postmenopausal women, and in postmenopausal women there is a positive correlation between weight and the risk of breast cancer. However, obese premenopausal women are likely to have longer menstrual cycles and more anovulatory cycles than nonobese premenopausal women, resulting in less total exposure to estrogen and a reduced risk of breast cancer.

Differences in exercise and dietary intake of certain nutrients may also influence exposure to estrogen. Studies of the relation between the risk of breast cancer and intakes of alcohol, fat, antioxidant vitamins, and fiber have had conflicting results. Plants contain phytoestrogens, which are structurally similar to physiologic estrogens. Soybeans are an abundant source of phytoestrogens, and when ingested in relatively large amounts, they have both estrogen agonist and antagonist effects in humans and animals. Flaxseed is a rich dietary source of both mammalian lignans and α-linoleic acid, which exert antiestrogenic effects by both binding to the estrogen receptor and inhibiting the synthesis of estrogen. The incidence of breast cancer is lowest in regions where the intake of soy and flaxseed is high. However, it is uncertain whether this inverse association is a direct result of phytoestrogen or flaxseed intake or whether it is a marker of other factors related to risk.

The association between exogenous sex steroids and the risk of breast cancer has been studied extensively.
Estrogen-replacement therapy has been implicated in the risk of breast cancer in women receiving estrogen or estrogen–progestin therapy, the overall mortality among these women is reduced because there are fewer deaths related to cardiovascular disease or osteoporosis.

**ESTROGEN SYNTHESIS**

Because of the close relation between the risk of breast cancer and exposure to estrogen, it is important to examine the key variables in estrogen homeostasis (i.e., the synthesis and catabolism of estrogen and the sensitivity of tissue to estrogen) (Fig. 1).

In premenopausal women, the ovaries, which are under the cyclic control of pituitary gonadotropins, are the predominant source of serum estrogen, and only a small proportion of serum estrogen comes from peripheral organs (Fig. 2). In contrast, the little estrogen that is produced in postmenopausal women comes predominantly from aromatization of adrenal and ovarian androgens in extragonadal tissues such as the liver, muscle, and fat tissues.

The mechanisms controlling estrogen production in postmenopausal women are unclear. Both cytochrome CYP17 (encoding P-450 17α-hydroxylase) and cytochrome CYP19 (encoding P-450 aromatase) are involved in estrogen biosynthesis (Fig. 1), and polymorphisms of both genes have been identified in the general population. Women who are heterozygous or homozygous for a cytochrome CYP17 polymorphism have high serum estradiol concentrations.

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in three studies, the polymorphism was not associated with an increase in the risk of breast cancer. In a fourth study of carriers of the polymorphism, there was also no increase in the overall incidence of breast cancer, but the risk of presenting with advanced disease was higher for carriers than for noncarriers (relative risk, 2.5). Ongoing studies assessing polymorphisms of the P-450 aromatase gene indicate that genetic variations may be associated with an increased risk of breast cancer.

There are also variations in tissue-specific promoters of aromatase gene expression that result in variations in estrogen production. For example, synthesis of aromatase messenger RNA (mRNA) in normal breast tissue is stimulated by the promoter I.4. However, in breast cancers a change of promoter from PI.4 to PI.3, which are more active, can result in increased synthesis of aromatase mRNA. The mechanism of promoter “switching” is unclear, but it may involve transcription factors specific to breast-cancer cells. In situ aromatization in breast tumors results in increased estrogen in breast tissue, which may contribute to the growth of breast tumors in an autocrine or paracrine fashion. Suppression of tissue-specific inhibitors of the promoter may also result in increased synthesis of aromatase mRNA. Thus, the aromatase gene may act as an oncogene that initiates tumor formation in breast tissue.

**SENSITIVITY OF TISSUE TO ESTROGENS**

Estrogens diffuse passively through cell and nuclear membranes. In specific cells and tissues containing estrogens, the expression of specific genes is regulated by the presence of estrogens. This process involves the binding of estrogen receptors to estrogen-response elements in the promoters of target genes. Activation of these receptors results in the transcription of specific genes, leading to growth stimulation and cell proliferation.

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**Figure 1.** Pathways of Estrogen Synthesis and Catabolism and the Sensitivity of Tissue to Estrogens.

3β-HSD denotes 3β-hydroxysteroid dehydrogenase, 17β-HSD 17β-hydroxysteroid dehydrogenase, 17-KSR 17-ketosteroid reductase, DHEA dehydroepiandrosterone, P-450 cytochrome P-450, SCC side-chain−cleavage enzyme, CYP17 17β-hydroxylase, CYP21 21-hydroxylase, CYP11 11β-hydroxylase, E estrone, E2 estradiol, 2-OH-E1 2-hydroxyestrone, 2-OH-E2 2-hydroxyestradiol, 2-MeO-E1 2-methoxyestrone, 2-MeO-E2 2-methoxyestradiol, 2-OH-3-MeO-E1 2-hydroxyestrone 3-methyl ether, 2-OH-3-MeO-E2 2-hydroxyestradiol 3-methyl ether, 4-OH-E1 4-hydroxyestrone, 4-OH-E2 4-hydroxyestradiol, 4-OH-3-MeO-E1 4-hydroxyestrone 3-methyl ether, 4-OH-3-MeO-E2 4-hydroxyestradiol 3-methyl ether, 16α-OH-E1, 16α-OH-E2 16α-hydroxyestrone, 16α-OH-E1, 16α-hydroxyestradiol, and COMT catechol O-methyltransferase.
Estrogen receptors, estrogen then binds to the receptor, and this ligand–receptor complex binds to and activates specific sequences in the regulatory region of genes responsive to estrogen, known as estrogen-response elements. These genes in turn regulate cell growth and differentiation.

This model has several layers of complexity that may result in variations in the risk of breast cancer within and between individual women at different ages and before and after menopause. First, although estrogen-receptor levels are low in normal breast tissue, they vary from woman to woman, and high levels have been directly correlated with an increased risk of breast cancer. Receptor levels also increase with age in some ethnic groups and are usually higher in white women than in black or Japanese women. It has been postulated that the loss of a tumor-suppressor gene may result in failure to down-regulate estrogen receptors as cells enter the cell cycle or failure to suppress the division of cells expressing estrogen receptors and thus may be a mechanism of breast carcinogenesis.

Second, there are two types of estrogen receptors, α and β, and the α receptor has a higher affinity for estrogen than the β. In vitro, the α and β receptors form heterodimers with each other, and the β receptor decreases the sensitivity of the α form to estrogen, thereby acting as a physiologic regulator of the proliferative effects of the α receptor. The degree of variability in the expression of α and β receptors in normal breast tissue is unknown, but the relative expression of the α to expression of the β receptor is higher in invasive tumors than in normal breast tissue, suggesting that a balance between the receptors is important in determining the sensitivity of tissue to estrogen and thus the relative risk of breast carcinogenesis.

Variations in the sensitivity of tissue — specifically, breast tissue — to given levels of estrogen may account for differences in the risk of breast cancer. The differences may also explain, in part, the association of other clinical markers of estrogen exposure, such as bone density and breast density, with the risk of breast cancer.

CATABOLISM OF ESTROGENS

Estrogens are catabolized mainly by hydroxylation reactions that result in the formation of 2-hydroxyestrone and 2-hydroxyestradiol, 4-hydroxyestrone and 4-hydroxyestradiol, and 16α-hydroxyestrone and 16α-hydroxyestradiol (Fig. 1). Of these compounds, 4-hydroxyestrone and 16α-hydroxyestradiol are known to be estrogenic and are thought to be carcinogenic. The 2-hydroxy and 4-hydroxy metabolites are con-
verted to anticarcinogenic methoxylated metabolites (2-methoxystroestrone and 2-methoxystrodiol, 2-hydroxyestrone and 2-hydroxyestriadiol 3-methyl ether, 4-methoxystroestrone and 4-methoxystrodiol, and 4-hydroxyestrone and 4-hydroxyestriadiol 3-methyl ether) by catechol O-methyltransferase. 2-Hydroxylation and 16α-hydroxylation therefore control the proportions of carcinogenic and anticarcinogenic metabolites formed. Thus, women who metabolize a larger proportion of endogenous estrogen through the 16α-hydroxylation pathway may have a higher risk of breast cancer than women who metabolize more estrogen through the 2-hydroxylation pathway.65-67

Two examples of alterations in the 2-hydroxylation pathway can be considered. First, 2-hydroxylation of estradiol is increased in women who smoke cigarettes,68 which may in part explain why they have a lower risk of uterine cancer and a higher risk of osteoporosis than women who do not smoke.69 These markers of reduced estrogen suggest that the risk of breast cancer should be lower in women who smoke. Although some studies have shown that the risk is lower in certain subgroups of female smokers,70 other studies have shown the opposite, and the carcinogenic effects of aromatic hydrocarbons have been implicated.71 A second example of the influence of 2-hydroxylation on cumulative exposure to estrogen is the observation that women with a polymorphism in the CYP1A1 gene (coding cytochrome P-450 1A1) have low basal levels of 2-hydroxylation of estrogen (and high levels of endogenous estrogens), but these findings have not been consistently linked to an elevated risk of breast cancer.72

Postmenopausal women with a variant allele that codes for a catechol O-methyltransferase with low activity have a higher risk of breast cancer than women with the wild-type allele (odds ratio, 2.2).73 This may be a consequence of decreased formation of 2-methoxyestrone and 2-methoxyestriadiol and of 2-hydroxyestrone and 2-hydroxyestriadiol 3-methyl ether, as well as retarded inactivation of catechol estrogen intermediates, particularly 4-hydroxyestrone, which is hormonally active.

Another group of enzymes that are important in estrogen catabolism are the 17β-hydroxyoestroid dehydrogenases, which catalyze the conversion of estrone to estradiol. 17β-Hydroxyoestroid dehydrogenase activity is higher in breast tumors than in normal breast tissue,74 and production of the more active estradiol therefore may be increased, providing cancer cells with an estrogenic environment favorable to growth.

In summary, several tissue-specific variations in estrogen production and catabolism cause differences in the cumulative exposure to estrogen and its metabolites, both between and within individual women. In one study, polymorphisms of cytochrome CYP17, cytochrome CYP1A1, and catechol O-methyltransferase were found to be associated with an increased risk of breast cancer.75 The catechol O-methyltransferase polymorphism was associated with the highest risk (increased by a factor of four). Furthermore, there was a trend toward an increased risk of breast cancer among women who had high-risk genotypes. The risk was even higher among women with prolonged exposure to estrogen, higher serum estrogen concentrations, and a higher body-mass index, supporting the notion that breast cancer can be initiated by exposure to estrogen.76

**CLINICAL MARKERS OF EXPOSURE TO ESTROGEN AND THE RISK OF BREAST CANCER**

**Serum Estrogen Concentrations**

Studies of the relation between serum estrogen concentrations and the risk of breast cancer in premenopausal women have had conflicting results, most likely because the measurements were made at various times during the menstrual cycle. However, in some epidemiologic studies, low serum estrogen concentrations were associated with a low risk of breast cancer, and conversely, high concentrations were associated with a high risk.76

There has been controversy about whether serum estrogen concentrations are associated with the risk of breast cancer in postmenopausal women, perhaps owing to the difficulty of measuring the very low serum estrogen concentrations in these women.77,78 However, in several large studies, postmenopausal women in whom breast cancer subsequently developed had higher serum concentrations of free estradiol than women in whom breast cancer did not develop.16,79 In the Study of Osteoporotic Fractures, serum samples were obtained from 9704 women and stored between 1986 and 1988. Subsequently, serum estradiol concentrations were measured in these samples from 97 women with newly diagnosed cases of breast cancer and from 244 randomly selected control women; the cases of breast cancer were confirmed by a review of the medical records during an average of 3.2 years. The relative risk of breast cancer was 3.6 (95 percent confidence interval, 1.3 to 10.0) for women with serum estradiol concentrations in the highest quartile, as compared with those in the lowest quartile.79 In a prospective, case-control study of 60 women with newly diagnosed cases of breast cancer and 178 controls, the risk of breast cancer increased as the baseline serum estradiol concentration increased.17 Breast cancer was approximately five times as likely to develop in the women with estradiol values in the top third of the group as in those with values in the bottom third (Fig. 3).

These data support the hypothesis that higher serum estrogen concentrations are associated with a higher risk of breast cancer in postmenopausal women. The effects of estradiol on both normal and ma-
lignant breast tissue suggest that this association may be causal.6,77 Other hormones such as testosterone and several growth factors are known to interact with breast tissue; however, they appear to be less directly implicated in the risk of breast cancer and may exert their influence through estrogen.6,16,78,79

Breast Density

The radiologic appearance of the breast varies depending on the relative amounts of fat, connective tissue, and epithelial tissue. Breast tissue ranges from tissue made up entirely of fat to tissue occupied by diffuse or nodular densities (Fig. 4).80 These variations in the density of breast tissue on mammography are referred to as the parenchymal pattern of the breast. Parenchymal density has been shown histologically to be inversely correlated with fat content and directly correlated with fibrous- and epithelial-tissue content.81 Breast density decreases with increasing age, postmenopausal status, increasing number of births, and declining body weight, suggesting that the tissue changes responsible for breast density are under hormonal control.82,83 Furthermore, women who have dense breasts on mammography have higher serum estrogen concentrations than women with less dense

![Figure 3](image)

**Figure 3.** Relative Risk of Breast Cancer in 238 Postmenopausal Women, According to the Serum Estradiol Concentration. The group of women was divided into thirds according to estradiol concentrations; median concentrations are shown in parentheses. There was a trend toward a significant association between the serum estradiol concentration and the relative risk of breast cancer (P for trend, <0.01). To convert the values for estradiol to picomoles per liter, multiply by 3.671. Data are from Thomas et al.87

![Figure 4](image)

**Figure 4.** Mammograms Showing a Normal Breast in One Woman (Panel A) and a Breast with Extensive Areas of Radiographically Dense Tissue in Another Woman (Panel B). Figure provided courtesy of Dr. K. Bukhanov.
Breast density has been associated with the risk of breast cancer. With the use of the medical records of 45,000 women assigned to mammography in the Canadian National Breast Cancer Screening Study, a case–control study of 345 cases with newly diagnosed cases of breast cancer and 354 controls was performed. The relative risk of breast cancer for the women in the highest category of breast density, as compared with those in the lowest category, was 6.0 (95 percent confidence interval, 2.8 to 12.9). In several studies of women with family histories of breast cancer, increased breast density on mammography was more common than expected, suggesting that it may be genetically determined, at least in part, but this association has not been confirmed by other studies.

Treatment with tamoxifen is associated with a reduction in breast density in both premenopausal and postmenopausal women, as are a low-fat, high-carbohydrate diet and the administration of gonadotropin-releasing hormone, which inhibits ovarian secretion of estrogen. However, the reduction in breast density in association with these factors has not yet been correlated with a reduction in the risk of breast cancer. If such a correlation is demonstrated, breast density on mammography could become useful for evaluating antiestrogenic and other chemopreventive therapies.

**Bone Density**

Bone contains estrogen receptors and is sensitive to estrogen. Bone mineral density declines and the risk of osteoporotic fracture increases after menopause. Bone mineral density is positively correlated with early menarche, late menopause, and high parity, whereas prolonged amenorrhea in premenopausal women, early natural menopause, and oophorectomy are associated with increased rates of bone loss.

Estrogens inhibit bone resorption and also increase the production of other hormones that promote bone density, including 1,25-dihydroxyvitamin D, growth hormone, and insulin-like growth factor 1.

There is a direct relation between serum estrogen concentrations measured at a single point in time and the risk of breast cancer, as noted above, but there are no data on the relation between the risk of breast cancer and serum estrogen concentrations over time. Since estrogen is an important determinant of bone mineral density, it may serve as a marker of cumulative exposure to estrogen. If so, conditions of estrogen deficiency, such as early menopause, a low body-mass index after menopause, and osteoporosis, should provide at least partial protection against breast cancer. Indeed, in two studies postmenopausal women with low bone mineral density and a history of osteoporotic fracture had a relatively low risk of breast cancer. Conversely, postmenopausal women with higher bone mineral density had a higher risk of breast cancer — the risk was 2.0 to 2.5 times as high for women with bone mineral density in the highest quartile as for those with bone mineral density in the lowest quartile. Among 1373 women in the Framingham Study, the incidence of breast cancer was 3.5 times as high for women with bone density in the highest quartile as for those with bone density in the lowest quartile (Fig. 5). Both these studies indicate that high bone density is a marker for postmenopausal exposure to estrogen (and perhaps for longer cumulative exposure) and is directly related to the risk of breast cancer.

Women with a family history of breast cancer may have a higher risk of breast cancer at a given level of bone density than women with no family history of the disease. If bone mineral density is a biologic marker of cumulative exposure to estrogen, then an interaction between family history and bone mineral density suggests that similar exposure to estrogens at the tissue level is associated with different risks, depending on the presence or absence of a family history of breast cancer. In other words, a particular subgroup of women, those with a positive family history, may be particularly sensitive to exposure to estrogen, as reflected by measurements of bone mineral density. A possible mechanism for this effect may be through estrogen and the BRCA1 gene. Wild-type BRCA1 can suppress estrogen-dependent transcriptional pathways related to the proliferation of epithelial cells in the breast, and mutation of BRCA1 can result in the loss of this ability, contributing to tumorigenesis. In addition, BRCA1 transcription can be induced through the mitogenic activity of estradiol in cells expressing estrogen receptors.

It is possible that the association between bone mineral density and breast cancer involves other hormones in addition to estrogen. For example, serum insulin concentrations are directly related to bone mineral density and may also be related to the risk of breast cancer, possibly through the interaction of insulin with the receptor for insulin-like growth factor 1. Insulin-like growth factors stimulate cell division in bone and are potent mitogens in breast-cancer tissue in vitro. The relation between bone mass and breast cancer may also involve endogenous androgens, which are determinants of bone mass and which have also been associated with the risk of breast cancer.

**CONCLUSIONS**

Genetic and environmental factors influence estrogen homeostasis and tissue-specific exposure to estrogen and its metabolites. The relative influence of the fluctuating serum estrogen concentrations associated with the menstrual cycle in premenopausal women and the more stable concentrations in postmenopausal women on the cumulative lifetime exposure to es-
estrogen is uncertain. Taken together, the body of data supports the hypothesis that estrogen and its metabolites are related to both the initiation and the promotion of breast cancer but that these associations are complex.

Further evidence of the association between estrogen and the risk of breast cancer comes from the recent results of large clinical trials of selective estrogen-receptor modulators. The antiestrogenic effect of tamoxifen resulted in a reduction in the risk of breast cancer in healthy premenopausal and postmenopausal women at increased risk for the disease, and raloxifene reduced the risk of breast cancer in postmenopausal women with osteoporosis.

Although a relation between exposure to estrogen and the risk of breast cancer has been identified in specific groups of women, we cannot accurately predict the risk in an individual woman. Clinical markers of exposure to estrogen, such as serum estrogen concentrations, breast density on mammography, and bone mineral density, may prove to be useful tools for assessing a woman’s risk of breast cancer. Composite determinations of risk based on these as well as other risk factors, such as family and reproductive histories, may lead not only to a more accurate assessment of risk in individual women but also to a better understanding of the role of estrogen in the pathogenesis of breast cancer.

REFERENCES

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CORRECTION

Estrogen and the Risk of Breast Cancer

Estrogen and the Risk of Breast Cancer. On page 276, the sentence that begins 11 lines from the bottom of the right-hand column should have read, “Flaxseed is a rich dietary source of both mammalian lignans and α-linolenic acid, which exert antiestrogenic effects by both binding to the estrogen receptor and inhibiting the synthesis of estrogen.” On page 278, Figure 1 and its legend contained errors. The corrected figure is reprinted with its legend below. On page 279, the last sentence in the right-hand column should have read, “The 2-hydroxy metabolites are converted to anticarcinogenic methoxyalted metabolites (2-methoxyestrone and 2-methoxyestradiol, 2-hydroxyestrone and 2-hydroxyestradiol 3-methyl ether) by catechol O-methyltransferase.”

Figure 1. Pathways of Estrogen Synthesis and Catabolism and the Sensitivity of Tissue to Estrogens.

3β-HSD denotes 3β-hydroxysteroid dehydrogenase, 17β-HSD 17β-hydroxysteroid dehydrogenase, DHEA dehydroepiandrosterone, P-450 cytochrome P-450, scc side-chain–cleavage enzyme, CYP17 17β-hydroxylase, CYP21 21-hydroxylase, CYP11 11β-hydroxylase, CYP19 P-450 aromatase, E1 estrone, E2 estradiol, 2-OH-E1 2-hydroxyestrone, 2-OH-E2 2-hydroxyestradiol, 2-MeO-E1 2-methoxyestrone, 2-MeO-E2 2-methoxyestradiol, 2-OH-3-MeO-E1 2-hydroxysterone 3-methyl ether, 2-OH-3-MeO-E2 2-hydroxyestradiol 3-methyl ether, 4-OH-E1 4-hydroxyestrone, 4-OH-E2 4-hydroxyestradiol, 4-OH-3-MeO-E1 4-hydroxyestrone 3-methyl ether, 4-OH-3-MeO-E2 4-hydroxyestradiol 3-methyl ether, 16α-OH-E1 16α-hydroxyestrone, 16α-OH-E2 16α-hydroxyestradiol, CYP1A1 cytochrome P-450 1A1, CYP1B1 cytochrome P-450 1B1, and COMT catechol O-methyltransferase.