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Authors
Feigelson, Heather Spencer
Henderson, Brian E.

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COMMENTARY

Estrogens and breast cancer

Heather Spencer Feigelson[1] and Brian E.Henderson

Department of Preventive Medicine, University of Southern California/ Norris Comprehensive Cancer Center, 1441 Eastlake Avenue MS no. 44, PO Box 33800, Los Angeles, CA 90033-0800, USA

[1]To whom correspondence should be addressed

The past 20 years of research have identified several risk factors and protective factors for breast cancer. All of these factors can be understood as measures of the cumulative exposure of the breast to estrogen and, perhaps, progesterone. These ovarian hormones affect the rate of cell division and thus manifest their effect on the risk of breast cancer by causing proliferation of breast epithelial cells (1). Proliferating cells are susceptible to genetic errors during DNA replication which, if uncorrected, can ultimately lead to a malignant phenotype.

In the following sections, this paper provides a brief overview of the primary risk factors for breast cancer, and reviews the evidence for the role of endogenous estrogens and the two most common sources of exogenous estrogens: combined oral contraceptives (COCs*) and hormone replacement therapy (HRT). Finally, the role of genetic susceptibility to breast cancer and the possible interaction between genetic polymorphism and estrogen exposure is presented.

Breast cancer risk factors

The known risk factors and protective factors for breast cancer are shown in Table I. Early menarche and late menopause maximize the number of ovulatory cycles and, therefore, the cumulative estrogen 'dose' to the breast epithelium. In general, about a 20% decrease in breast cancer risk results from each year menarche is delayed, and women who experience natural menopause before age 45 are estimated to have only half the breast cancer risk of those whose menopause occurs after age 55 (2).

The primary source of estrogens in post-menopausal women is from the conversion of androstenedione to estrone in adipose tissue; thus, post-menopausal obesity increases risk of breast cancer through increased production of estrogens. Obesity is also associated with decreased sex hormone-binding globulin (SHBG) production, and increased proportions of free- and albumin-bound estradiol which are understood to be the biologically active estrogens (3). Alcohol appears to increase plasma estrogen levels. Alcohol consumption may confer a small increased risk for breast cancer; however, results across studies have been inconsistent. As summarized in a meta-analysis by Howe *et al.* (4), women who consume three or more alcoholic drinks per day have about 50–70% increase in breast cancer risk compared to non-drinkers. For lower levels of consumption, the risks are correspondingly lower and confidence intervals generally include 1.0.

The protective effect of early age at first birth is complex. During the first trimester of pregnancy, the level of free estradiol rises rapidly. However, as the pregnancy continues, prolactin and free estradiol levels lower, while SHBG levels rise, giving a net overall benefit with respect to the endogenous estrogen profile which permanently reduces breast cancer risk (3). Prolonged lactation and, more importantly, physical activity can reduce the number of ovulatory cycles. Bernstein *et al.* (5) found that the risk of breast cancer among women who exercised 4 or more hours per week during their reproductive years was nearly 60% lower than that of inactive women.

Endogenous estrogens

Animal studies have repeatedly demonstrated that estrogens can induce and promote mammary tumors in rodents and that removing the ovaries or administering an antiestrogenic drug has the opposite effect (6). Epidemiological evidence of the role of endogenous estrogens in breast cancer etiology has come from numerous studies of serum and urine hormone levels in populations at low and high risk, and in case-control and cohort studies comparing serum hormone levels in breast cancer cases and healthy women. Key and Pike (7) summarized the results of early studies and concluded that post-menopausal breast cancer cases are exposed to more endogenous estrogen than controls. While early cohort studies failed to find an association between serum hormone levels and breast cancer (8,9), recent cohort studies have shown strong relationships between endogenous hormone levels and breast cancer risk (10,11).

Several studies have evaluated serum and urine estrogen levels in populations at low and high risk. Shimizu *et al.* (12) reported higher levels of serum estrone and estradiol in post-menopausal white women in the USA, compared to post-menopausal women living in rural Japan. Bernstein *et al.* (13) found higher serum estradiol levels in premenopausal cases compared to controls in two concurrent studies in Shanghai and the USA after carefully controlling for day of menstrual cycle. Furthermore, they showed that US controls had higher estradiol concentrations than their Shanghai counterparts. Higher levels of estrone and estradiol were also found in post-menopausal cases of breast cancer compared to controls in Los Angeles (14).

In a recent population-based case-control study which included 122 pairs of postmenopausal women, Lipworth *et al.* (15) found a positive association with serum estrone [odds ratio (OR) = 1.20, 95% confidence interval (CI): 0.93–1.55], androstenedione (OR = 1.32, 95% CI: 1.05–1.65), and inverse association with SHBG (OR = 0.71, 95% CI: 0.48–1.04) after

*Abbreviations: COCs, combined oral contraceptives; HRT, hormone replacement therapy; SHBG, sex hormone-binding globulin; BMI, body mass index; RR, relative risk; DHEAS, dehydroepiandrosterone sulfate; CEE, conjugated equine estrogens; ERT, estrogen replacement therapy; OR, odds ratio; CI, confidence interval; ER, estrogen receptor; IGF-1, insulin-like growth factor 1; E1, estrone; E2, estradiol; CYP17, cytochrome P450c17d; EDH17B2, 17β-hydroxy steroid dehydrogenase 2; 17HSD1, 17β-hydroxy steroid dehydrogenase type 1.

Table I. Risk factors and protective factors for breast cancer

Risk factors (increased exposure to estrogen and progesterone)
Early menarche
Late menopause
Post-menopausal obesity
Hormone replacement therapy
Alcohol consumption
Protective factors (decreased exposure to estrogen and progesterone)
Early first full-term pregnancy
Lactation
Physical activity

mutual adjustment for hormonal variables and body mass index (BMI). Although neither of the adjusted associations of estrone or androstenedione are large, some of the effect of estrone would be underestimated when androstenedione is included in the model, since androtenedione is a precursor of estrone. (The OR for estrone adjusted only for matching factors and BMI was 1.35, 95% CI: 1.07–1.70.) Furthermore, the authors found some evidence of statistical interaction between BMI and SHBG. The OR for women with high SHBG and high BMI was 0.14, 95% CI: 0.04–0.53 after adjusting for the other hormonal variables compared to women with low BMI and SHBG. As the authors discuss, one explanation for this finding may be that reduced levels of SHBG imply higher estrogen bioavailability. Alternatively, low SHBG may reflect higher circulating levels of insulin or insulin-like growth factor 1 (IGF-1) which are powerful negative regulators of SHBG synthesis *in vitro* (15). One potential source of bias in this study is the possibility that the recent surgery among cases altered the serum steroid hormone levels. However, serum samples were all drawn at least 1 week post-operatively which should be sufficient time for steroid levels to normalize. Such bias can be eliminated by using a prospective study design.

Toniolo *et al.* (10) found that free estradiol, albumin-bound estradiol and estrone were all associated with increased risk of breast cancer after adjusting for BMI among 130 cases and 251 controls in a prospective study. Comparing the highest quartile to the lowest quartile, the adjusted OR for free (i.e. unbound) estradiol was 2.9 (95% CI: 1.3–6.6), the adjusted OR for albumin-bound estradiol was 3.3 (95% CI: 1.4–7.4), the adjusted OR for estrone was 2.5 (95% CI: 0.8–7.8) and the adjusted OR for estrone comparing the third to the lowest quartile was 3.7 (95% CI: 1.4–10.2). Levels of total estradiol and SHBG-bound estradiol were also elevated among cases, but did not reach statistical significance.

Among 24 post-menopausal breast cancer cases and 88 matched control subjects from a prospective study, Berrino *et al.* (11) found higher serum levels of total estradiol, dehydroepiandrosterone sulfate (DHEAS), total testosterone and free testosterone, and lower levels of SHBG among cases compared to controls. The age-adjusted relative risk (RR) of breast cancer comparing the highest serum tertile to the lowest tertile was 5.5 (95% CI: 1.5–22.2) for total estradiol, 7.0 (95% CI: 1.4–36.4) for total testosterone, 5.7 (95% CI: 1.5–22.2) for free testosterone, 2.6 (95% CI: 0.6–11.1) for DHEAS and 0.3 (95% CI: 0.1–1.3) for SHBG. Although the authors carefully matched the cases and controls on time of enrollment (to control for age of the stored sera), daylight saving period (to control for possible circadian rhythm) and storage location of frozen sera (top, middle or bottom of freezer), the results of this study must be viewed with caution. These results may be biased because the authors failed to adjust for body mass in the analysis. It also would have been interesting to see the results of a model that adjusted for all the hormone levels simultaneously in addition to age and body mass.

Finally, Hankinson *et al.* (16) conducted a cross-sectional study to examine possible associations between known risk factors for breast cancer and plasma hormone levels in 216 healthy post-menopausal women. After controlling for age, BMI and alcohol use, they observed inverse correlations between estrone sulfate and parity ($r = -0.15$, $P = 0.03$) and between percentage bioavailable estradiol and age at first birth ($r = -0.17$, $P = 0.02$). No statistically significant associations were seen between serum hormone levels and either family history or age at menarche. These results must be viewed with caution due to the number of comparisons made. The authors evaluated eight plasma hormones against four known risk factors, so one may expect one or two statistically significant correlations by chance alone.

Taken together, the results of these studies support the theory that endogenous estrogens play a crucial role in breast carcinogenesis. This is in spite of the well known problems that arise when attempting to accurately measure steroid hormones. Serum hormone measurements are subject to variation by many factors, for example time of day, age, disease status and laboratory imprecision. As discussed later, underlying genetic differences in hormone metabolism among individuals may also introduce unmeasured confounding that may distort the results of studies of serum hormone levels.

Oral contraceptives

Combination oral contraceptives (COCs) have been widely used since the early 1960s. By 1978, the World Health Organization estimated that more than 80 million women had been exposed to these drugs worldwide. A substantial body of literature now exists on the relation between COC use and risk of breast cancer (17); however, the conclusions are mixed and the issue remains controversial. The picture that seems to be emerging is that COC use increases the risk of breast cancer in young women and that this risk increases slightly with increasing duration of use. Whether early age at first use, use before first full-term pregnancy, frequency of use, family history of breast cancer or other risk factors modify this risk is uncertain.

As summarized by Pike *et al.* (18), three of six studies that have investigated the association of breast cancer risk and COC use in women over age 45 years at diagnosis show a positive association, but none was statistically significant. The five studies that included information on duration of use were statistically consistent with each other and, overall, showed no increase in breast cancer risk. What cannot be easily discerned from these studies is the effect on breast cancer risk from COC use during the perimenopausal years. One can argue that COC use during the perimenopausal period may increase breast cancer risk if COCs provide greater hormonal exposure to estrogens and progestogens than would occur naturally at this time, thereby masking the onset of menopause by producing a hormonal status approximating that of normal ovulation.

Pike *et al.* (18) also summarized the population-based studies of COC use and breast cancer among women under 45 years of age that had been published through 1990 and derived a weighted average for the RR for 10 years of COC use. This

Table II. Summary of recent studies of oral contraceptive use and breast cancer

Authors/year	Type of study	Location	Age range (years)	Cases/controls	Age group Duration use	RR or OR (95% confidence interval)
Brinton *et al.* (1995)	Population-based case-control	USA	20–54	1648/1505	20–35 years old	
					10 years of use	2.25 (1.2–4.1)
					20–45 years old	
					10 years of use	1.29 (1.0–1.6)
La Vecchia *et al.* (1995)	Hospital-based case-control	Italy	20–64	1991/1899	All ages	
					8 years of use	1.20 (0.7–1.9)
Primic-Zakelj *et al.* (1995)	Population-based case-control	Slovenia	25–54	624/624	All ages	
					8 years of use	1.16 (0.8–1.7)
Rosenberg *et al.* (1996)	Hospital-based case-control	USA	25–59	3540/4488	25–34 years old	
					10 years of use	2.50 (1.4–4.8)
					25–59 years old	
					10 years of use	0.90 (0.7–1.1)

RR estimate was 1.36, which is equivalent to a 3.1% (95% CI: 1.7–4.6) increase in breast cancer risk per year of COC use. The weighted RR for young women who took COCs for 10 years before their first full-term pregnancy was 1.45 compared to women who never took COCs.

A 1993 review by Malone *et al.* (17) provided a comprehensive overview of the literature on COCs since 1990. The authors concluded that, overall, there was no apparent relation between ever use of COCs and breast cancer risk, but that ever use is probably too crude a measure of exposure to be accurate. The most consistent positive associations they observed were from studies of women under age 45. Possible associations with duration of use before first full-term pregnancy, use before age 25 or overall long duration of use, while not consistent across all studies, was suggestive of an increased risk for breast cancer in younger women.

Five studies have recently been published evaluating COC use and breast cancer risk (19–23). The results of these studies are summarized in Table II. Two of these studies (21,22) are population-based, while the remaining three are hospital-based studies (19,20,23). One hospital-based case-control study (19) is not included in Table II because it did not provide information on the age range of study subjects, and only 4.4% of cases (36 women) and 4.1% of controls (63) reported ever using COCs. The authors (19) reported an OR = 0.47 (95% CI: 0.13–1.70) for women aged 45 years or younger who had used COCs for three or more years compared to never users, but this was based on very small numbers (three cases and 15 controls were 'exposed').

The two population-based studies give somewhat conflicting results. Primic-Zakelj *et al.* (22) evaluated breast cancer risk and COC use in Slovenian women aged 25–54 years. There was no association in ever-users of COCs. For women who had used COCs for 8 years or longer, the adjusted OR for breast cancer was 1.16 (95% CI: 0.76–1.73) compared to never users. There was no increase in risk with interval since first use, age at first use, use before first full-term pregnancy or time between menarche and age at first use. Increased risk was observed in current COC users or those who had stopped COC use within 6 months of diagnosis compared to never users (OR = 2.31, 95% CI: 1.19–4.49).

Brinton *et al.* (21) examined COC use and breast cancer risk among younger women residing in three geographic areas of the USA. The RR associated with use of COCs was significantly elevated among women younger than 35 years of age (RR = 1.7; 95% CI: 1.2–2.6). The risk was less marked among women aged 35–39 years (RR = 1.4; 95% CI: 1.0–1.8), while no significant elevation in women aged 40–45 years was observed. The RR for breast cancer for those whose COC use began early (before age 18 years) and continued long term (10 or more years of use) was even higher (RR = 3.1; 95% CI: 1.4–6.7). Like Primic-Zakelj *et al.* (22), risk was elevated among women with more recent use. The RRs observed for those who used COCs within 5 years of cancer diagnosis were higher than those who had not, with the effect most marked for those under 35 (RR = 2.0; 95% CI: 1.3–3.1). However, this did not emerge as a more important determinant of risk than duration of use.

Because COC use was very common among both cases (85%) and controls (82%) younger than 45 years of age in the Brinton *et al.* study (21), the referent group of 'non-users' actually was comprised of women who had either never used COCs or used them for less than 6 months. This is probably a better referent group than one defining never users as 1 month of COC use or less. Many women who experience side effects from COCs will try different formulations in an attempt to find a COC formula they can tolerate for a few months before turning to a different method of contraception. The common side-effects, such as nausea, breast tenderness and water retention, are believed to be due to the estrogen component. These women who cannot tolerate the COC side-effects probably have a different endogenous estrogen profile than women who take COCs with minimal or no side-effects and, therefore, should probably not be combined with longer term users. However, this may also make them non-comparable to true 'never users' who may or may not have experienced COC side-effects if they had been exposed. Thus, it may introduce bias to include them in either the 'exposed' or 'unexposed' group. Where possible, analyses should be conducted excluding these short-term users to see if the RR changes.

Hormone replacement therapy

The most commonly prescribed HRT for menopausal women in the United States includes conjugated equine estrogens (CEE), with a preferred dose of 0.625 mg/d for 25 days in a 28-day treatment cycle. This dose is lower than those commonly prescribed during the 1970s. When estrogen is the only

Table III. Summary of recent USA population-based studies of hormone replacement therapy and breast cancer

Authors/year	Design	Age range (years)	Cases/controls	Classification of HRT use	RR or OR (95% confidence interval)
Colditz *et al.* (1995)	Cohort	Post-menopausal	972/–	Ever use of HRT	1.41 (1.2–1.7)
				⩾10 years of use	1.46 (1.2–1.8)
Newcomb *et al.* (1995)	Case-control	Under age 75	3130/3698	Ever use of HRT	1.05 (0.9–1.2)
				⩾15 years of use	1.11 (0.9–1.4)
Stanford *et al.* (1995)	Case-control	50–64	537/492	Ever use of HRT	0.9 (0.7–1.3)
				⩾8 years of use	0.4 (0.2–1.0)

component of replacement therapy the term estrogen replacement therapy (ERT) is used. Progestogens, usually 10 mg/d of medroxyprogesterone acetate, are sometimes added during days 14–25. When progestins are added along with estrogen the combination is referred to as HRT.

Most early studies of the possible effects of ERT on risk of breast cancer were uncontrolled follow-up studies. Early case-control studies that reported findings on menopausal estrogens and breast cancer were often limited by small numbers, insufficient data on dose and duration of use, and definite possibility of bias. A new round of carefully conducted case-control studies using healthy population controls and results of larger cohort studies has been published. Overall, these studies found small to moderate increases in breast cancer risk after long-term use of estrogen replacement alone, although some variation exists across studies for ovarian status (intact versus removed) or antecedent surgical menopause.

Pike *et al.* (18) summarized the population-based epidemiological studies that had been published through 1990 and derived a weighted average of the RR of ERT use on breast cancer risk. Of the 10 studies included, nine showed a positive association and the results of five were statistically significant. Based on these studies, the average annual increase in breast cancer risk is 3.1% per year of ERT. For women with 10 years of ERT, the risk of breast cancer is 1.36 times that of women who have never used these preparations. The studies conducted in the USA allow the estimation of breast cancer risk associated with use of a standard CEE dose of 0.625 mg/d; based on these studies, the increase in breast cancer risk is estimated to be 2.2% per year of ERT use, which translates into breast cancer RRs of 1.1 after 5 years of use, 1.2 after 10 years of use and 1.4 after 15 years of use. In fact, this figure may be an under-estimation because some of these studies made inadequate adjustment for age at menopause. This would tend to produce estimates of breast cancer risk that are too low because the use of ERT is associated with early menopause, which is a protective factor for breast cancer.

Of six other recent meta-analyses published, four found a small increased risk associated with long-term use (24–27), while two found no increased risk (28,29). Those with positive findings had results of similar magnitude to Pike *et al.* (18). Subsequently, three large population-based studies conducted in the USA have been published and are summarized in Table III.

The Nurses' Health Study (30), a large cohort established in 1976, found an increased risk for breast cancer with ever use of ERT (RR = 1.32; 95% CI: 1.14–1.54), HRT (RR = 1.41; 95% CI: 1.15–1.74) and progestin only use (RR = 2.24; 95% CI: 1.26–3.98). When evaluating current compared to past use, no association was seen with past use, not even for long duration (10 or more years) of past use. Among current users, risk of invasive breast cancer was increased for all categories of duration with increasing duration associated with increased risk; however, only use of 5 years or more showed statistically significant increased risk: 5–9 years of use, RR = 1.46 (95% CI: 1.22–1.74); 10 or more years of use, RR = 1.46 (95% CI: 1.20–1.76). Women aged 60–64 years who had used hormones for 5 or more years were at greatest risk: RR = 1.71 (95% CI: 1.34–2.18). These results included all hormone users, the type of hormone(s) used are not specified in the analysis.

In a population-based case-control study by Newcomb *et al.* (31) that included 3130 cases and 3698 controls, ERT did not increase the risk of breast cancer. There was no association with ERT and breast cancer in ever, former or recent users of ERT, or in women who had used ERT for long duration, even 15 or more years. The authors found similar results for users of combination HRT. When all types of users (ERT and HRT) were considered together, there was a suggestion of a small increased risk of breast cancer associated with 15 or more years of use, although the estimate is statistically imprecise (RR = 1.11, 95% CI: 0.87–1.43).

Stanford *et al.* (32) found no association between ERT use and breast cancer in a population-based case-control study even when considering long-term users of 20 or more years. No association was seen between all types of HRT and breast cancer (RR = 0.9, 95% CI: 0.7–1.3 for ever users). If anything, women who used estrogen–progestin HRT for 8 or more years had a reduced risk of breast cancer (RR = 0.4, 95% CI: 0.2–1.0), although data on use over 8 years were sparse.

While these studies vary by design, they are all large, well-designed population-based studies. Unfortunately, they do not bring us any closer to resolving the concerns about the risk of breast cancer attributed to HRT. It does appear that the use of ERT increases the risk of breast cancer, although the magnitude of this effect is small (approximately 2.2% per year). Insufficient data exist on combined estrogen and progestin therapy (HRT) to draw meaningful conclusions about its possible association with breast cancer. However, Key and Pike (7) have asserted that HRT could be more carcinogenic than estrogen alone.

Numerous sources of bias must be considered when evaluating any study of menopausal hormone use and breast cancer risk. Perhaps the most important confounder is the interaction between onset of menopause and onset of hormone use. Timing of menopause (early age of onset versus later age of onset) is associated with risk of breast cancer. Replacement therapy typically begins at the onset of menopausal symptoms and,

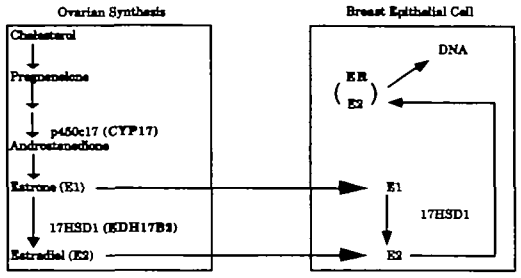

Fig. 1. Schematic presentation of estrogen metabolism in the ovaries and breast epithelium and three candidate genes which may play a role in breast cancer etiology. The genes of interest are the 17β-hydroxy steroid dehydrogenase 2 (*EDH17B2*) gene, the cytochrome P450c17α (*CYP17*) gene and the estrogen receptor (*ER*) gene.

therefore, masks the actual onset of menopause. Women who have early age at menopause have a reduced risk of breast cancer, but this may be confounded by replacement therapy at the onset of symptoms. Similarly, onset of menopause is masked in women who have a hysterectomy without bilateral oophorectomy. Furthermore, hysterectomized women may receive estrogen-only therapy, while all other women are much more likely to receive progestin also. This confounding may be impossible to account for accurately in observational studies.

Other important differences between women who are prescribed ERT or HRT compared to never users exist. Women with a family history of breast cancer are more likely to be never users, but are at increased risk of breast cancer, which may result in bias toward the null. Women who use HRT are more likely than never users to be better educated and of higher social class; they are also more likely to have regular physician visits and mammograms. Laya *et al.* (33) have provided direct evidence that current HRT use reduces the sensitivity and specificity of mammographic screening, most likely by increasing radiographic breast density. This differential misclassification could result in more breast cancer being missed on mammographic examination among HRT users, and thus an underestimation of the true risk of breast cancer associated with HRT use. Reductions in sensitivity and specificity with ERT or HRT use could decrease the effectiveness of screening and impact the physical, psychological and financial costs of mammography. All these factors must be considered when designing and subsequently analysing studies of ERT or HRT and breast cancer. Finally, an important source of confounding that has not been addressed in any study to date is the possible role of underlying genetic susceptibility to breast cancer which may be mediated by both endogenous and exogenous ovarian hormones.

Genetic susceptibility

Remarkable advances in molecular biology and careful study of cancer-prone families have recently led to the identification of two breast cancer susceptiblity genes, *BRCA1* and *BRCA2*. These genes may cause as much as 90% of breast and ovarian cancer in some families, but probably no more than 5–10% of all breast cancer in the USA is attributable to these two loci (34). Clearly, additional genes likely contribute to breast cancer risk. Much more common are multiple susceptiblity genes which have low absolute risk, but potentially higher population attributable risk. One such class of genes is that which codes for enzymes or receptors that control the metabolism and intracellular transport of estrogens.

We have used the paradigms that have been developed from studies of bladder cancer to propose a model for individual susceptibility to breast cancer (35). We have assumed that within and between ethnic groups there exist genetic differences that affect steroid hormone metabolism and transport. Markers (i.e. genetic polymorphisms) of these differences are likely to provide a more precise measure of risk than circulating levels of steroid hormones. The polygenic model that we have developed for breast cancer assumes that there are funtionally important polymorphisms in genes that encode enzymes involved in steroid hormone biosynthesis and metabolism that lead to differences in individual susceptiblity to breast cancer and may interact with exogenous hormone exposures.

Figure 1 shows the schematic presentation of estrogen metabolism in the ovaries and breast epithelium, and three candidate genes which may play a role in breast cancer etiology. The genes of interest are the 17β-hydroxy steroid dehydrogenase 2 (*EDH17B2*) gene, the cytochrome P450c17α (*CYP17*) gene and the estrogen receptor (*ER*) gene. The *EDH17B2* gene codes for the enzyme 17β-hydroxy steroid dehydrogenase type 1 (17HSD1) which catalyzes the final step of estradiol biosynthesis, namely the interconversion of estrone (E1) into the more biologically active estrogen fraction, estradiol (E2). 17HSD1 acts in the theca cells of the ovary and is expressed in both normal and malignant breast epithelium (36). CYP17 codes for the cytochrome P450c17α enzyme that mediates both steroid 17α-hydroxylase, and 17-20-lyase activities and functions at key branch points in human steroidogenesis (37). 17α-Hydroxylase activity converts steroids to precursors of the glucocorticoid cortisol, and 17-20-lyase activity yields precursors to estradiol and testosterone. The primary role of steroid receptors, like ER, is to regulate the rate of transcription of certain genes by binding as a hormone-receptor complex to specific sequences of DNA called hormone response element (HRE). Interaction between the receptor and HRE can result in either up- or down-regulation of transcription, depending upon binding and action of auxiliary factors specific to the target gene and the tissue. Polymorphisms in the *ER* gene may affect estrogen binding and subsequent transcription in target genes.

Perspectives

It is widely accepted that cancer causation is the result of the combined influence of genetic susceptibility and environmental exposures (including endogenous hormone exposure). To understand and ultimately prevent breast cancer, we must understand both the genetic and environmental components.

The primary risk factors for breast cancer can be understood as regulators of the lifetime endogenous estrogen exposure on breast epithelium. Exogenous estrogens, namely COCs and HRT, likely make modest contributions to breast cancer risk. However, these risks must be weighed against the well known benefits afforded by their use. Metabolic genes and their role in carcinogenesis is a relatively new area of research with scant information at present. Individual differences in estrogen metabolism attributed to genetic polymorphisms and mutations should help us define women who may be at greater risk of breast cancer for certain exposures, such as exogenous estrogens, compared to other women who may be relatively genetically 'insensitive' to the same exposure.

Explicit epidemiological studies of gene-cancer relationships need to be conducted to further our understanding of breast cancer etiology, control and, ultimately, prevention. Although these types of investigations are still in their infancy, it is time to begin to capitalize on the rapid advancement of molecular biology techniques and integrate them into epidemiological studies.

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