Published in final edited form as:
Best Pract Res Clin Endocrinol Metab. 2008 August ; 22(4): 573–585. doi:10.1016/j.beem.2008.08.001.

Exogenous and endogenous hormones and breast cancer

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Abstract

Exposure to higher levels of both exogenous and endogenous hormone is associated with breast cancer risk. Because of the association between breast cancer and HRT, only the minimal duration of HRT use is recommended for symptom control, and it is not recommended for chronic disease management. Current research issues include the role of progestins, other types of HRT, duration of unopposed estrogen use, and characteristics of cancers that develop on HRT. Circulating sex steroid levels are associated with breast cancer risk, but multiple issues need to be addressed before they are used routinely in clinical practice. Current research issues include measurement of levels for routine clinical practice, integration with standard breast cancer risk models and genetic polymorphism data, and applicability to estrogen-receptor-negative cancers.

Keywords

breast cancer; hormone replacement therapy; estrogen; sex steroids

For over 100 years – since Dr George Beatson described the regression of metastatic breast cancer after an oophorectomy[1] – it has been recognized that breast cancer is strongly influenced by hormonal factors. In the 1960s and 1970s, reproductive risk factors such as ages at menarche, first birth, and menopause, and parity were also found to be associated with breast cancer risk and were synthesized by Dr Malcolm Pike into an age–incidence model for breast cancer.[2] Later, it became recognized that other breast cancer risk factors such as postmenopausal obesity/weight gain and alcohol consumption also operate through a hormonal mechanism. Finally, the role of exogenous hormones in the form of hormone replacement therapy (HRT) on breast cancer incidence is now being appreciated.[3] This chapter will review the influence of both endogenous and exogenous hormones on breast cancer risk.

HORMONE REPLACEMENT THERAPY AND BREAST CANCER

Until the results from the randomized Women's Health Initiative (WHI) trial in the United States were released in 2002, HRT was widely used by postmenopausal women for a variety of reasons, including menopausal symptoms and prevention of chronic diseases such as cardiovascular disease and osteoporosis. After the publication of the WHI, and shortly thereafter the observational Million Women's Study from the United Kingdom,[4] multiple professional societies worldwide changed their HRT prescribing guidelines and recommended

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only short-term use, if at all. Consequently, HRT use in the United States[5] and Europe[6,7] decreased dramatically. However, many women feel frustrated regarding the lack of efficacy of non-hormonal alternatives, such as selective serotonin reuptake inhibitors (SSRIs) and gabapentin for control of menopausal symptoms, so it is important to quantify the magnitude of risk associated with HRT use. When reviewing the literature, it is also crucial to separate the studies evaluating combination estrogen and progesterone therapy and unopposed estrogen, and also to consider the types of progesterone and estrogen utilized since they can vary substantially in terms of their potency and composition.

Main results of the randomized clinical trial: Women's Health Initiative

The largest randomized placebo-controlled trial evaluating the overall health effects of HRT was the WHI. This was a large, multicenter trial conducted in the United States that randomized 16,608 postmenopausal women with a uterus to either placebo or the combination of 0.625 mg conjugated equine estrogen and 2.5 mg medroxyprogesterone acetate daily (E+P)[8] and 10,739 postmenopausal women without a uterus to either 0.625 mg daily of conjugated equine estrogens (E alone) or placebo.[9] After a mean follow-up of only 5.2 years, the study was unblinded for the E+P arm alone when event rates for breast cancer and a global index for 'overall harm' exceeded predetermined stopping rules.[8] With a mean follow-up of 5.6 years, there was a 24% increase in the risk of invasive breast cancer with E+P compared to placebo (95% CI 1.10–1.54, $P = 0.003$), with the risk becoming apparent in the third year of use among women who had previously used HRT and by the fourth year of use among women who had never used HRT. It was also noted that use of E+P was associated with a higher risk of an abnormal mammogram[10] and increased breast density[11] even after only 1 year of use. In contrast, there was no increased breast cancer risk in the E alone arm compared to placebo, even after an average of 7.1 years of follow-up. In fact, there was a non-significant decrease in breast cancer risk (RR 0.80; 95% CI 0.62–1.04, $P = 0.09$). However, similarly to E+P, there was an increased risk of an abnormal mammogram for women using E alone.[12] Data on mammographic density for the E-alone arm has not been published to date. On the basis of the WHI data and multiple observational studies,[4,13] most professional societies do not recommend HRT for chronic disease prevention, and recommend minimizing exposure when HRT is used for treatment of menopausal symptoms.[14,15]

Use of HRT in breast cancer survivors

Many breast cancer survivors develop menopausal systems, whether as a consequence of treatment-induced menopause or side-effects of treatment. SSRIs and other non-hormonal interventions may provide some relief, but are still inferior to HRT for treatment of menopausal symptoms. Two small prospective studies – which were closed early due to slow accrual and concerns regarding HRT use in the breast cancer population – did not observe an increased recurrence risk with HRT, but were clearly underpowered.[16,17] However, the HABITS trial from Stockholm, beginning in 1997, enrolled 447 breast cancer survivors and assigned them to either hormone therapy (health-care provider's choice) or none, and was terminated in December 2003 when the event rate in the HRT exceeded predetermine stopping rules. However, follow-up was continued, and at 4 years median follow-up and 56 events, the HRT group was found to have over twice the risk of breast cancer recurrence compared to controls, with absolute differences in event rates at 2 and 4 years of 5.7% (95% CI 3.5–7.9) and 14.2% (95% CI 10.9–17.5%) respectively.[18] Results were similar regardless of estrogen receptor (ER) status of the tumor and tamoxifen use, but power was limited for the subgroup analyses. Therefore, among breast cancer survivors, regardless of the ER status of the tumor, even short-term HRT use would not be recommended.

Unanswered questions on exogenous estrogens and breast cancer

Effects of progestins—Before the release of the WHI results, many had assumed that the increased breast cancer risk seen in the observational studies of HRT were due to the effects of estrogens, and many of the earlier studies did not separately analyze the types of HRT regimens. However, with the results of the WHI, focus has shifted to progesterone. It is hypothesized that progesterone may increase cell division and thereby lead to the accumulation of DNA damage. For example, proliferative activity is noted to be highest during the luteal phase of the menstrual cycle, a time when endogenous progesterone levels are high. However, in-vivo and in-vitro studies have not always been consistent in their findings about whether exogenous progesterone increases proliferation in breast tissue.[19]

Longer duration of unopposed estrogen—Although the WHI did not see an association between unopposed estrogen alone and breast cancer risk with an average follow-up of 7.1 years, the effect of longer-term use of unopposed estrogen and breast cancer risk still needs to be considered. In both the combined analysis of 51 epidemiological studies led by the Oxford group and in the large observational Nurses' Health Study (NHS) cohort (which was included in the Oxford pooled analysis), no increase in breast cancer risk was seen with less than 5 years of unopposed estrogen. However, with more than 5 years of current estrogen-alone use, the Oxford group reported a pooled RR 1.34 (S.E. 0.09).[13] In the Nurses' Health Study, when we analyzed only women who had undergone a hysterectomy, similarly to the WHI, we did not observe an increased risk of breast cancer with shorter periods of use. However, with much longer durations of use we did observe an increased risk of breast cancer: RR 1.42 (95% CI 1.13–1.77) for 20+ years of use. When limited to ER^+/PR^+ cancers, we observed an increase in breast cancer after 15 years of current use of unopposed estrogen (RR 1.48; 95% CI 1.05–2.07).[20] Therefore, for durations of unopposed estrogen use similar to that in the WHI (i.e. <7 years), there does not appear to be an increased breast cancer risk. However, the impact for longer-term users is less clear.

Characteristics of breast cancer that develop on HRT—In the WHI, the women who took combination estrogen and progesterone (E+P) had a greater chance of being diagnosed with a node-positive or more advanced stage breast cancer than those on placebo.[10] This finding has not been consistently seen in the observational studies, and the clinical significance of these findings is not clear. Interestingly, there was no difference seen in the ER and PR (progesterone receptor) status of the tumors between the placebo and the E+P arms, contrary to what was seen in the observational studies and what physiologically would seem most logical. It is well known that medications that block the estrogen receptor, such as tamoxifen, or lower estrogen levels, such as the aromatase inhibitors, only affect the growth of hormone-receptor-positive cancers, but not hormone-receptor-negative ones. Therefore, it would seem reasonable to hypothesize that HRT would preferentially stimulate the growth of hormone-receptor-positive cancers, as was seen in multiple observational studies.[21] Part of the discrepancy may be that the WHI study had only a limited number of breast cancer cases with known ER status (182 on E+P and 127 on placebo). In addition, both ER and PR status was selectively more likely to be missing among the placebo group as compared to the E+P group, introducing a potential source of bias. Therefore, although no difference was seen in the distribution of tumors by hormone receptor status in the WHI, given the biological mechanism and the additional power of the observational studies to evaluate differences by receptor status, it is still likely that HRT is more strongly associated with hormone-receptor-positive cancers than negative ones.

Other forms of HRT—In the United Status the most common form of prescription HRT is conjugated equine estrogens given alone or with medroxyprogesterone acetate. However, in Europe, many other formulations of estrogens and progestagens are used, and their effects on

breast cancer have not been as well quantified. It should be noted that none of these studies were randomized, and many had only limited numbers of users of the other types of hormones.

Estrogen: The single largest prospective study conducted in Europe was the Million Women's Study (MWS) in the UK. This study did not observe any variation in risk between conjugated estrogens and ethinylestradiol or for the mode of delivery (oral/transdermal/implanted). In addition, it also reported an increased risk of breast cancer with tibolone, a progestin analog that is considered a selective estrogen enzyme modulator.[4] Another prospective study done in Denmark, in which the predominant estrogen used was estradiol rather than conjugated estrogens, also observed an increased risk with estrogen-only and combination E+P regimens and tibolone.[22] However, it should be noted that the risk of breast cancer observed with estrogen-only in both of the studies was higher than that seen in the WHI. Both ethinylestradiol and estradiol would be considered 'medium-potency' estrogens similar to conjugated estrogens. None of the large studies described above had sufficient power to evaluate doseS of conjugated equine estrogens <0.625 mg daily or lower-potency estrogens.

Progesterone: Interest has also focused on the type of progesterone. The WHI utilized medroxyprogesterone acetate, a synthetic progesterone. In contrast, the prospective French E3N cohort analyzed the association with natural progesterone and did not observe an increased breast cancer risk.[23] However, other large studies that evaluated more androgenic progestins, such as norethisterone and norgestrel, still observed an increased breast cancer risk when given in combination with estrogens.[4,22] In sum, further research needs to be done to determine whether differences in the cancer risk vary according to the type and properties of the progesterone used.

Testosterone: Only a few studies have evaluated the use of testosterone-based HRT, so power has been limited. In the largest prospective study of oral testosterone given alone or in combination with oral estrogen (n = 32) to date, we observed over a two-fold increase risk of breast cancer within the Nurses' Health Study compared to never users (multivariate RR 1.77 for current users; 95% CI 1.22–2.56).[24] An increased risk was also seen in a Danish study evaluating injectable estrogen and testosterone.[25] Finally, as described in the following section, higher endogenous testosterone levels have been associated with increased breast cancer risk in pre- and postmenopausal women. Therefore, although data are only preliminary, testosterone-based HRT should be used with caution in postmenopausal women.

SEX STEROIDS AND BREAST CANCER

Given the associations between breast cancer and HRT and other hormonal risk factors, the role of endogenous sex steroids and breast cancer risk would be an important avenue of investigation. Specifically, many of the reproductive risk factors that increase breast cancer risk (later age at menopause, earlier age at menarche, etc) imply that longer duration of estrogen exposure would increase breast cancer risk. Therefore, it would be reasonable to hypothesize that endogenous hormone levels may represent a final common pathway and function as a biomarker encapsulating a woman's hormonal exposure over her lifetime. However, the clinical utility of sex steroid assays has been limited by the fact that most clinical laboratories do not have assays sensitive enough to reliably quantify the low circulating levels of estradiol in postmenopausal women. In addition, premenopausal women represent an additional challenge since there is a large amount of intra- and inter-individual variation in circulating hormone levels according to the menstrual cycle. First, I will summarize studies evaluating surrogates for endogenous estrogen exposure, such as body mass index (BMI) and bone density, then focus on studies measuring actual levels.

Surrogates for lifetime estrogen exposure

Body mass index—Multiple studies have linked an increased risk of breast cancer with postmenopausal obesity and weight gain. For example, a pooled analysis of seven prospective cohort studies, mainly from North America, reported a multivariate RR of 1.27 (95% CI 1.03–1.55) for women with a BMI ≥33 kg/m^2 compared to those with a BMI<21 kg/m^2.[26] Similar results were seen in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.[27] Within the Nurses' Health Study (NHS), in addition to current BMI, weight change since age 18 was specifically evaluated, and a 45% increased risk (95% CI 27–66%) was seen among women who gained at least 25 kg since age 18.[28]

BMI is highly correlated with circulating estrogen levels, and is considered a surrogate for endogenous estrogen exposure. For example, in the Endogenous Hormones and Breast Cancer Collaborative Group (EHBCCG) pooled analysis of eight prospective studies, the mean estradiol level among women with BMI <22.5 kg/m^2 was 30.0 pmol/L compared to 54.9 among women weighing ≥30 kg/m^2. The increase in postmenopausal breast cancer risk seen with obesity is thought to be almost entirely driven by the increased aromatization of androgens to estrogens in adipose tissue and a decrease in serum sex-hormone-binding globulin levels. In the EHBCCG analysis, the increased risk of breast cancer with increasing BMI could be almost completely explained by adjusting for serum estrogen levels. In contrast, adjustment for androgens had little effect on the relative risk.[29] Finally, the lower levels of sex-hormone-binding globulin seen with increasing BMI would lead to higher free (unbound) estradiol levels in heavier women.[30]

Bone density—Bone density has also been considered as another possible surrogate for endogenous estrogen exposure, although the data are less clear than with BMI. Bone tissue contains estrogen receptors, and exogenous estrogens are well known to increase bone density. Although multiple studies have reported an increased risk of breast cancer with increased bone density, with women in the highest quartile of bone density having roughly 2–3 times the risk of women in the lowest quartile,[31,32] several studies did not find a strong association.[33]

Circulating hormone levels

The hope with circulating sex steroid levels would be that they represent the best overall measure of endogenous estrogen exposure and a final common pathway for all the different risk factors that may influence a woman's breast cancer risk throughout her lifetime, and may be the 'best' breast cancer risk predictor. Although the data for postmenopausal women are stronger than for premenopausal women, the use of blood estrogen levels in the clinical setting is still far from routine for a number of reasons, including inter-laboratory variability, especially for the low levels of circulating estrogens in postmenopausal women.[34] Many of the earlier studies focused on circulating estrogen levels, but more recent studies have also evaluated androgen levels (Figures 1 and 2).

Postmenopausal women—The body of evidence supporting a link between circulating estrogen levels and breast cancer risk for postmenopausal women are more consistent than for premenopausal women.[35–37] For example, in the EHBCCG analysis of nine prospective studies of endogenous hormone levels and breast cancer risk, levels of multiple sex steroids – including total estradiol, free estradiol, estrone, and estrone sulfate – were associated with increased breast cancer risk. In general, those in the highest quintile of circulating hormone levels had twice the risk compared to those in the lowest quintile.[36] Similar results were seen within EPIC.[38] The Nurses' Health Study further evaluated the association by hormone receptor status of the tumor, and as expected a stronger association with circulating estrogen levels was found with ER$^+$/PR$^+$ tumors.[37]

Among postmenopausal women not currently on HRT, a single blood sample seems to be a fairly good reflection of longer-terms levels, based upon reproducibility studies in which several samples were collected over time.[39] Furthermore, many of the prospective studies had blood samples drawn years earlier and were still able to predict breast cancer risk.[37] In addition to circulating estrogens, many of these studies also observed an association between breast cancer risk and circulating androgens, such as testosterone, androstenedione, and DHEA. The risk associated with circulating androgens appeared to be independent of that with circulating estrogens, since associations were still observed after mutual adjustment.[36–38] It should be noted that all of the studies excluded women who were taking HRT. Interestingly, despite the data on exogenous progesterone use and breast cancer risk, endogenous progesterone levels have not been consistently associated with increased breast cancer risk in postmenopausal women.[37]

Premenopausal women—Data linking circulating estrogen levels and premenopausal breast cancer have been less clear, but these studies have been more difficult to analyze because of large intra-individual variation related to the menstrual cycle and inter-individual variability. Stronger evidence exists for associations between breast cancer risk and premenopausal androgen levels. The largest prospective study to date is EPIC, which reported an association between breast cancer and premenopausal levels of testosterone, androstenedione, and DHEAS (RR comparing highest to lowest quartile range 1.48–1.73), but not for estradiol or estrone.[40] However, another large prospective study (the Nurses' Health Study, NHS) presented slightly different results. It should be noted that the NHS blood samples were timed to the menstrual cycle, rather than simply matching cases and controls to the day of the menstrual cycle as was done in EPIC. Similarly to EPIC, the NHS investigators also observed an association with breast cancer risk and premenopausal testosterone levels. In contrast to EPIC, they also observed an increased breast cancer risk with estradiol levels drawn in the early follicular phase. In premenopausal women, estrogen levels are generally lower in the early follicular phase.[41] In summary, for premenopausal women, the associations with circulating androgens appears to be stronger than the data for circulating estrogens, but it is not known how much of the observed differences are due to measurement issues, since androgens can be more reliably measured and have less variation according to the menstrual cycle than estrogens.

Unanswered questions on sex steroids and breast cancer

Laboratory assay methods—From the standpoint of risk prediction, the field of breast cancer could follow the lead of cardiovascular disease in which both epidemiological risk models (such as the Framingham risk score) and biomarkers (such as C-reactive protein and lipid levels) are used to target interventions according to the risk of disease development. However, several issues need to be overcome before circulating sex steroid levels are used routinely in clinical practice. As noted previously, measurement of low estradiol levels require ultra-sensitive assays that even in capable hands at academic research laboratories still do not provide reproducible and comparable absolute levels. For example, in the EHBCG analysis of nine prospective studies, median levels for estradiol ranged from 21.7 to 101 pmol/L among the controls.[29] Therefore, study-specific cutoffs were used, but in order to be adopted for widespread clinical use, standard absolute values for the levels will need to be agreed upon and reproducible. Although some inter-individual variability is to be expected, much of the variation in published studies is felt to be due to laboratory variation. Despite the heterogeneity in the laboratory assays, there was little heterogeneity in the association between hormone levels and breast cancer across studies, underscoring the strength of the association with breast cancer risk.

Integration with epidemiological risk prediction models—Currently, the Gail model is the most widely available model for breast cancer risk prediction; this utilizes several

standard breast cancer risk factors (age, race, ages at menarche and first live birth, family history of breast cancer, number of benign breast biopsies, and history of atypical hyperplasia) to estimate absolute 5-year risks of developing invasive breast cancer.[42] Although circulating sex steroid levels add additional information to risk prediction even after controlling for standard breast cancer risk factors, it is still not clear how to integrate the epidemiological and biomarker data together. In the Nurses' Health Study, it has been previously shown that even after stratifying by Gail model score, estradiol, estrone, and testosterone levels were still associated with an increased risk and therefore were important as independent risk predictors.[43]

In addition, data on the use of hormone levels to identify women as candidates for chemoprevention has been mixed. The chemoprevention trials utilizing tamoxifen and raloxifene have all shown that these drugs only target the formation of hormone-receptor-positive cancers, but not hormone-receptor-negative ones, and the Gail model was used as part of the eligibility criteria for the NSABP P-1 (tamoxifen versus placebo among healthy high-risk women) and STAR (tamoxifen versus raloxifene among healthy high-risk postmenopausal women) prevention trials in order to identify women at higher risk of developing breast cancer.[44–46] In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, which randomized postmenopausal women with osteoporosis to either raloxifene or placebo, women at the lowest (undetectable) estradiol levels did not seem to benefit from the use of raloxifene.[47] In contrast, a nested case–cohort study within the NSABP P-1 trial showed a similar relative risk reduction across all quartiles of estradiol levels.[48] However, estradiol levels overall within the NSABP P-1 cohort did not appear to be predictive of breast cancer risk, in contrast to the multiple other observational studies detailed previously, which called into question the additional value of estradiol levels in women who were already identified as high-risk by the Gail model. Therefore, it is still not clear whether circulating estrogen levels can be used to identify women for chemoprevention.

The 'best' hormone to assay—Although estradiol is known to have the highest binding affinity for the estrogen receptor among the circulating estrogens,[49] it is still not clear which measurement would be best for breast cancer risk prediction. Although both total and free estradiol levels are associated with breast cancer risk, so are estrone and estrone sulfate, with fairly similar relative risks. It is not known whether this is due to the fact that they are correlated with each other or represent related but separate biological effects. In addition, it is not known how well circulating levels reflect exposure at the mammary tissue level. Normal mammary tissue contains enzymes that catalyze the conversion of androgens into estrogens, and estradiol levels in breast tumors have been found to be much higher than circulating levels.[50,51] It is also not known whether androgens independently influence breast cancer risk or simply provide additional substrate at the tissue level for conversion into estrogens (androstenedione and estradiol can be converted directly by aromatization into estrone and estradiol, respectively). Finally, testosterone and other androgens can be more reliably assayed than estradiol, which may decrease measurement error and strengthen any observed associations.

Genetic polymorphisms in estrogen-etabolizing genes—A detailed review of all the estrogen-etabolizing genes would require a separate chapter, but clearly has been an area of intense interest. Most studies have focused on low-penetrance, high-prevalence polymorphisms in genes related both to estrogen synthesis (e.g. CYP17, CY19) and catabolism (e.g. CYP1B1, COMT). Although some relationships have been seen between individual polymorphisms and circulating estrogen levels, the associations have been modest and often have conflicting results across studies. In addition, given the multiple pathways and feedback controls inherent in the estrogen metabolism pathway, it is unlikely that a single genotype by itself would significantly influence estrogen levels.[52]

Relation with estrogen-receptor-negative cancers—It is increasingly recognized that breast cancer represents a heterogeneous disease rather than a single disease entity. Although different classification systems of varying complexity have been proposed, the most basic one distinguishes between hormone-receptor-positive and -negative cancers (as defined by ER and/or PR status). The few studies that have evaluated the associations with circulating hormone levels and breast cancer separately by hormone receptor status have found a stronger association with ER^+/PR^+ compared to ER^-/PR^- ones.[37,41] In fact, many of the standard breast cancer risk factors with presumed hormonal mechanisms are more closely related to ER^+ than ER^- cancer. History of benign breast disease and family history of breast cancer which presumably operate through non-hormonal mechanisms are related to both ER^+ and ER^- cancers.[21]

SUMMARY

Both higher levels of exogenous and endogenous hormone exposure are associated with breast cancer risk. Because of the association between breast cancer and HRT, only the minimal duration of HRT use is recommended for symptom control, and it is not recommended for chronic disease management. Current research issues include the role of progestins, other types of HRT, duration of unopposed estrogen use, and characteristics of cancers that develop on HRT. Circulating sex steroids levels are associated with breast cancer risk, but multiple issues need to be addressed before they are used routinely in clinical practice. Current research issues include measurement of levels for routine clinical practice, integration with standard breast cancer risk models and genetic polymorphism data, and applicability to estrogen-receptor-negative cancers.

Practice Points

Exogenous hormones

1. Hormone replacement therapy with combination estrogen and progesterone increases the risk of developing invasive breast cancer. Combination HRT should only be used for the minimal duration for symptom management and should not be used for chronic disease management.
2. The use of conjugated equine estrogen alone for less than 7 years has not been shown to increase breast cancer risk.

Endogenous hormones

1. Among postmenopausal women, circulating estrogen and androgen levels have been associated with breast cancer risk, but currently clinical laboratories do not have sensitive and reliable assays to use these levels for routine breast cancer risk prediction.
2. Among premenopausal women, circulating androgens also appear to be associated with breast cancer risk, but the data on circulating estrogens are less clear.

Research Agenda

Exogenous hormones

1. Observational studies of longer durations of unopposed estrogen (>15 years) suggests that there may still be an increase in breast cancer risk.
2. The mechanism of the increased breast cancer risk associated with progestins is not well understood.

3. The effect of other formulations of HRT besides those tested in the randomized trial on breast cancer is not known.

Endogenous hormones

1. The "best" predictor of breast cancer among the circulating sex steroids needs to be better understood.
2. Research needs to be done to integrate endogenous hormone levels with current breast cancer risk prediction models and indications for chemoprevention.
3. Research needs to focus on non-hormonal causes of breast cancer to better understand the etiology of hormone receptor negative breast cancers.

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(Note: References [4], [9, 10, 13, 29, 36][28], and [52] should have an asterisk as the most important references. I could not do so in Endnote below without disrupting the program)

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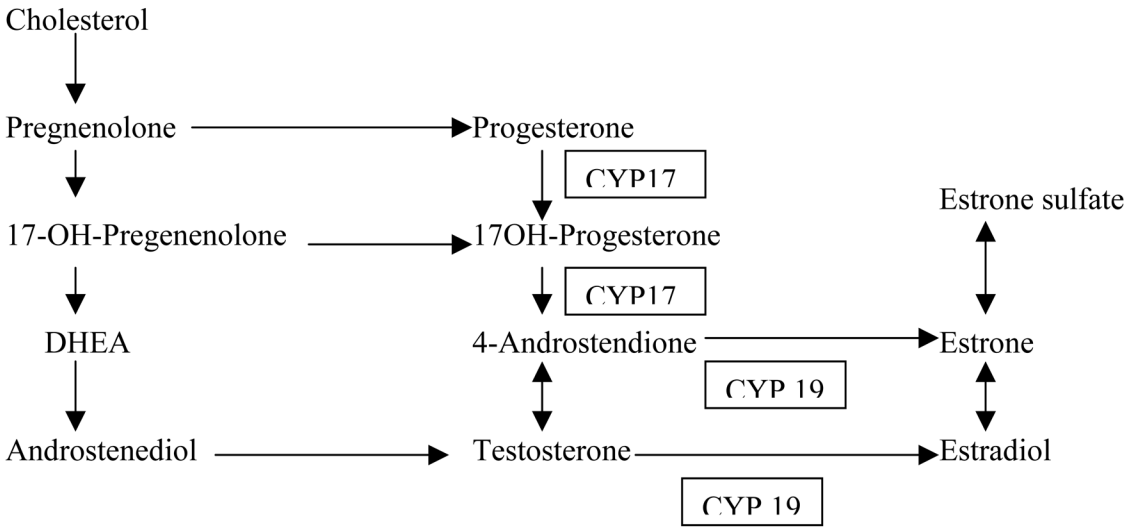

Figure 1.
Estrogen synthesis. DHEA, dehydroepiandrosterone. Adapted from Kendall et al (2007, *Journal of Steroid Biochemistry and Molelcular Biology* **103:** 99–109) with permission.

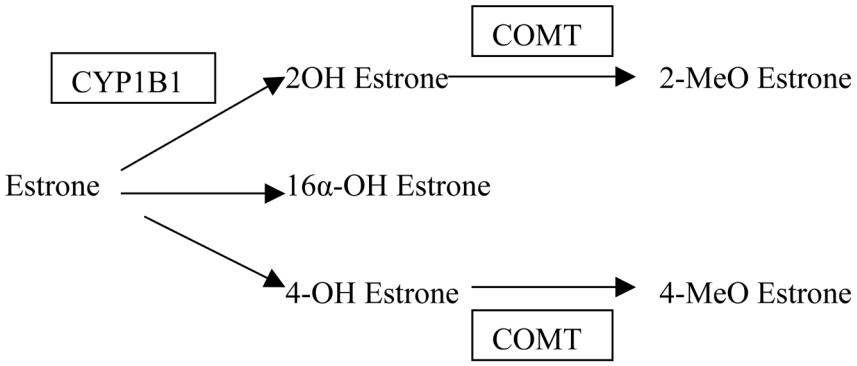

Figure 2.
Estrogen catabolism. Adapted from Kendall et al (2007, *Journal of* Steroid Biochemistry and Molelcular Biology **103:** 99–109) with permission.