Published in final edited form as:
Endocrinol Metab Clin North Am. 2011 September ; 40(3): 509–518. doi:10.1016/j.ecl.2011.05.006.

Postmenopausal Hormone Therapy and Breast Cancer Risk: Current Status and Unanswered Questions

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Synopsis

Although postmenopausal hormone therapy (HT) use declined significantly after publication of the Women's Health Initiative (WHI) results, many women still continue taking HT for menopausal symptom relief. It is clear that the breast cancer risk associated with combination estrogen and progesterone therapy (EPT) is greater than that with estrogen therapy alone (ET), but questions still remain about the safety of longer term ET use. Studies since the WHI have tried to clarify whether various factors can modify the risk of HT, such as the age at initiation, dose, or type of HT or characteristics of the individual, such as family history of body mass index. At this point, the relative risks breast cancer associated with HT across various subgroups of women should still be considered similar, but absolute risks can vary significantly among women and this may inform individual decision making. For breast cancer survivors, systemic HT should be discouraged.

In 2002, the use of postmenopausal hormone therapy (HT) declined dramatically world-wide with the first publication of results from the Women's Health Initiative (WHI), the landmark randomized clinical trial that demonstrated an increased risk of breast cancer among women randomized to combination estrogen and progesterone therapy (EPT) compared to placebo.[1-3] Although use of HT dropped significantly after 2002, millions of women still take HT for menopausal symptom control, so it is crucial to understand the data on HT and breast cancer risk and the unanswered questions.

Main results for breast cancer: Women's Health Initiative

The largest randomized placebo-controlled trial evaluating the overall health effects of HT was the Women's Health Initiative (WHI). The WHI was a large, multicenter trial conducted in the United States that randomized 27,347 postmenopausal women depending upon their hysterectomy status: 16,608 women with a uterus were randomized to either the combination of 0.625 mg conjugated equine estrogen and 2.5 mg medroxyprogesterone acetate daily (EPT)[4] or placebo and 10,739 women without a uterus were randomized to either 0.625 mg of conjugated equine estrogens daily (ET) or placebo.[5] After mean follow-up of 5.2 years, the study was unblinded for the EPT arms when event rates for breast cancer and a global index for “overall harm” exceeded predetermined stopping rules.[4] With mean

follow-up of 5.6 years, there was a 24% increase in the risk of invasive breast cancer with EPT compared to placebo (95% confidence interval (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 HT and by the fourth year of use among women who had never used HT.[6] The increased breast cancer risk was seen in all subgroups when stratified by Gail risk score, prior HT use, or body mass index. Compared to placebo, EPT was associated with higher risk of an abnormal mammogram and increased breast density.[7] In addition, the use of EPT was associated with significantly poorer diagnostic accuracy for mammography,[8] a finding that has also been described in observational studies.[9] After discontinuation of HT, breast cancer risk fell rapidly.[10]

In contrast, there was no increased breast cancer risk in the ET arm compared to placebo after an average of 7.1 years of follow-up. In fact, there was a non-significant decrease in invasive breast cancer risk (Hazard Ratio (HR) 0.80 (95% CI 0.62-1.04)).[11] However, ET was also associated with a significant increase in mammographic density compared to placebo, although the magnitude of increase was less than that seen with EPT.[12] Similar to EPT, there was an increased risk of an abnormal mammogram for women using ET. But, unlike EPT, there was no increase in risk of more serious findings and there was only a short-term impact on diagnostic accuracy of mammography.[13]

Current Guidelines from professional societies on HT use

Based upon the WHI data and multiple observational studies[14, 15], most professional societies do not currently recommend HT for cardiovascular disease prevention and they recommend minimizing duration and dose when HT is used for treatment of menopausal symptoms.[16-19] However, some characteristics of the WHI participants have called into question the generalizability of the results to women taking HT in the United States. Additional unanswered questions regarding HT and breast cancer risk including the effects of age at initiation of HT, longer term ET therapy, the effects of different doses and formulations of HT besides those evaluated in the WHI, the characteristics of breast cancers that develop on HT, and identification of lower risk groups for HT use.

1. Age of initiation of HT

In the WHI, the mean age at randomization in both the EPT and ET arms was 63-64 with only about one-third of subjects aged 50-59, which is older in general than women who take HT for menopausal symptoms in clinical practice.[4, 5] Because of this concern, subgroup analyses by age at initiation were performed within the WHI randomized trial.[20] To increase statistical power, the EPT and ET arms were combined for this subgroup analysis. For women aged 50-59, there was a lower risk of mortality for those taking HT (HR 0.70 (95% CI 0.51-0.96) that was not seen in women aged 60-69 or 70-79, although the p for trend across age groups was 0.06. For coronary heart disease (CHD), lower risks were also seen for women < 10 years since menopause at randomization, compared to women >10 years since menopause (HR 0.76 (95% CI 0.50-1.16, p for trend by years since menopause =0.02). Most of the benefit appeared to be in the ET arm. Relative risk for stroke was similar across age groups, but the absolute risks were much lower in women younger than 50.

To further evaluate “gap time” (defined as the time from menopause to first use of HT) and the effects of age at initiation of menopause as well as control for prior HT use, a later analysis pooled data from the WHI randomized trial with data from the parallel WHI observational study which consisted of 93,676 postmenopausal women in the same age range as participants in the WHI randomized trial. This subgroup analysis pooled participants from the WHI randomized trial with a known age at menopause and known age at first HT use (9129 from the ET trial (~85% of the original participants) and 15188 from

the EPT trial (90-93% of original participants)) and from the WHI observational study who would have met criteria for entry onto the randomized trial and also had known ages at menopause and first HT use (20,117 who had hysterectomy (10,582 taking ET and 9535 not on ET) and 24,186 with an intact uterus (6756 who used EPT and 24,186 who were not using HT)). There did not appear to be a significant effect of "gap time" for most of the outcomes evaluated. However, for breast cancer, women who began EPT within 5 years of menopause had a higher breast cancer risk than those who started EPT 5 or more years after menopause. It should be noted that "gap time" was closely correlated with both age and duration of HT use, so there may have still been some residual confounding. In addition, the relative risks were quite sensitive to the modeling parameters and assumptions, suggesting that the findings were not robust and may not represent a true biologic effect.

Only one other observational study also evaluated the impact of "gap time" drawing upon a prospective cohort of 98,995 French women. They seemed to show similar results with a higher risk of breast cancer among women who began HT within the 3-year period after menopause onset (HR 1.54 (95% CI 1.28-1.86)), compared to those who started it after 3 years (HR 1.00 (95% CI 0.68-1.47))(p=0.04 for heterogeneity). However, this was only seen in a specific subgroup of short-term (≤ 2 years) recent EPT users and in no other subgroup, calling into question whether this may represent a chance finding or lack of power to detect an effect among women with gap time greater than 3 years given the smaller number of cases in that strata (786 cases with ≤ 3 years gap time versus only 151 cases with > 3 years gap time among recent EPT users).[21] Overall, the randomized WHI trial data would still be considered the strongest data and these clearly show an increased risk of breast cancer across all age subgroups.[6]

Nevertheless, interest remains about a possible "window of opportunity" for HT in the prevention of cardiovascular disease among recently premenopausal women, but at this point the data remain speculative and more definitive results are awaited. The Kronos Early Estrogen Prevention Study (KEEPS) has completed enrollment and should provide important additional data on the effects of HT closer to menopause.[22] KEEPS randomized 728 postmenopausal women aged 42 to 58 (mean 52.7) who were 6 to 36 months within their last menses to one of three arms: 1) daily oral conjugated equine estrogen + oral progesterone 12 days/ month, 2) transdermal 17β-estradiol patch + oral progesterone 12 days/month, or 3) placebo. Primary endpoints include surrogates for cardiovascular disease, including changes in carotid intimal-media thickness and coronary artery calcification.

2. Characteristics of breast cancer that develop on HT

In a recently published update on breast cancer incidence and mortality comprising 678 breast cancer cases in the WHI clinical trial, cancers that developed in women taking EPT were generally similar to those on placebo in terms of tumor size, histology, and HER2 and hormone receptor status, but did have a greater chance of being node-positive (23.9% on EPT vs 16.2% on placebo, p=0.03).[23] More women died of breast cancer in the EPT arm (n=25 deaths) compared to placebo (n=12 deaths)(p=0.049). It should be noted that re-consent was required after 2005 and approximately 17% of participants did not re-consent, so were censored in 2005 for both the incidence and mortality analyses.

In contrast, the observational studies have shown somewhat different results in terms of the characteristics of the breast cancers that develop in women on HT. Most notably, although the WHI did not observe differences in the ER (estrogen receptor) and PR (progesterone receptor) status of the tumors between the placebo and the EPT arms, this is contrary to what was reported by most observational studies and what physiologically would be most plausible.[24] 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.[25] Therefore, one would hypothesize that HT would preferentially stimulate the growth of hormone receptor positive cancers, as was seen in multiple observational studies.[24] Part of the discrepancy may be that the WHI study only had a limited number of breast cancer cases with known ER status (356 on EPT and 264 on placebo), compared to the larger observational studies. Therefore, although no difference was seen in the distribution of tumors by hormone receptor status in the WHI, given the biologic mechanism and the additional power of the observational studies to evaluate differences by receptor status, it is still possible that HT is more strongly associated with hormone receptor positive cancers than negative ones.

In terms of the increased breast cancer mortality reported by WHI, it should be noted that this recent analysis combined both incidence and mortality.[23] Given the higher incidence of breast cancer in the EPT arm, it would be expected that there would be more breast cancer deaths. Currently, there are not enough events to compare survival after breast cancer between the two groups, which would be the more relevant comparison to understand whether the biology of breast cancers that develop on HT differ from sporadic ones. In addition, breast cancer treatment was not controlled for in the analyses, since data were not available, and this could have been an important confounder.

3. 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 epidemiologic studies led by the Oxford group and in the large observational Nurses' Health Study 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 relative risk (RR) 1.34 (standard error 0.09).[14] In the Nurses' Health Study, when we analyzed only women greater than 50 who had undergone a hysterectomy so that the population would be comparable 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).[26] Although ET was not associated with an increased risk of breast cancer in the WHI trial, there was an increased risk of benign proliferative breast lesions (HR 2.11 (95% CI 1.58-2.81).[27] If one considers the sojourn time required for tissue to progress from proliferative lesions to atypia to invasive breast cancer, this finding would be consistent with the association of longer-term ET with breast cancer risk. Therefore, for durations of unopposed estrogen use similar to that in the WHI (i.e. less than 7 years), there does not appear to be an increased breast cancer risk. However, the impact for longer-term users is less clear.

4. Other forms of HT

In the United States, the most common form of prescription HT remains conjugated equine estrogens alone or given with medroxyprogesterone acetate. However, in Europe, many other formulations of estrogens and progestins 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 only had limited numbers of users of the other types of hormones.

Estrogen—The predominant form of estrogen used in the United States is oral conjugated equine estrogen, the same formulation used in the WHI clinical trial.[2] However in Europe,

more variation exists in terms of the type of estrogen used. The single largest prospective study of HT conducted in Europe was the Million Women's Study (MWS) in the UK. They did not observe any variation in risk between conjugated estrogens and ethinylestradiol. In addition, they also reported an increased risk of breast cancer with tibolone, a progestin analog that is considered a selective estrogen enzyme modulator.[15] Other large prospective studies done in Denmark and France, in which the predominant estrogen used was estradiol, rather than conjugated estrogens, also observed an increased risk with estrogen-only and combination estrogen + progesterone regimens and tibolone.[28-30] It should be noted that the risk of breast cancer observed with estrogen-only in some of the studies was higher than that seen in WHI. Both ethinylestradiol and estradiol would be considered “medium-potency” estrogens similar to conjugated 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 did not see an increased breast cancer risk with natural progesterone or its isomer dydrogesterone,[28] nor did a Finnish study evaluating dydrogesterone; both studies only had a limited number of women taking these regimens.[30] However, studies that evaluated more androgenic progestins, such as norethisterone and norgestrel, still observed an increased breast cancer risk when given in combination with estrogens.[15, 29, 30] In sum, although limited data suggest that natural progesterone may be associated with less breast cancer risk then synthentic progesterone, further research needs to be done to confirm these differences and evaluate long-term safety of the natural progesterone.

Testosterone—Only a few studies have evaluated the use of testosterone-based HT and most studies have a small number of cases, so power has been limited. In the largest prospective study of oral testosterone given alone or in combination with oral estrogen to date (E + T), we observed a twofold 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)).[31] The WHI Observational cohort reported similar findings with a non-significant increased risk of breast cancer for users of any type of E+T (RR 1.42 (95% CI 0.95-2.11) and a significantly increased risk associated with Estratest, the most common E +T preparation (HR 1.78 (95% CUI 1.05-3.11), compared to never users. Paradoxically, they observed higher risk with shorter term, rather than longer-term use.[32] An increased risk was also seen in a Danish study evaluating injectable estrogen and testosterone.[33] Finally, higher endogenous testostone levels have been consistently associated with increased breast cancer risk in both pre- and postmenopausal women.[34, 35] Therefore, although data are limited, caution should be used for testosterone-based HT among postmenopausal women.

Dose or route of administration of HT—All of the professional societies recommend using the lowest HT dose possible for menopausal symptom relief. However, there are no randomized trial data to determine whether a lower dose is associated with a more favorable risk-benefit ratio than the doses evaluated in the WHI (0.625 mg conjugated equine estrogen alone or with 2.5 mg medroxyprogesterone acetate). Although transdermal ET has become more popular since publication of the WHI results, again no randomized controlled data exist to determine whether the overall risk-benefit ratio would be more favorable than for standard oral HT. Observational studies suggest that risks are similar regardless of the route of administration (oral/transdermal/implanted).[15, 30, 36] In addition for women with an intact uterus, transdermal ET would still need to be taken with oral progesterone for endometrial protection.[19]

5. Can “low-risk” groups be identified for HT use?

Since HT still remains the gold standard for menopausal symptom relief, besides minimizing dose and duration, clinicians have often wondered whether some women a priori could be classified as higher or lower risk for HT complications. In general, the effect of HT on breast cancer risk does not appear to be modified by many of the traditional breast cancer risk factors, such as family history. That is, both family history and HT are independently associated with breast cancer risk but do not appear to interact either negatively or positively.[37-39] However, there is an exception in that several studies have suggested that body mass index (BMI) may modify the effect of HT in that breast cancer risk was greater in women with lower BMI and attenuated in heavier women.[14, 40-43] In addition, one study suggested that women with low breast density would not be at increased risk of breast cancer, regardless of HT use, but no detail was provided on type or duration of HT use or the distribution of ET compared to EPT users, so it is not known if these findings pertain to short-term users or long-term users or what type of HT.[44] As discussed previously, the relative risks for breast cancer observed in the WHI randomized trial were similar across a large variety of subgroups, although power was limited and the study was not designed to evaluate effect modifications by any of these risk factors.[6] Overall, the relative risk for breast cancer by HT should still be considered similar across subgroups, but clearly absolute risks would differ in that younger women without a family history of breast cancer would have lower absolute risks than older women with a family history. Therefore, the absolute risks could vary quite a bit by individual which could influence individual decision making, even if the relative risks were similar.

6. Use of HT in breast cancer survivors

Many breast cancer survivors develop menopausal systems, whether as a consequence of treatment-induced menopause or side effects of treatment. SSRI's and other non-hormonal interventions may provide some relief, but are still inferior to HT for treatment of menopausal symptoms. Two small prospective studies were closed early due to slow accrual and concerns regarding HT use in the breast cancer population, but did not observe an increased recurrence risk with HT but were clearly underpowered.[45, 46] However, the HABITS trial from Stockholm enrolled 447 breast cancer survivors beginning in 1997 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 HT exceeded predetermined stopping rules. However, follow-up was continued and at 4 years median follow-up and 56 events, the HT 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.[47] Results were similar regardless of estrogen receptor (ER) status of the tumor and tamoxifen use, but power was limited for the subgroup analyses. Similar results were seen in a randomized trial of tibolone 2.5 mg daily compared to placebo (n=3148 women randomized) with an increased risk of recurrence in the tibolone arm after median follow-up of 3.1 years median (HR 1.40 (95% CI 1.16-1.79).[48] Therefore, among breast cancer survivors regardless of the ER status of the tumor, even short-term systemic HT use would not be recommended.

Conclusions

Although HT use declined significantly after publication of the WHI results, many women still continue taking HT for menopausal symptom relief. It is clear that the breast cancer risk associated with EPT is greater than that with ET, but questions still remain about the safety of longer term ET use. Studies since the WHI have tried to clarify whether various factors can modify the risk of HT, such as the age at initiation, dose, or type of HT or characteristics of the individual, such as family history of body mass index. At this point, the relative risks

breast cancer associated with HT across various subgroups of women should still be considered similar, but absolute risks can vary significantly among women and this may inform individual decision making. For breast cancer survivors, systemic HT should be discouraged.

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