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EDITORIAL

Reassuring data regarding the use of hormone therapy at menopause and risk of breast cancer

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Controversy continues to surround the association between estrogen alone (ET) and estrogen combined with progestogens (EPTs) and the risk of breast cancer. Some of this confusion exists because the data on menopausal hormone therapy and the risks of breast cancer are disparate. The publications from the 2 distinct Women's Health Initiative (WHI) trials, the largest randomized controlled trials (RCTs) assessing the safety of systemic hormone therapy, found a difference between ET (conjugated equine estrogen [CEE] alone and EPT conjugated equine estrogen combined with the synthetic progestin medroxyprogesterone acetate [MPA]).[1-3] Notably, the results of smaller randomized trials are convergent with those of the WHI findings, whereas findings of larger observational studies are, in some cases, discordant with WHI's results.[4]

In the WHI, with 20 years of median follow-up, ET was found to reduce the risk of incident breast cancer and mortality from breast cancer,[5] whereas in many observational studies, an increased relative risk (RR) has been reported. Estrogen combined with progestogen (a term that encompasses bioidentical micronized progesterone as well as synthetic progestins including MPA and norethindrone acetate) has been associated with a higher risk of incident breast cancer in the WHI trials and many observational trials, with differences seen in the risk with different types of progestogens. The discrepancies between studies may result from different studied populations, the methodologic advantages of RCTs, biases inherent in observational data or RCTs, and types and durations of hormone therapy regimens used.

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ESTROGEN ALONE

In the narrative review published in the current issue of *Menopause* by Pan et al,[4] the authors evaluated the differences between RCT and observational data, which assess associations between menopausal ET and incident invasive breast cancer. This review included findings from the large WHI trials and 5 smaller RCTs.

In the WHI RCT, after a median of 7.2 years of CEE alone compared with placebo in women with a prior hysterectomy, no significant association with risk of breast cancer was noted (hazard ratio [HR], 0.77; 95% CI, 0.59-1.01).[1]

The CEE-alone trial was stopped after participants had taken study medication for a mean of 7.2 years. With a cumulative median of 20-year follow-up, almost 13 years after discontinuation of study medication, investigators found that the use of CEE significantly reduced the incidence of breast cancer (HR, 0.78; 95% CI, 0.65-0.93), with a significantly reduced breast cancer mortality (HR, 0.60; 95% CI, 0.37-0.97).[5]

Pan and colleagues[4] identified 5 smaller RCTs, which included data on ET use and incident breast cancer. Combining the results of these smaller RCTs, the authors found that, as with WHI, ET did not significantly impact the risk of breast cancer (RR, 0.61; 95% CI, 0.34-1.09). Combining the 5 smaller trials with the WHI CEE alone data (384 overall cases of breast cancer), the authors noted that ET significantly reduced the risk of invasive breast cancer (RR, 0.77; 95% CI, 0.64-0.93), thus providing more support for the WHI RCT trial findings (long-term follow-up) that ET reduces breast cancer incidence and breast cancer mortality.

These findings are similar to the large observational US Nurses' Health Study[6] for ET in postmenopausal women with prior hysterectomy. Use for 5.0 to 9.9 years showed no increased risk of breast cancer (RR, 0.87; 95% CI, 0.71-1.07). However, longer duration of use, which was unable to be examined in the WHI, was associated with a trend toward higher risk at 15 years, which was significantly increased at 20 or more years (RR, 1.42; 95% CI, 1.13 to 1.77).[6]

However, as Chlebowski and colleagues[4] point out, the previously mentioned findings are markedly different from those of the updated findings from the Collaborative Group on Hormonal Factors in Breast Cancer (Collaborative Group)[7] and the Million Women's Study,[8] both of which showed an increase in breast cancer with ET (see hereinafter).

In the Nurses' Health Study,[6] longer duration of use, which was not able to be examined in the WHI, was associated with a trend toward higher risk. For estrogen users for 20 or more years, an increased risk of breast cancer was seen (RR, 1.42; 95% CI, 1.13-1.77), especially for estrogen and progesterone receptor positive cancer (RR, 1.73; 95% CI,1.24-2.43).

ESTROGEN AND PROGESTOGEN

In the WHI combined estrogen progestin trial (CEE, 0.625 mg; MPA, 2.5 mg), stopped after 5.6 years, the absolute risk of breast cancer was an excess of 8 cases/10,000 person-years at an average of 5.2 years after randomization.[2] While there were more deaths from breast cancer in the CEE plus MPA group, the finding was only significant through 11 years of follow-up.[9] Continued follow-up found that the excess breast cancer risk persisted during 13 years of cumulative follow-up (434 cases for CEE plus MPA vs 323 for placebo; HR, 1.28; 95% CI, 1.11-1.48).[9]

After more than 20 years of cumulative follow-up, CEE plus MPA therapy continued to be associated with a significantly increased risk of breast cancer compared with those on placebo (HR, 1.28; 95% CI, 1.13-1.45; $P < 0.001$).[5] Mortality rates between EPT and placebo users, however, were not significantly different (HR, 1.35; 95% CI, 0.94-1.95; $P = 0.11$).

Abenhaim et al[10] used a nested British population–based case-control study with administrative data available in Clinical Practice Research Datalink along with provider prescriptions to evaluate the effect on the risk of breast cancer of the type of progestogen, either micronized progesterone or synthetic progestins (mostly MPA) when combined with estradiol for menopausal symptom relief. This large case-control study included 43,183 cases of breast cancer in the case group and 431,830 women not diagnosed with breast cancer in the matched control group (10:1 ratio of controls to cases). In the stratified analysis, a significant increase in the risk of breast cancer was found for women who reported ever use of menopausal HT (odds ratio [OR] 1.12; 95% CI, 1.09-1.15) with neither type of estrogen associated with an elevated risk of breast cancer: estradiol (OR, 1.04; 95% CI, 1.00-1.09) and CEE (OR, 1.01; 95% CI, 0.96-1.06). For women using EPT with synthetic progestins, the risk of breast cancer was significantly increased (OR, 1.28; 95% CI, 1.22-1.35), including among those ages 50 to 60 years. In contrast, the use of EPT with micronized progesterone was not associated with an elevated risk of breast cancer (OR, 0.99; 95% CI, 1.22-1.35).

In the Collaborative Group analysis in *Lancet*,[8] of 108,647 postmenopausal women who developed breast cancer, 51% had used menopausal HT. Every menopausal hormone therapy (including estradiol and CEE), except for vaginal estrogen use, was associated with excess breast cancer risk, increasing with the duration of use.

Regarding combining estrogen and progestogen, particularly more potent synthetic progestins, findings from both the Collaborative Group on Hormonal Factors in Breast Cancer[7] and the Million Women's Study cohort[8] are largely congruent with findings from the WHI randomized trial evaluating CEE plus MPA. In the Collaborative Group, the risk of breast cancer was greater for estrogen plus progestin than for ET preparations. Even short-duration (1-4 years) use was associated with excess risk in current users, with excess risk persisting more than 10 years after use in the Collaborative Group.[7]

The Million Women Study, updated in 2019 after 20 years of follow-up, analyzed 907,167 postmenopausal women free from breast cancer at recruitment and found that estrogen-alone and estrogen-plus-progestin use were associated with excess breast cancer mortality ($P < 0.0001$).[8]

EFFECT OF TYPE OF PROGESTOGEN

Progestogens prevent estrogen-induced endometrial neoplasia when dosed adequately. Progestogens do not seem to exert a class effect as the effect on the risk of breast proliferation and potential for cancer risk differs depending on the progestogen type, whether synthetic progestins or micronized progesterone.[11] A systemic review by Stute et al[12] found that micronized progesterone did not seem to alter breast density assessments or breast biopsy results. More potent synthetic progestins seem to increase cell division in mammary tissue, which could lead to a higher risk of proliferation of cells, thus increasing the risk of breast cancer. Breast density increases seem less with less potent progestins. Dydrogesterone and micronized progesterone have a lower affinity for the progesterone receptor and are subsequently metabolized into 20α-dihydrodydrogesterone, a metabolite devoid of estrogenic and androgenic effects. The half-life and metabolism of various progestogens are different, progesterone being rapidly degraded with a short half-life.[13,14]

Estrogen use combined with synthetic progestins (MPA, norethisterone, levonorgestrel, and norgestrel) has been associated with an increased risk of breast cancer,[7,15-17] whereas less breast cancer has been seen in studies associated with micronized progesterone.[15-19]

The French E3N EPIC population–based study by Fournier et al[16,17] found that women who received estrogen combined with synthetic progestin had a higher risk of breast cancer, age-adjusted RR of 1.4 (95% CI, 1.2-1.7), which was not seen in those receiving estrogen combined with micronized progesterone. Nine hundred forty-eight women were identified with breast cancer of which 268 used synthetic progestins.

A case-control study of 1,555 women (739 breast cancer group, 816 control) showed an increased risk of breast cancer with estrogen-progestin therapy (OR, 1.72; 95% CI, 1.11-2.65), compared with no increased risk for micronized progesterone (OR, 0.80; 95% CI, 0.44-1.43).[20] A Swedish population–based cohort study of 290,186 women (2005–2012) showed an increased rate of breast cancer for estrogen-progestin (OR, 1.40; 95% CI, 1.36-1.45).[21]

Both the cohort of Abenhaim et al[10] and the long-term outcome WHI RCT trial data[5] showed a significant contributing effect of the synthetic progestin MPA on breast cancer risk.

RACE

The 2 WHI RCTs included diverse racial and ethnic populations. Post hoc analysis of the 1,616 Black hysterectomized women in the WHI CEE alone RCT showed a significantly

decreased breast cancer incidence with ET (HR, 0.47; 95% CI, 0.26-0.82).[22] Similarly, after 20 years of cumulative follow-up of the WHI trial,[23] estrogen-alone use significantly reduced breast cancer incidence in Black women, without any adverse effect on coronary heart disease, global index, or all-cause mortality, fewer cases of venous thromboembolism, and with a favorable global index for Black women in their 50s and those with vasomotor symptoms.

As with the WHI, data from the Carolina Breast Cancer Study,[24] a population-based case-control study of Black and White women in North Carolina from 1993 to 2001, found that associations between the use of hormone therapy and the risk of breast cancer were similar in White and Black women. The Carolina Breast Cancer Study[24] included 1,474 invasive breast cancer cases and 1,339 controls. Overall, Black women were less likely to use menopausal hormone therapy than Whites; however, among users, the use of ET was more prevalent among Black participants. Estrogen alone in women with prior hysterectomy was not associated with the risk of breast cancer in women of either race. Combined estrogen-progestin use was associated with increased odds of breast cancer in White (adjusted odds ratio [OR], 1.48; 95% CI, 1.03-2.13) and Black (OR, 1.43; 95% CI, 0.76-2.70) women. The association between hormone therapy and breast cancer risk seems similar in Black and White women, accounting for differences in hysterectomy rates and type of therapy used.

USE OF HORMONE THERAPY AMONG WOMEN WITH AN ELEVATED BASELINE RISK OF BREAST CANCER

Women at elevated risk of breast cancer due to family history and/or carriage of deleterious mutations are often reluctant to consider the use of menopausal hormone therapy. The WHI EPT RCT found that among women with an elevated baseline risk of breast cancer based on family history, the impact of EPT on the risk of breast cancer was similar to women without a high-risk family history.[25] Santen et al[26] re-evaluated the findings from the Collaborative Group on Hormonal Factors in Breast Cancer[7] based on underlying breast cancer risks and determined that women in the highest breast cancer risk group had higher attributable risks of breast cancer, amplified by duration of use.

Women with deleterious *BRCA1* and *BRCA2* mutations have a high lifetime risk for breast and ovarian/tubal cancer. Highly effective in preventing ovarian/tubal cancer in these high-risk women, risk-reducing bilateral salpingo-oophorectomy (BSO) can be lifesaving. However, women with these high-risk mutations may be reluctant to undergo risk-reducing gynecologic surgery due to concerns regarding bothersome menopausal symptoms after surgical menopause and their assumption that menopausal hormone therapy would increase their already elevated risk of breast cancer. Only observational data are available regarding the impact of menopausal hormone therapy in women with deleterious mutations in *BRCA1* or BRCA2 who have undergone BSO and intact breasts. Marchetti et al[27] performed a meta-analysis of 3 studies, including 1,100 *BRCA* gene–positive women with intact breasts who had undergone risk-reducing BSO and either received or did not receive hormone therapy. Use of hormone therapy was not associated with breast cancer risk for *BRCA 1* or *BRCA 2* mutation carriers who received HT after risk reducing salpingo oophorectomy (HR, 0.98; 95% CI, 0.63-1.52). There was a reduced risk of breast cancer that did not achieve statistical significance for mutation carriers who used ET compared with those who received EPT (OR, 0.53; 95% CI, 0.25-1.15). The Marchetti analysis plus another from Gordhandas[28] (4 studies) provide reassurance that among women with deleterious *BRCA* mutations with intact breasts who have undergone risk-reducing gynecologic surgery, menopausal hormone therapy, at least over the short term, does not increase breast cancer risk.[27,28]

SUMMARY: REASSURANCE REGARDING MENOPAUSAL HORMONE THERAPY AND RISK OF BREAST CANCER

Noting the congruent findings between the large WHI trial of ET and smaller RCTs, Pan and colleagues[4] make a strong case that when prescribed to women after hysterectomy, menopausal ET, whether CEE or micronized estradiol, does not elevate the risk of invasive breast cancer. These findings, along with observations Chlebowski et al[5] make regarding the reduction in breast cancer mortality resulting from ET use, should provide reassurance to women and clinicians regarding the safety of ET when used at menopause. Longer durations of ET use may increase risk.

For women with an intact uterus who use combined estrogen and progestogen, the overall risk of breast cancer is increased and persists after discontinuation. This risk was seen in WHI, other smaller RCTs, and observational data. However, not all progestogens seem to carry the same risk. Although large RCT data addressing this issue are not available, the best available evidence indicates that the use of estrogen with micronized progesterone and dydrogesterone, which is not available in the United States, does not elevate breast cancer risk to the same degree, if at all, and are safer with respect to risk of breast cancer.

Among women using menopausal hormone therapy, clinicians should periodically re-evaluate the benefits and risks of this treatment.[29,30] The reassuring findings presented by Chlebowski and colleagues[4,5] regarding ET along with our summary of available evidence regarding EPT with different progestogens should factor into shared decision making as patients consider initiating or continuing systemic menopausal hormonal therapy.

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