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Combined Hormone Therapy at Menopause and Breast Cancer: A Warning – Short-term Use Increases Risk

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Observational epidemiological studies have repeatedly demonstrated that breast cancer risk is associated with current and long-term use of combined estrogen plus progestogen hormone therapy (HT), with an excess risk of 5-9% per year of HT use.¹ Yet, it was not until the dissemination of results from the Women's Health Initiative (WHI) clinical trial in 2002² that the medical community began to acknowledge that the risks associated with combined therapy outweighed the benefits. Beginning in 2003-2004, the United States Food and Drug Administration (FDA) issued draft guidelines for labeling estrogen containing products suggesting that the only appropriate use of hormone therapy was short-term use to relieve menopausal symptoms.³ A number of organizations followed with similar guidelines, further recommending discontinuation of any use of HT for disease prevention.⁴⁻¹⁰ A major stimulus for these recommendations was the WHI clinical trial results showing that women receiving daily estrogen (0.625 mg conjugated equine estrogen) combined with a progestin (2.5 mg medroxyprogesterone acetate) (E+P) had greater risk of coronary heart disease than did women receiving a placebo;¹¹ yet, the most notable impact of this randomized trial has been the marked decline in US breast cancer incidence rates beginning in mid-2002¹²⁻¹⁵ after decades of increasing incidence.^{14,16,17} These reductions in incidence have been observed primarily for estrogen receptor positive breast cancer^{12,14} and among non-Hispanic white women ages 50 years or older¹⁸ living in urban more affluent counties in the US,¹⁹ areas where the prevalence of HT use would have been expected to be high. In parallel with other studies of declining incidence rates, the WHI observational study of more than 41,000 postmenopausal women also showed a marked decline in breast cancer incidence in 2003 among women who had been taking E+P at entry into the cohort.²⁰

The WHI E+P clinical trial, which included more than 16,000 postmenopausal women with an intact uterus who were aged 50 -79 years, found that, overall, women in the treatment arm had 24% greater breast cancer risk over the intervention period, which averaged 5.6 years, than did women in the placebo arm.^{2,21} Shortly after dissemination of the WHI results for breast cancer and cardiovascular disease, the number of prescriptions for hormonal therapies dropped by more than 50 percent in the US.^{14,22-24}

Although E+P may act as a direct carcinogen, initiating a new tumor, the immediate decline in breast cancer incidence following a decline in E+P prescribing and usage suggests that E+P is a strong promoter of occult, mammographically and clinically non-detectable cancers. Subgroup results published from the WHI E+P clinical trial initially suggested a delay in response. For example, Chlebowski and colleagues showed that breast cancer rates did not increase during the first two years after randomization,²⁰ which suggests that any proliferative impact of E+P on existing occult tumors requires a longer lead period to become detectable. This is consistent with additional analyses showing that the adverse impact of E+P was more evident among women with previous exposure to HT than among women with no prior HT use.²⁵ Further, breast cancer risk did not appear to increase until after 5 years of treatment among women who had no HT exposure prior to randomization to the E+P arm.²⁵ Although excess breast cancers were observed on the E+P arm after the clinical trial was halted, the increase in the risk of breast cancer relative to the placebo group during the 2.4 year post-intervention phase of the trial was no longer statistically significant and the relative risk gradually declined to 1.0 with increasing time since the end of the trial.²⁰ In total, these results suggest a delay in the increase in breast cancer risk of about two years after initial use (when prior users and new users are combined), and a decline in the increased risk that disappears within a 2-3 year time period. The former finding is consistent with findings in the Heart and Estrogen/progestin Replacement Study (HERS), a clinical trial of E+P use among postmenopausal women with established coronary disease, which showed an increase in breast cancer risk in the E+P arm in the first 2-5 years after initiation of treatment.²⁶ The latter finding of declining incidence rates within 2-3 years of cessation of HT use was also observed in the French E3N cohort²⁷ described in more detail below and in the postintervention phase of HERS.²⁸

A criticism of the WHI that has often been raised is the clinical relevance in relation to cardiovascular risk of a trial in which the majority of recruited women had been menopausal for many years.²⁹⁻³¹ An analysis of the WHI in recently postmenopausal women showed no cardioprotective effects of E+P.^{32,33} This has raised another important question regarding breast cancer: is short-term E+P use at menopause, when most needed for moderate to severe menopausal symptoms, safe in relation to breast cancer risk? Prentice and colleagues³⁴ attempted to look at this issue, combining data from the WHI E+P clinical trial and the WHI observational study, and comparing women who initiated HT use at menopause (defined as having a zero “gap time” between menopause and the initiation of first E+P use) with those who had no E+P use. For women on the E+P trial, the hazard ratio (HR) was elevated among those who initiated treatment within 5 years of menopause but not among women with gap times of 5 or more years. For example, among those with no prior E+P exposure before entering the WHI clinical trial, the HR was 1.77 with a 95% confidence interval (CI) of 1.07-2.93 for a gap time <5 years, whereas it was 0.99 (95% CI=0.74-1.31) for a gap time ≥ 5 years. In the combined trial and observational study analysis, breast cancer risk was statistically significantly elevated by more than 2-fold in the intervals 2-5 years after first use and 5+ years after first use among women with no gap between menopause and first E+P use. Risk estimates did not appear elevated during the first 2 years of E+P use at menopause, although too few cases occurred in the clinical trial (n=20) or the observational study (n=6) to make the results meaningful.

In this issue of the *Journal of Clinical Oncology*, Fournier and colleagues use data from the E3N cohort, one of the contributing cohorts to the European Prospective Investigation into Cancer and Nutrition, to focus more closely on use of estrogen and progestogen at menopause, addressing with greater statistical power than was available in the Prentice et al report³⁴ the question of use shortly after menopause, and also whether duration of estrogen and progestogen use near menopause matters. This is a carefully designed analysis of data collected at cohort formation and supplemented by data collected approximately every two years over the follow-up period from 1992 through 2005. Onset of natural menopause (defined as having at least 12 months elapse since a woman's last menstrual period), surgical menopause and use of combined estrogen and progestogen therapy, were collected prospectively permitting analyses of gap times since menopause that were ≤ 3 years and > 3 years. Importantly, 60% of the more than 32,000 users of estrogen-progestogen therapy had gap times of one year or less. The bottom line: women who initiated HT close to menopause had, approximately, a 50% increased breast cancer risk relative to non users, even when they had used use this regimen for 2 years or less. Although late initiators of HT (gap time > 3 years) did not have an increased risk of breast cancer for durations of use of 2 years or less, their risk was elevated for longer durations of use, and was similar to that of women who initiated use close to menopause. The overall results are fairly stable and based on 1,726 breast cancers occurring among more than 53,000 postmenopausal women during an average follow up of 8.1 years. These patterns of elevated risk with a short gap time and short durations of HT use were not observed among women on an estrogen plus progesterone regimen (as opposed to women receiving estrogen combined with other progestagens); however, the number of events among women starting this regimen within 3 years of last menstrual period and using this regimen for no more than 2 years was small (n=23). Although these authors have previously reported no increase in risk for women using estrogen plus progesterone,²⁷ this current report shows elevated risks when durations of use exceed 5 years among women who started use close to menopause.

The current report contributes significantly to our knowledge about the potential hazards associated with current clinical practice guidelines indicating that E+P can be used as needed for a limited time period to ameliorate vasomotor and other symptoms of menopause. An immediate 50% increase in breast cancer risk observed within the first two years of use is alarming. But, the results are not completely generalizable to other populations as the estrogen plus progestogen regimens used in France as studied in the E3N cohort differ from the most commonly used regimens in the US, such as the E+P regimen studied in the WHI clinical trial. Women in the E3N study cohort used mainly transdermal or percutaneous estradiol combined with synthetic progestogens including dydrogesterone, norgestrel acetate, norgestrel, chlormadinone acetate, medrogestone and cyproterone acetate.²⁷ Few women took oral estrogens combined with medroxyprogesterone acetate.²⁷ Thus, it will be important for other cohorts that focus on use of HT in US populations to evaluate breast cancer risk associated use immediately following menopause.

An important issue is the complexity of clinical management of patients. A segment of the medical community has remained skeptical of the WHI clinical trial results^{31,35-37} and hence is likely to remain unconvinced by the current report by Fournier and colleagues. One view that has been advanced is that the adverse effects of combined E+P therapy as

identified in the WHI have been blown out of proportion, do not consider the usual context of HT use at menopause in relation to coronary heart disease risk, and have not been presented fairly in the context of other potential breast cancer risk factors.³⁸ One commentary has taken a controversial view, arguing that E+P therapy has a beneficial impact because it promotes early detection of preexisting non-detected tumors, thereby leading to better outcomes following breast cancer diagnosis.³⁹

Finally, we must be aware that some women may turn to so-called “natural hormones” in the belief that because these hormones are not synthetic, chemically formulated hormones, they are safe. This belief is fostered by the increasing promotion of the use of bioidentical hormone replacement therapy, a regimen of so-called natural hormones being recommended by several influential entertainers,⁴⁰⁻⁴² but criticized in the news media^{40,41} and in an FDA news release, dated January 10, 2008,⁴³ that warns health care providers and patients that claims made about bio-identical hormone replacement therapy are not supported by medical evidence and are considered false and misleading.

A number of factors come into play in the decision as to whether a woman will or will not use combined E+P therapy in the period immediately following menopause. The increase in risk of breast cancer shown in the current report by Fournier and colleagues in this journal issue, may influence some decisions about use immediately following menopause. But, further data are needed to confirm these results and generalize them to other formulations such as E+P. In the meantime, it would seem that a conservative approach regarding use of combined hormone therapy at menopause is warranted, using hormones briefly and only when menopausal symptoms are so intense that no other approach will work.

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