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EDITORIALS

The Influence of Time From Menopause and Mammography on Hormone Therapy–Related Breast Cancer Risk Assessment

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In this issue of the Journal, the Million Women Study (MWS) collaborators update breast cancer findings and report that hormone therapy–related risk for breast cancer is greater if begun soon after menopause (1), providing substantial support for similar findings previously reported in the Women's Health Initiative (WHI) (2–4) and the French E3N cohort (5).

Many other findings from the MWS cohort (1,6) parallel those in the WHI randomized placebo-controlled clinical hormone trials (4,7–9), especially with respect to combined hormone therapy use. In both, the use of an estrogen–progestin formulation for a moderate duration was associated with increased breast cancer incidence. An increased risk of breast cancer was also associated with increased hormone use duration, increased risks of node positive disease, and breast cancer mortality. Both studies also observed that breast cancer incidence rates declined rapidly after cessation of estrogen–progestin formulation use. Given the considerable methodological differences between these studies, the similarity of results is remarkable and increases confidence in the validity of the conclusions.

In the WHI estrogen–progestin randomized trial, women who first used hormones within 5 years of menopause had somewhat greater breast cancer risk compared with those who first used hormones 5 years or more after menopause (<5 years of menopause, hazard ratio [HR] = 1.41, 95% confidence interval [CI] = 1.14 to 1.74 vs ≥5 years after menopause, HR = 1.15, 95% CI = 0.96 to 1.37, $P_{interaction}$ = .08) (4). This finding is consistent with that observed in the MWS, although the magnitude of the effect observed in the WHI estrogen–progestin randomized trial was less than that observed in the MWS. Similarly, in the WHI estrogen-only trial, there was evidence of a similar time from menopause effect, although breast cancer risk among estrogen-only users who first used hormones 5 years or more after menopause was somewhat reduced (HR = 0.63, 95% CI = 0.42 to 0.93), whereas no effect was seen in women initiating hormone therapy closer to menopause (HR = 1.06, 95% CI = 0.74 to 1.51) [$P_{interaction}$ = .07, modified from Prentice et al. (3)].

Although the similarities between the patterns of breast cancer risk observed in these two methodologically diverse studies increase the likely validity of the results, the difference in the magnitude of effects remains of interest, particularly for estrogen-only users, for which the interpretation is still unclear. In the MWS, statistically significant increases in breast cancer risk are associated with estrogen-only formulation use except in overweight and obese women, and in women who initiated hormone therapy further from menopause (1). Whereas many observational studies also find estrogen-only formulation use is associated with increased breast cancer incidence, especially for longer durations of use (10,11), other studies have reported conflicting results (12–14). After a mean 7.1-year intervention period in the WHI randomized trial, while there was less evidence for estrogen-only formulations reducing breast cancer incidence in women beginning hormone therapy closer to menopause, there was no evidence for estrogen-only formulations increasing breast cancer risk in any subgroup (15). In addition, a sensitivity analysis indicated that statistically significantly fewer breast cancers were diagnosed in WHI participants administered estrogen-only formulations who were adherent to study medication (HR = 0.67, 95% CI = 0.47 to 0.97, P = .03) (15). Similarly, in a large cohort of women with detailed information on mammogram frequency, a lower breast cancer incidence with estrogen-only formulation use for a period of 5 years or more was observed (relative risk = 0.92, 95% CI = 0.84 to 1.00) (14).

Beral et al. (1) indicate that the apparent discrepancy in findings between the MWS and the WHI is explained by the number of WHI participants who were obese and began estrogen therapy more than 5 years from menopause. However, in the WHI trial with 4692 women (of 10739 total) initiating estrogen therapy within 5 years from menopause by clinical decision or by entering the trial, no interaction between breast cancer risk and body weight and estrogen-only formulation use was observed (3). In our view, time from menopause differences may not be sufficient to completely explain these discordant results.

The distribution and assessment of mammography between hormone and non-hormone users also could have influenced the findings presented in the two reports regarding estrogen-only formulation use and breast cancer risk. Because of concerns of breast cancer incidence and effects on other breast symptoms, postmenopausal hormone therapy users have mammograms at more regular intervals then nonusers (16,17). Mammogram screening in these patients more commonly identifies slow growing hormone receptor–positive breast cancers with diagnosis occurring at an earlier stage (18,19). As a result, studies that cannot reliably control for mammogram frequency are potentially confounded because screened populations have substantially more breast cancers identified (20,21). In addition, prior mammography also is a risk factor for subsequent breast cancer in these patients and will likely influence the use of mammographic tumor detection in the future. Thus prior, and especially, subsequent mammography increases breast cancer detection compared to the rate seen with single mammograms.

In many observational studies, mammogram frequency has not been prospectively determined or included in analyses (10,22). Even when information on mammography is included, a concern arises because retrospective capture of mammogram history has

not proven reliable in previous studies (23). The MWS addressed many of these concerns by giving participants a mammogram on entry and by offering subsequent screening at 3-year intervals through the National Health Service. However, this does not necessarily assure comparability of subsequent screening between hormone therapy use groups. In addition, breast cancers identified by the entry mammogram were included in the analyses, introducing a cross-sectional component. In contrast, in the WHI randomized trials, all potential participants had screening mammograms and clinical breast examinations with clinical clearance required before entry into the trial. Subsequent mammograms were mandated yearly, and study medication was provided only when mammography and clinical examination clearance was provided (7,24). As a result, the frequency of yearly mammograms was closely comparable in placebo and hormone users with annual compliance exceeding 80% (7,25). If hormone users in the MWS had more mammograms after entry compared with non-hormone users, the estimated relative risks of breast cancer for hormone therapy users would be increased (16,17). Given the importance of reliable information regarding the frequency of mammograms in studies describing hormone therapy influences on breast cancer, future observational studies should use datasets in which reliable quantitative information on mammography is available.

Although a potential lower incidence in coronary heart disease risk is observed when hormone therapy is begun close to menopause (26), the findings from the current MWS report and the WHI randomized trial indicate that the opposite is true for breast cancer risk. Women who begin hormone therapy closer to menopause, as is the current common clinical practice, have a greater breast cancer risk than those beginning use further from menopause (1–4).

In summary, both the large MWS and the WHI randomized hormone therapy trial find time from menopause effects, and increased breast cancer risk are associated with estrogen–progestin formulation use. However, findings regarding estrogen-only formulation use are less congruent where the WHI randomized trial does not provide evidence supporting increased breast cancer risk. These conflicting data may be because of methodological differences in the two studies. Consequently, the question of the effect of estrogen-only formulation use on breast cancer risk in postmenopausal women, even with longer-term hormone use, still stands unanswered. Additional postintervention follow-up of the WHI estrogen-only clinical trial currently under way should lead to further clarification of this issue.

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