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The Collaborative Group on Hormonal Factors in Breast Cancer reported results of their study published in the *Lancet*. The study used combined data from 58 studies, 24 of which were prospective cohort studies, using a nested case-control design to examine breast cancer risk and accounting for factors such as age at first use, duration of use, and time since last use. Their nested case-control design is similar to a traditional case-control study in which the unaffected control population is selected from the same prospective cohort population as the cancer cases. This refinement of the case-control design reduces study-population differences; however, the limitations and biases of this approach are similar to the traditional case-control design.

The investigators compared users of estrogen alone versus never users and users of estrogen plus progestogen (continuous and intermittent) versus never users. Included in the meta-analysis were 108,647 incident cases of invasive breast cancer (mean age at time of diagnosis, 65 y) that were matched with up to four controls by age, year of birth, and geographic location. Results showed that the relative risks (RR) were greater for users of estrogen-plus-progestogen preparations than for estrogen alone, were greater in current than in past users, and increased with duration of use (in current and past users). For each hormone therapy (HT) type, there was a significant excess risk, even during years 1 to 4 of current use (RR, 1.6; 95% confidence interval [CI], 1.52-1.69 for estrogen plus progestogen; RR, 1.17; 95% CI, 1.10-1.26 for estrogen alone). The risks were greater with 5 to 14 years of use (RR, 2.08; 95% CI, 2.02-2.15 for estrogen plus progestogen; RR, 1.33; 95% CI, 1.28-1.37 for estrogen alone). Risks during years 5 to 14 were greater with daily use than with less frequently administered progestogens (RR, 2.30; 95% CI, 2.21-2.40 vs RR, 1.93; 95% CI, 1.84-2.01, respectively). No excess risk was seen with vaginal estrogen use. In past users, the authors report that excess risk persisted for more than a decade after stopping HT. The risk was attenuated with adiposity, with little risk seen in estrogen-alone users who were obese.

### **How should these results be interpreted?**

Most of the findings in this report are not new, and these results are associations. Therefore, cause-and-effect conclusions are not possible. In addition, the absolute risks are low and could be the result of bias rather than of any true effect of exposure. Further, this report does not speak to risk of breast cancer associated with current HT prescribing practices. The HT regimens used in this report included cases in women who were primarily taking oral estrogens, and most cases involving combined estrogen and progestogen regimens used medroxyprogesterone acetate (MPA) or norethindrone, which are now uncommonly used, given known adverse effects. In the prospective studies included in this report, micronized progesterone was used in only 50 cases, making it impossible to draw conclusions about risk associated with the preferred progestogen in the United States.

The WHI randomized trials still provide the best estimate of absolute risk for breast cancer associated with the use of HT. The hazard ratio (HR) was 1.21 (95% CI, 0.81-1.80) in women aged 50 to 59 years at randomization with conjugated equine estrogen (CEE) plus MPA versus placebo, accounting for six additional cases of invasive breast cancer per 10,000 person-years. The HR was

0.82 (95% CI, 0.50-1.34) versus placebo with CEE alone, accounting for five fewer cases of invasive breast cancer per 10,000 person-years.<sup>1</sup> The significant differences in the absolute risks for breast cancer between the WHI trials and this new [Lancet report](#) are concerning and may relate to potential biases associated with breast cancer epidemiologic studies.

The authors theorize that the difference in risk associated with estrogen alone in this trial compared with the WHI estrogen-alone trial could be the result of the timing of initiation of HT being later in WHI or because of potential masking of tumors related to increased breast density and resulting in decreased mammographic detection. These explanations are problematic. The analysis of women aged 50 to 59 years at randomization in the WHI still showed a reduced risk of breast cancer in the cumulative follow-up analyses (HR, 0.76; 95% CI, 0.52-1.11),<sup>1</sup> and the 18-year mortality data showed a 45% reduction in breast cancer mortality associated with estrogen alone,<sup>2</sup> thus essentially ruling out a masking effect. In addition, the effect of HT on breast density appears to be primarily related to the progestogen component rather than to estrogen.<sup>3,4</sup>

An important finding in this study is the association of increased breast cancer risk with obesity such that obesity attenuated the risk associated with both estrogen alone and estrogen with progestogen. Thus, the risks did not appear to be additive in women who are obese. In fact, the risk associated with being obese was about the same as being of normal weight and using estrogen alone for 5 years. The absolute risk of developing breast cancer over the 20-year-age range of 50 to 69 years was 6.3% and 7.2% for women who were overweight and obese who were not using HT, respectively. The 20-year risk was 7.4% for users of estrogen alone and 9% to 10% for users of estrogen plus progestogen therapy.

A concerning message in this study is the “increased” risk associated with HT used in younger postmenopausal women compared with younger postmenopausal women not on HT. It is known that breast cancer risk is reduced in women undergoing early menopause.<sup>5</sup> However, HT use in this younger population merely “increases” risk of breast cancer to that of their premenopausal peers. It is important to note the well-established increased risk for adverse long-term consequences associated with premature or early menopause (including increased risk for cognitive impairment, dementia, parkinsonism, osteoporosis, coronary artery disease, and increased mortality) without adequate HT given at least until the natural age of menopause.<sup>6</sup>

### **What does this mean for clinical practice?**

Now, more than ever, the management of menopause symptoms should be individualized, taking into account the severity of symptoms and a woman's risk factors as well as treatment goals and her personal preferences.<sup>7</sup> Overweight/obesity is an important risk factor for not only breast cancer but also for cardiovascular disease, and clinicians should counsel these women regarding lifestyle modification strategies. The timing of menopause is also an important consideration, with women undergoing premature/early menopause at increased risk for multiple potential adverse long-term health consequences if HT is avoided.

### **References**

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