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Editorial

Hormones and Breast Cancer: What's the Story?

Louise A. Brinton and James V. Lacey, Jr.

Hormonal and Reproductive Epidemiology Branch, National Cancer Institute, Rockville, Maryland

It has now been 30 years since the first epidemiologic report linked menopausal estrogen therapy—the exogenous estrogens that, along with progestins, came to be known as "hormone replacement therapy"—with an increased risk of breast cancer (1). Today, the body of evidence on this association is substantial and, perhaps, unique. This includes a pooled analysis published in 1997 by the Collaborative Group on Hormonal Factors and Breast Cancer based on over 50,000 cases and 100,000 controls (2). In addition, several clinical trials embedded in the Women's Health Initiative have generated experimental data allowing direct comparisons with a wealth of observational studies (3, 4). Furthermore, recent declines in population-based breast cancer incidence seem to be related to the fact that, starting around 2000 but especially after 2002 (when the Women's Health Initiative findings were published), millions of women stopped taking menopausal hormone therapy (5, 6).

Nonetheless, risk relationships with usage patterns of different regimens continue to generate considerable controversy (7), leading to questions regarding how hormones fully relate to breast cancer risk. Why has this exposure generated such diverse data? The answer undoubtedly relates to a combination of the intricacies of the drug exposures, intervening and modifying influences on these exposures, and etiologic and clinical complexities of breast malignancies.

Menopausal hormones were originally given almost exclusively as unopposed estrogens. Recognition that this formulation substantially increases the risk of endometrial cancer led to estrogens being prescribed in conjunction with a progestin for women with an intact uterus. Progestins were initially prescribed sequentially (e.g., for 10 or 15 days each month). To some extent, this reflected attempts to counter-balance recognized mitogenic effects of progestins on breast tissue (8) with antiproliferative effects of progestins on estrogen-induced changes in the endometrium (9). However, breakthrough bleeding, often associated with withdrawal of the progestins, led to increased preference for continuous administration of progestins. Temporal changes in availability of hormone therapies and patterns of use, such as shifts from unopposed estrogen to combined therapy, have obviously complicated epidemiologic interpretation of their effects. For many women and their health care providers, optimal management of associated bleeding was more art than science (10), and little attention was paid to whether these clinical experiences might, in fact, reflect underlying hormonal constitutions that were themselves clues to breast cancer risk.

What was clear, even early on, was the logical and plausible link between exogenous estrogens and breast cancer, as many recognized breast cancer risk factors, especially type and age at menopause, implicated a role for endogenous hormones. Yet these relationships raise issues of both confounding and self-selection bias. Early menopause, particularly surgical menopause caused by bilateral oophorectomy, is associated with a substantial reduction in breast cancer risk, but the resulting precipitous and sudden decline in endogenous hormone levels often leads to severe menopausal symptoms and a higher probability of use of menopausal hormone therapy. Evaluation of confounding effects, however, is complicated by the fact that, in many studies, it has not been possible to distinguish simple hysterectomy from total hysterectomy plus bilateral salpingo-oophorectomy. For the former, determining when menopause would have occurred if simple hysterectomy had not been performed invites substantial bias due to unknown ages at menopause (11, 12). Other major predictors of hormone use, such as severity of menopausal symptoms, might be independently associated with breast cancer risk and access to the medical system (which certainly affects breast cancer screening and detection), but have not been accounted for in many prior studies. Furthermore, because only half of the occurrence of breast cancer can be explained on the basis of identified risk factors (13), what about other life-style factors?

These lingering questions have not precluded numerous studies from demonstrating strong relations between breast cancer risk and use of combined estrogen-progestin therapy, particularly current and long-term use (7). However, other issues remain less clear. Comparisons of continuous versus sequential estrogen-plus-progestin regimens have produced varying results: most studies have found continuous exposures to be related to stronger increases in risk (14–16), but one has found just the opposite (17), and still others have found no notable differences (18, 19). The Women's Health Initiative estrogen-plus-progestin trial (4, 20) evaluated one regimen of continuous estrogen plus progestin (0.625 mg/day of conjugated equine estrogen plus 2.5 mg/day of medroxyprogesterone acetate) and essentially confirmed earlier findings from observational studies of increased risks among combined therapy

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Requests for reprints: Louise A. Brinton, Hormonal and Reproductive Epidemiology Branch, National Cancer Institute, NIH, DCEG, 6120 Executive Boulevard, EPS 5018, MSC 7234, Rockville, MD 20852-7234. Phone: 301-496-1693; Fax: 301-402-0916. E-mail: brinton@nih.gov

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users. However, the estrogen-alone trial among women who had had a hysterectomy, by reporting reduced risks among estrogen users (3), starkly contradicted 30 years' worth of observational studies that showed significantly increased risks (2). Why this divergence? If the potential selection and recall biases of observational studies were to blame for the discrepant results, why did observational and experimental studies agree about estrogen-plus-progestin risks but disagree on unopposed estrogen risks? And what does this say about the hormonal etiology of breast cancer, if estrogens alone did not affect breast cancer risk in a well-designed clinical trial?

In fact, results on unopposed estrogens from observational studies have varied from null associations to increased risks, albeit lesser increases than those noted for combined therapy. In contrast to many U.S. studies, most European observational studies have generally noted increases in breast cancer risk associated with unopposed estrogens (21, 22). This has prompted the suggestion that differences in results may have reflected the more common usage in Europe of estrogens with more androgenic properties, namely estrogen 17β-estradiol, as contrasted with conjugated equine estrogens in the United States. However, data from the recent Million Women Study in the United Kingdom showed no difference in breast cancer risk according to the type of estrogen used (23). What may be a more viable explanation are the differences in user characteristics between European and American women, including obesity, which is emerging as a fairly consistent effect modifier of hormone effects. Numerous studies have now shown stronger hormone relationships among thinner women (2, 19, 21, 23–27), supporting the notion of higher endogenous hormones in heavier women due to peripheral conversion of androgens to estrogens in adipose tissue (28) and less effective metabolism of exogenous hormones. In fact, the high prevalence of overweight and obesity in the Women's Health Initiative estrogen-alone trial (nearly 80% of study participants) may explain the reported inverse association between unopposed estrogens and breast cancer.

An additional explanation for divergent effects relates to duration of exposure to unopposed estrogens, based on recent findings from the Nurses' Health Study that effects on breast cancer risk did not become apparent until after 15 years of use (24), consistent with the notion of a long latency period for chemicals that affect breast cancer risk. With only 7.1 years of follow-up in the Women's Health Initiative estrogen alone trial (3), it would have been difficult to observe such effects. Thus, the combination of limited exposure and relatively few thin women (in whom effects would be most enhanced) could easily have resulted in the null results for unopposed estrogens that were reported from the WHI trial and a number of observational studies. Additional studies that fully consider the effects of obesity, as well as other hormonally related risk factors, on specific usage pattern should continue to be pursued to fully understand these complex relationships.

A final consideration is the increasing recognition of etiologic heterogeneity for breast cancer. Thus, recent studies have shown the strongest effects emerging for early-stage, lobular histology, and hormone receptor–positive malignancies. Earlier work suggested that combination therapy specifically increased the risk of lobular tumors (14, 18, 29, 30), but new methods to disentangle the effects of highly correlated tumor characteristics (31) are showing instead that combination therapy is more strongly related to early-stage than late-stage tumors, regardless of histology. Further work in this area will be watched closely, provided improved methods of understanding the etiologic heterogeneity of breast cancers can be merged with the proper attention to currency, duration, regimen, and mode (few studies have evaluated effects of pills versus other modes, such as patches or creams) of hormone therapy exposure.

Breast cancer epidemiology, not to mention women's health on the whole, is better off for having spent the last 30 years chipping away at how menopausal hormones might affect breast cancer risk. However, the unanswered questions highlighted here loom even larger as hormone therapy use patterns continue to change, as clues emerge about the tremendous complexity and importance of the menopausal transition in women's health, and as new genetic, molecular, and clinical tools emerge for understanding how breast cancers develop. Although we anticipate that the effects of menopausal hormones will continue to generate considerable controversy, the last 30 years have provided the groundwork for further developing and improving methods for assessing and understanding breast cancer risks.

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