Hormone Replacement and Breast Cancer Risk: Reconsidering the Data

November 12, 2009
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In their recent commentary (Oncology 23:639-641, 2009), Labriola and colleagues reviewed the data on “natural” hormone replacement and breast cancer risk. The “natural” agents were bioidentical and phytoestrogen supplements to manage vasomotor symptoms in breast cancer patients.

In their recent commentary (*ONCOLOGY* 23:639-641, 2009), Labriola and colleagues reviewed the data on “natural” hormone replacement and breast cancer risk. The “natural” agents were bioidentical and phytoestrogen supplements to manage vasomotor symptoms in breast cancer patients. The rationale for the alternative was the fact that in one large study, the women who took conventional hormone replacement therapy (HRT) preparations had a higher risk for breast cancer, and therefore, similar preparations could not be used in breast cancer survivors with vasomotor symptoms. The authors justified that statement by citing the 2002 Women’s Health Initiative (WHI) study.[1] This study compared estrogen plus progestin with a placebo. Another prospective randomized group mentioned by the authors received estrogen alone compared to a placebo, but this study was not referenced.

We remain amazed at the literature that incriminates estrogen/progestin and estrogen alone, quoting the 2002 WHI article for estrogen/progestin even though there have been over 100 articles from the WHI since then, in which a significant amount of the 2002 data have been temporized or shown not to support the conclusions of the 2002 publication. Many articles have been written severely criticizing the methodology of the WHI study, including eligibility, surveillance, presentation of nonadjudicated data, and certainly the age of the participants, to name a few. We are not writing to reiterate those faults, but to suggest that recent WHI data do not note an increase in breast cancer risk.

Evolving WHI Data

The 2002 article stated that the hazard ratio (HR) for estrogen plus progestin was 1.26 (95% confidence interval [CI] = 1.0–1.59), which is not statistically significant but was the reason for stopping the study. In a 2003 article, the HR was 1.24 (95% CI = 1.01–1.54), now barely significant as the number of breast cancers had increased since the 2002 publication.[2]

In the 2006 publication on estrogen plus progestin, the adjusted HR was 1.20 (95% CI = 0.94–1.53).[3] Although the WHI investigators may have been under significant pressure to publish data from the study, we suggest that it may have been reported prematurely, and the bulk of the patients were elderly women upon enrollment. More women who were 50 to 59 years of age, or less than 10 years from menopause should have ben enrolled. In truth, how many 70-year-old women are placed on HRT for the first time? In the 50- to 59-year-old age group, not only was there no increased risk, but the HR was actually less than 1.[4] In their rather detailed article on younger women with cardiovascular disease, the investigators commented that women less than 10 years since menopause had an HR of 1.19 (95% CI = 0.84–1.70) for breast cancer.[4] This is certainly not statistically significant.

In 2004, the data on estrogen alone was presented for the first time (a prospective randomized study of about 10,000 women compared to over 16,000 women in the estrogen/progestin study). The HR for breast cancer was 0.77 (95% CI = 0.59–1.01).[5] In the 50- to 59-year-olds, the HR was 0.72 (95% CI = 0.43–1.21). In 2006, a 7.1-year follow-up of estrogen and breast cancer risk was published. If a woman had no prior replacement therapy history, her HR was 0.76 (95% CI = 0.58–0.99), her risk for ductal cancer was 0.71 (95% CI = 0.52–0.99), and if she was adherent in regard to taking her medication, the HR was 0.67 (95% CI = 0.47–0.97).[6] Therefore, we question the assumption that estrogen/progestin and estrogen alone increase the risk of breast cancer using the studies that the commentary referenced.

Historical Perspective

That being the case, why is traditional HRT contraindicated in women who have had breast cancer? From a historical perspective, for many years estrogen was used as primary treatment for postmenopausal women with recurrent or metastatic breast cancer. In the 1970s and early 1980s, several prospective randomized studies compared estrogen with tamoxifen in such women. The results were similar.[7] Since alternatives, as noted in the commentary, are not very effective, numerous published articles have noted that recurrence rates in breast cancer survivors who chose to take HRT for symptom relief were very low. Yes, these were retrospective studies with built-in bias. One bias may come from the woman herself, as she chooses to take the hormones. Several case control and cohort studies have compared HRT with such controls, and in over 1,200 cases and 3,800 controls, there was twice as many recurrences in the controls as in those on hormones.[6] Two prospective randomized studies have compared hormones with controls. Both of these studies originated in Sweden. In the HABITS study, 442 women were randomized to receive hormones or no hormones for 2 years. The initial report in 2004 noted an HR of 3.3 (95% CI = 1.5–7.4), and the study was stopped.[9] A 4-year follow-up noted an adjusted HR of 2.2 (95% CI = 1.0–5.0).[10] The other study (the Stockholm trial) randomized 359 breast cancer women to 5 years of hormones or no hormones. Data reported in 2008 noted an HR of 0.8 (95% CI = 0.35–1.9).[11] The investigators found no difference in breast cancer deaths between the hormone and no-hormone groups in either study.

Importance of Options

These data on HRT in breast cancer patients are not well disseminated. In many instances, women are told that HRT is absolutely contraindicated, yet we are unaware of any clinical data to substantiate that statement. In view of the present data, we feel it is important for women to know there are choices, and current data would suggest that there is no increased risk of recurrence with HRT. Once women are given data and they have made a decision, we as health-care professionals should support them and not criticize that decision.

Why is HRT contraindicated in a 50-year-old newly menopausal breast cancer survivor who was successfully treated for her cancer at 40 years of age? Hasn't she been getting endogenous estrogen for the last 10 years? This question and others make these authors question the tenet that postmenopausal estrogen therapy is always contraindicated in a woman who has had breast cancer.

The Authors Reply: Dan Labriola, Kathleen Pratt, and Patrick Bufi respond to this Letter to the Editor

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