

Editorial

Hormone Replacement Therapy: A Promoter and Modulator of Breast Cancer

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Pappo and colleagues¹ present a convincing argument that hormone replacement therapy (HRT) leads to a distinct malignant phenotype in women developing breast cancer. It is clear that the risk of breast cancer increases according to the length of exposure to exogenous estrogens and decreases with time following cessation of therapy.² What has also become apparent is that the types of cancers developing in hormone users are more likely to carry a more favorable prognosis.^{1,3} It is surprising that, according to most reports,^{1,3} estrogen and progesterone receptor expression is not modulated by HRT.

Findings from the Women's Health Initiative (WHI) have had a significant impact on prevalent sentiments in the medical community and in women considering HRT. There has been a prompt shift from an increasingly supportive stance in favor of HRT over the past 2 decades to one of increased reservation. Initial enthusiasm for HRT was based upon nonrandomized observations of an overall mortality reduction, attributed to a dominating decrease in cardiovascular mortality and a diminishing increase in breast cancer.⁴ Perceptions were altered when the WHI reported the first randomized trial to evaluate the risks and benefits of HRT. Unexpectedly, the main endpoint of the study, cardiovascular disease, was increased with the use of hormones.⁵ As anticipated, the incidence of osteoporosis and colorectal cancer decreased while breast cancer and thromboembolism increased. The study was concluded early, as increased numbers of invasive breast cancers, cardiovascular events, strokes, and pulmonary emboli were not offset by smaller reductions in hip fractures and colorectal carci-

nomas. Among over 16,000 women randomized to the two treatment arms, there was a 26% increase in breast cancer (38 versus 30 cases per 10,000 person-years), with no difference in the incidence of in situ disease. There was no difference in breast cancer mortality or overall mortality between the two treatment arms. Although these observations were significant, important quality-of-life variables such as urogenital atrophy and vasomotor instability were not assessed. A simultaneous strength and limitation of the trial was that the analysis was limited to a single drug regimen, consisting of 0.625 mg of conjugated equine estrogen and 2.5 mg of medroxyprogesterone acetate (Prempro; Wyeth Ayerst, Philadelphia, PA), raising the possibility of a different outcome with single-agent HRT or combination HRT at a different dose. In the absence of any differences in overall mortality observed in the WHI study or any other report, it is difficult to support a blanket recommendation against HRT.

Rather than viewing HRT as an initiator of breast cancer, a promoter concept is supported by observations in the reports of Pappo et al.¹ and others.^{1,5} Equivalent percentages of in situ carcinoma in users and nonusers of HRT suggest that invasive cancers that are initiated through a stepwise process from atypia to in situ and invasion are not affected by exogenous hormones.^{1,5} The promoter concept is also supported by the observation of a younger average age at diagnosis of cancer for patients using HRT as compared to those with no history of hormone use.^{3,6} In this context, HRT can be viewed as an accelerant, advancing the progression of an already evolving malignancy to a point of clinical detection at an earlier age in a user. The strongest evidence in favor of the promoter theory is the rapid drop in breast cancer risk after cessation of HRT. Five years following cessation of therapy and lack of this promoter, patients assume a risk of breast cancer equivalent to that observed in nonusers.²

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The perception that HRT selectively promotes tumors sensitive to hormones is oddly inaccurate by most reports, as the distribution of estrogen receptor–positive tumors is similar between users and nonusers.^{1,3} In experimental models, exogenous hormones are known to downregulate receptor concentrations. Upregulation of cellular receptors is also thought to occur in aging postmenopausal patients, accounting for a steadily increasing incidence of estrogen receptor–positive tumors with advancing age. The observation that tamoxifen is effective in preventing only estrogen receptor–positive tumors⁷ suggests that prevention and promotion of hormone-sensitive tumors occur through different molecular pathways.

A consistently recognized difference between tumors in users and nonusers of HRT has been favorable characteristics of tumors in users. Smaller, low-grade tumors with desirable histologic categories, lower proliferation rates, and lower stage are more prevalent in users.^{1,3,6,8} A time-dependent proliferation index in chronic users points to HRT as a genuine modulator of phenotype expression.⁸

Breast cancer mortality but not overall mortality appears to be dependent upon length of therapy.⁴ This delay and the lack of a mortality difference observed in the WHI study may reflect more frequent but less aggressive breast cancers that are promoted and modulated with HRT. What remains unclear is whether HRT modulates tumors early in carcinogenesis, serving as a selective

stimulant of a specific subset of cancer cells, or later in the progression of established tumors. The future challenge will be to identify patients who will and will not experience the negative effects of HRT or to identify a superior substitute that selectively exhibits the same desirable qualities.

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