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The effects of hormone replacement therapy on postmenopausal breast cancer biology and survival

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Abstract

BACKGROUND: The goal of this study was to compare the characteristics of breast cancers and survival rates in HRT users versus nonusers.

METHODS: Data were analyzed for 1055 patients ≥50 years of age who had definitive therapy for breast cancer from 1994 through 2002.

RESULTS: There were 471 (45%) HRT users. The median age at diagnosis was 61.0 years for HRT users and 68.0 years for HRT nonusers (P < .001). HRT users more often had tumors that were <1 cm (P = .007), node negative (P = .033), and grade I (P = .016). HRT users had a decreased risk of death versus nonusers (hazard ratio = .438, 95% confidence limit = .263 to .729, P = .002).

CONCLUSIONS: HRT users developed breast cancer at a younger age than nonusers; HRT use was associated with the development of biologically more favorable cancers than those that developed in nonusers; and overall and disease-free survival rates were higher in HRT users than nonusers.

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An association between postmenopausal hormone replacement therapy (HRT) and an increased risk of developing breast cancer was suggested by results from the Women’s Health Initiative (WHI) trial, which was published in 2002.¹ These highly publicized results led promptly to a 50% decrease in prescriptions for HRT in the United States between 2000 and mid-2003.² Data from the Surveillance, Epidemiology, and End Results (SEER) database then demonstrated a 7% decrease in the age-adjusted incidence rate for invasive breast cancer in 2003 versus 2002.³ The reduction in incidence was most evident in women ≥50 years old and was confined almost exclusively to those with ER+ versus ER-cancers. These data were thought by many to provide insight into the etiology of postmenopausal invasive breast cancer.

Although there may be risk enhancement for the development of postmenopausal invasive breast cancer in those who take HRT, separate studies have been reported in which breast cancers associated with HRT use were biologically more favorable than those in HRT nonusers.⁴–⁶ There has also been considerable debate regarding whether HRT has an impact on breast cancer survival rates.⁷–⁹

This single-institution long-term study, performed in the setting of a community service screening mammography program, was designed prospectively to test whether breast cancer in HRT users was more favorable than in nonusers.

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Patients and Methods

From 1994 to 2002, data on 1055 patients ≥50 years of age with breast cancer (including ductal carcinoma in situ) were collected concurrently with definitive surgical treatment. After obtaining informed written consent from patients, information regarding demographics, diagnostics, and treatment was entered into a comprehensive database approved by the Institutional Review Board. Data on tumor characteristics, such as size, axillary lymph node involvement, histologic features, grade, ploidy, and estrogen-receptor (ER) status, were prospectively collected. Follow-up data on patient status were obtained by direct patient contact as well as use of the hospital Tumor Registry and National Death Index.

Statistical analyses

Independent 2 sample Student t tests, Wilcoxon 2-sample tests, and chi-squared tests were used to assess patients’ characteristics between groups. Cox proportional hazard (PH) models and Kaplan-Meier survival plots were used to perform time-to-event analyses, and a piece-wise exponential model was used to estimate the annual risk of recurrence.10 In univariate Cox PH models, potential variables had to satisfy proportional hazard assumptions, which were examined by log (−log[S(t)]) plots and tested as time-dependent covariates in the Cox models. Intrasubject correlation was adjusted in the Cox PH models using the robust sandwich variance estimate of Lin and Wei.11 Covariates with P < .25 in univariate analyses were put into multivariable models using a backward selection method. Covariates satisfying a “stay” criterion (alpha .05) were retained in the multivariable models. Hazard ratios with 95% confidence intervals were estimated for the Cox models. Statistical analyses were performed using SAS version 9.1 software (SAS Institute, Cary, NC).

Results

Tumor characteristics and survival for women ≥50 years old

The operational definition of the onset of menopause can be problematic. Thus, to compare homogeneous subsets of patients, analyses of tumor characteristics and survival were done for 1055 patients who were ≥50 years of age. There were 471 patients (45%) who used HRT. The median age at diagnosis of breast cancer was 61.0 years for HRT users and 68.0 years for HRT nonusers (P < .001). However, the age of onset of menopause and the number of patients with a first-degree relative having breast cancer were similar for HRT users and nonusers. The frequency of ductal carcinoma in situ was similar for HRT users (16.1%) and nonusers (14.5%). ER status was positive in 66% of HRT users and in 64% of nonusers.

Compared with HRT nonusers, HRT use was associated with cancers that were more often smaller rather than larger than 1 cm (P = .007), more often node negative than node positive (P = .033), and more often low grade (I) rather than high grade (II and III) (P = .016).

In a univariate analysis, HRT use was associated with better overall survival than HRT nonuse. Significant variables from the univariate analysis used in the subsequent multivariable Cox PH model were HRT use, size, stage, and ploidy. After adjusting for these variables, HRT users independently had a lower risk of death than HRT nonusers (hazard ratio (HR) .438, 95% confidence limit .263 to .729, P = .002).

Table 1 lists the statistically significant variables, HRs, and P values derived from Cox PH analyses of overall survival. The 5-year overall survival (OS) and disease-free survival (DFS) rates were stratified according to ER status. As shown in Figs. 1 and 2, 5-year OS and DFS rates were significantly better in HRT users than nonusers, regardless of the cancer’s ER status. The use of adjuvant therapy was not a significant variable in either the OS or DFS analysis.

Comments

Review of the literature on HRT and breast cancer

The controversy regarding HRT and its relationship to breast cancer was initiated by a case-control study by Ross et al.12 Since then, a plethora of studies eventually led to the publication of a meta-analysis of >150,000 women, which confirmed that women who had received HRT for >5 years had a relative risk of 1.35 for the development of breast
cancer, accruing a 2.3% increase in breast cancer risk for each year of HRT use. Of perhaps equal importance, risk reverted to baseline for those who had stopped HRT for 5 years. Stated differently, the increased risk appeared to be confined to the time during which HRT was used. These data were confirmed using a longitudinal population-based prescription database and cancer registry from Denmark. In the United States, results from the WHI randomized trial of estrogen plus progestin versus placebo demonstrated an increased risk (relative risk = 1.26) of developing breast cancer 5 years after initiating combined estrogen–progestin HRT.

In addition to demonstrating increased risk of developing breast cancer with HRT use, studies have also evaluated the effect of HRT on the histology of breast cancers. Gapstur et al, using data from the Iowa Women’s Health Study, identified an increased incidence of invasive cancers with favorable histology (medullary, mucinous, tubular, and papillary carcinomas) in HRT users. In the UK 1 Million Women study, Reeves et al reported that invasive lobular and tubular cancers were more strongly associated with HRT use than invasive ductal cancer. These investigators also performed a meta-analysis of 10 previous studies that had assessed the effects of HRT on histologic types of breast cancer. Despite slight differences in definitions of histologic types, there was consistent evidence for a greater effect on the risk of lobular and tubular cancers compared with ductal cancer not otherwise specified. Using a Kaiser Permanente of Northern California database linking cancer registry and pharmacy data, Kumar et al found that women ≥50 years old who were prescribed any estrogen-containing HRT were more likely to have low-grade and early-stage tumors than HRT nonusers. Increasing duration of any progesterone use was also significantly associated with a higher proportion of low- and intermediate-grade than high-grade tumors. In contrast, data from the WHI trial did not demonstrate a tendency toward biologically more favorable cancers in those receiving estrogen plus progestin versus placebo. However, the data in this trial were confounded by 2 factors: the mean age at entry of subjects was 63 years, and 27% of subjects had previous exposure to HRT. In addition, with short-term follow-up, an overall survival difference was not demonstrated in the trial. Perhaps low-grade and favorable-stage cancers associated with HRT use, such as those seen in the current study and presenting at a mean age of 61 years, would have already been detected, rendering women with those cancers ineligible for enrollment in the WHI trial. The corollary possibility exists that the effects of HRT on carcinogenesis are time sensitive and most prominent during the early menopausal years.

Evaluating the linkage between favorable biology and survival, Bonnier et al noted that HRT users had more low-grade tumors and a tendency toward better survival rates (P = .05) than HRT nonusers. Using data from the Breast Cancer Detection Demonstration Project, Schairer et al found that HRT users had decreased breast cancer mortality, although the decrease was not caused by differences in tumor size, stage, or grade between HRT users and nonusers. HRT use at the time of diagnosis was reported by Fletcher et al to be associated with modestly improved survival rates from breast cancer. These differences appeared to be explained in part by the influence of HRT on tumor grade. From all of these observational studies, it is possible to conclude that favorable histology or improved survival in those using HRT may be caused by: (a) biases in surveillance or selection; (b) the “healthier estrogen-user” phenomenon; or (c) a real modulating effect of HRT on tumor biology.

Limitations of the study

Three potential limitations of this study bear discussion. First, this was an observational analysis of an opportunistic community-based screening program, not a randomized study. Treatment for all breast cancer patients in this program was routinely discussed at a weekly multidisciplinary conference. Therefore, although there was a uniformly applied treatment strategy for most patients, there was no standardized treatment plan across subsets of breast cancer.

Figure 1 OS for 1055 patients ≥50 years of age according to HRT use and ER status of the cancer.

Figure 2 DFS for 1055 patients ≥50 years of age according to HRT use and ER status of the cancer.
patients. Second, with the data from this study, it was not possible to address the “healthier estrogen-user” phenomenon, which implies that HRT users may be generally healthier or more health conscious individuals than HRT nonusers, thus accounting for the differences in survival rates by unmeasured variables. It may be that there is a disproportionately high number of “healthier estrogen-users” in observational studies, which could skew tumor characteristics and survival analyses in favor of HRT users. Furthermore, data on other potentially confounding variables, such as body-mass index, were not collected routinely throughout the course of the study. Third, the duration of HRT use, type of pill (pure estrogen vs combinations of estrogen and progestin), and total hormone dose were not accurately accounted for in this study, thus limiting comparisons of these data with previous publications that have addressed the relationship between breast cancer risk and hormone exposure. Observational studies of the relationship between HRT and breast cancer have typically been confounded by multiple drug doses, schedules, and routes of administration.

In closing, the following conclusions were drawn from this single-institution prospective study of 1055 women ≥50 years of age with breast cancer detected in a community service screening program:

1. Despite a similar age for onset of menopause between the 2 groups, HRT users developed breast cancer at a younger age than nonusers.
2. HRT use was associated with the development of biologically more favorable cancers (smaller, lower grade, node negative) than those developing in nonusers.
3. Breast cancer OS and DFS rates were higher in HRT users than nonusers regardless of the tumor’s ER status.

References


Discussion

Margo C. Shoup, M.D. (Maywood, IL): I congratulate you on conducting a very large series of breast cancer patients with and without HRT use. I have 3 questions, some of which you have already touched on. First, were all the patients in the HRT group using HRT at the time of their cancer diagnosis, or do you know the interval between time of discontinued HRT use and the diagnosis of cancer?

Second, you said you could not account for the duration of HRT use, but do you have any sense of the duration? In the WHI, there was a significantly higher relative risk of breast cancer with HRT use >5 years versus <5 years. What explanation do you have for why HRT users had biologically better cancers? It seems to me it would simply be that these patients are being followed-up more closely, are undergoing more regular mammograms, have physical examinations more vigilantly, and just have better medical care in general. Finally, because HRT users had better survival than nonusers, should breast cancer patients be taking HRT?

Stephen F. Sener, M.D. (Evanston, IL): First, approximately 70% of HRT users were on hormones at the time of their breast cancer diagnosis. There was a smaller subset of older women >70 years of age who had taken estrogen or combined estrogen/progesterone for >10 years and then stopped it and had been off HRT for 10 to 15 years.

Second, I wish I had an answer to explain the mechanism for why HRT users had biologically more favorable cancers. However, the issue of the “healthier estrogen-user” phenomenon is a problem here that we have not quite figured out. One way to examine the question might be to look at the intervals between mammograms leading up to the diagnosis in HRT users versus nonusers.

Third, I do not know the answer to whether women who have had breast cancer should be on estrogen stimulation; it’s a provocative question. However, women with breast
cancer have already demonstrated that they have the initiating agent present. If you believe that HRT promotes cancer, it would be problematic to expose patients to a promoter who have an already-demonstrated initiator. Such a clinical trial could be a tough sell.

Lynne Jalovec, M.D. (Peoria, IL): When I first started to hear of your article, I thought, “Well, I’m just going to hear what I’ve heard before.” However, there’s some very interesting information in this paper. Survival of these patients who were on hormones and who had ER-negative tumors was better than for those never on hormones who had ER-positive tumors. This is a piece of information I have never seen written before, so I think this is a strong point of your article. Were the rates of mammographically detected tumors different in the HRT patients?

Stephen F. Sener, M.D. (Evanston, IL): Approximately 44% of HRT users and nonusers had their tumors detected only by mammography. Therefore, there’s no difference between the 2 groups regarding method of cancer detection.