Prediagnostic Use of Hormone Therapy and Mortality After Breast Cancer

Polly A. Newcomb,[1,2] Kathleen M. Egan,[3] Amy Trentham-Dietz,[2] Linda Titus-Ernstoff,[6] John A. Baron,[6] John M. Hampton,[2] Meir J. Stampfer,[4,5] and Walter C. Willett[4,5]

[1]Fred Hutchinson Cancer Research Center, Seattle, Washington; [2]University of Wisconsin Paul P. Carbone Comprehensive Cancer Center, Madison, Wisconsin; [3]H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida; [4]Harvard School of Public Health and [5]Harvard Medical School, and Brigham and Women's Hospital, Boston, Massachusetts; and [6]Norris Cotton Cancer Center, Lebanon, New Hampshire

Abstract

Background: **A few studies have observed reduced breast cancer mortality in women who used hormone therapy before diagnosis. Due to the high prevalence of past and current hormone use, it is important to investigate whether these preparations are related to breast cancer mortality.**

Methods: **To evaluate the influence of prediagnostic use of hormone therapy on breast cancer mortality, a prospective cohort of 12,269 women ages 50 years or more diagnosed with incident invasive breast cancer and residents of Wisconsin, Massachusetts, or New Hampshire were enrolled in three phases beginning in 1988. They were followed for death until December 31, 2005, using the National Death Index. Cumulative mortality and multivariable adjusted hazard rate ratios for breast cancer and other mortality causes were calculated for women according to any hormone therapy use, and for exclusive use of estrogen or estrogen-progestin (EP).**

Results: **During an average 10.3 years of follow-up, 1,690 deaths from breast cancer were documented. Cumulative mortality from breast cancer was lower among hormone therapy users, specifically current users at the time of diagnosis, and EP users, compared with nonusers. Adjusted survival varied by type and duration of hormone therapy before diagnosis. A reduced risk of death from breast cancer was associated with EP preparations (hazard rate ratio, 0.73; 0.59-0.91) and with ≥5 years of EP use (0.60; 0.43-0.84). No association was observed for women who were former or current users of E-alone preparations.**

Conclusions: **Although use of combined EP preparations increases breast cancer risk, in this study, use of these hormones before diagnosis was associated with reduced risk of death after a breast cancer diagnosis. The better survival among users, particularly of EP, persisted after adjustment of screening, stage, and measured confounders.** (Cancer Epidemiol Biomarkers Prev 2008;17(4):864–71)

Introduction

Compelling evidence shows that hormone therapy use, particularly formulations containing progestins, increases breast cancer incidence (1, 2). However, reduced breast cancer mortality has been observed among women using hormone therapy before breast cancer diagnosis in several studies (3-11). It is not yet clear whether associations with survival are attributable to the hormones themselves or to the healthier profiles, screening habits, or treatment choices of women prescribed hormones (8-10). An inverse relation between hormone therapy use and breast cancer mortality might also be explained by more favorable tumor profiles, and therefore improved prognosis among hormone therapy users compared with nonusers (11-14).

A substantial proportion of women in the United States have used hormone therapy in their lifetimes, including about half of postmenopausal U.S. women ages 50 to 69 years (15, 16). Given the large number of women with a history of hormone therapy use, an established risk factor for breast cancer incidence, it is important to establish whether the use of these preparations is also related to survival. Previous studies have been limited by modest sample sizes, restriction to high-risk groups, and inability to evaluate the characteristics of users and subtypes of tumors (3-6, 11, 17-19). We therefore examined the relation between prediagnostic hormone therapy use and mortality (from breast cancer and all causes) in a study that addressed these limitations, using data from a well-characterized cohort of 12,269 women with incident invasive breast cancer (20, 21).

Materials and Methods

Collaborative Breast Cancer Study Cohort. The Collaborative Breast Cancer Study Cohort began in 1988 as a multisite population-based case-control study of risk factors for breast cancer (20, 21). A total of 18,269 women with incident invasive breast cancer were enrolled during three successive phases of this study. Age eligibility varied over the course of the study, which included women ages 20 to 74 years in phase 1 (1988-1991), ages 50 to 79 years in phase 2 (1992-1995), and ages 20 to 69 years in phase 3 (1997-2001). Approximately 81% of eligible case women participated in the case-control study.

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Requests for reprints: Polly A. Newcomb, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, Seattle, WA 98109. Phone: 206-667-3476; Fax: 206-667-7850. E-mail: pnewcomb@fhcrc.org

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Table 1. Baseline characteristics of 12,269 women with breast cancer by hormone therapy use

Characteristics	HT never users	HT ever users		
	Never (n = 8,071)	E-only (n = 2,258)	E+P (n = 1,340)	Other/unknown (n = 600)
Age at diagnosis				
50-54	1,342 (16.63%)	335 (14.84%)	379 (28.28%)	107 (17.83%)
55-59	1,116 (13.83%)	445 (19.71%)	479 (35.75%)	152 (25.33%)
60-64	1,586 (19.65%)	497 (22.01%)	324 (24.18%)	154 (25.67%)
65-69	2,079 (25.76%)	517 (22.90%)	132 (9.85%)	112 (18.67%)
70-74	1,332 (16.50%)	344 (15.23%)	22 (1.64%)	67 (11.17%)
75-79	616 (7.63%)	120 (5.31%)	4 (0.30%)	8 (1.33%)
Menopausal status				
Postmenopausal	7,109 (88.08%)	2,094 (92.74%)	1,154 (86.12%)	550 (91.67%)
Premenopausal	807 (10.00%)	35 (1.55%)	115 (8.58%)	28 (4.67%)
Unknown	155 (1.92%)	129 (5.71%)	71 (5.30%)	22 (3.67%)
BMI				
<22.8	1,724 (21.36%)	577 (25.55%)	409 (30.52%)	192 (32.00%)
22.8-25.5	1,878 (23.27%)	565 (25.02%)	348 (25.97%)	152 (25.33%)
25.6-29.1	2,014 (24.95%)	574 (25.42%)	314 (23.43%)	140 (23.33%)
≥29.2	2,164 (26.81%)	493 (21.83%)	245 (18.28%)	108 (18.00%)
Unknown	291 (3.61%)	49 (2.17%)	24 (1.79%)	8 (1.33%)
Smoking history				
Never	3,971 (49.20%)	1,114 (49.34%)	572 (42.69%)	262 (43.67%)
Former	2,509 (31.09%)	752 (33.30%)	524 (39.10%)	222 (37.00%)
Current	1,575 (19.51%)	389 (17.23%)	242 (18.06%)	115 (19.17%)
Missing	16 (0.20%)	3 (0.13%)	2 (0.15%)	1 (0.17%)
History of mammography screening				
Never	2,293 (28.41%)	249 (11.03%)	40 (2.99%)	73 (12.17%)
Ever	5,064 (62.74%)	1,842 (81.58%)	37 (2.76%)	40 (6.67%)
Extent of disease/stage				
Local	4,836 (59.92%)	1,470 (65.10%)	914 (68.21%)	381 (63.50%)
Regional	2,191 (27.15%)	539 (23.87%)	322 (24.03%)	159 (26.50%)
Distant	249 (3.09%)	36 (1.59%)	13 (0.97%)	10 (1.67%)
Unknown	795 (9.85%)	213 (9.43%)	91 (6.79%)	50 (8.33%)
Histologic type				
Lobular	729 (9.03%)	219 (9.70%)	155 (11.57%)	56 (9.33%)
Nonlobular	7,342 (90.97%)	2,039 (90.30%)	1,185 (88.43%)	544 (90.67%)

Abbreviation: HT, hormone therapy.

Ascertainment of Exposure. All subjects completed a structured telephone interview that included detailed information on prediagnosis use of hormone therapy, including formulation; routes of administration; frequency for each episode of use; and information on other breast cancer risk factors, specifically reproductive and menstrual history, consumption of specific foods and beverages including alcohol, physical activity, height and weight history, medication use, and personal and family history of cancer. Women were asked to report exposures occurring in the year before diagnosis, ~2 years before interview. Format of the questions on hormone therapy use varied slightly depending on period of data collection; all versions after 1989 elicited a standard history of hormone therapy, including type, duration, age started, and time since last use. Other questions were phrased somewhat differently but were readily summarized across study periods. For example, questions on mammography screening always asked about regular screening the year before diagnosis but the completeness of history differed somewhat by study instrument.

Clinical information obtained from state cancer registries included date of diagnosis, extent of disease (local, regional and distant), and histology (22). In Wisconsin only, information was available on the first course of treatment (surgery, chemotherapy, radiation, and hormonal treatment).

Population for Analysis. The analysis was limited to women ages 50 years or more at the time of diagnosis, for consistency with all three studies (n = 14,462). The following women were excluded: 1,407 were interviewed before complete hormone therapy questions were included in the interview; 662 had missing information on hormone therapy usage; 116 used hormones before age 40 years or surgical menopause, and 8 women were lost during follow-up. Thus, 12,269 women were included in the analysis.

Identification of Deaths. Deaths were ascertained up to December 31, 2005, using automated searches of the National Death Index (23). The underlying cause of death on the death certificate was assigned according to the International Classification of Diseases, Ninth Revision (ICD-9; through 1998; ref. 24) and ICD-10 (1999-2005; ref. 25). We evaluated both death from breast cancer (ICD-9 codes 174 and ICD-10 codes C50) and all-cause mortality. Deaths from other causes, specifically cerebrovascular (ICD-10 I60-I69) and cardiovascular diseases (ICD-10, I00-I09, I11, I13, I20-I51), were also examined.

Statistical Analysis. Survival time was calculated as the number of months from date of diagnosis to date of death, or December 31, 2005, for surviving women. Women were classified as ever/never having used hormone therapy; women who had ever used hormone therapy were then further classified by current use or

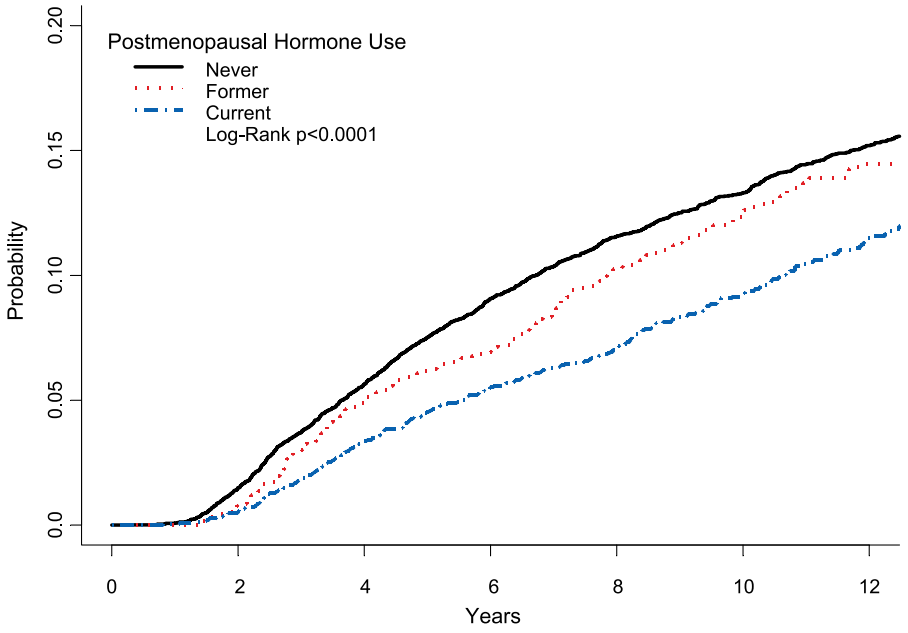

Figure 1. Kaplan-Meier cumulative incidence of breast cancer mortality according to history of hormone therapy use.

former use of hormone therapy in the year before diagnosis. Hormone therapy exposure by type of preparation was assessed as estrogen alone (''E-alone'') or combined estrogen and progestin (''EP'') when women had exclusively used one of these hormone therapy types; otherwise, hormone therapy was assessed as use of any preparation (''any hormone therapy''). We also examined the duration (<5, ≥5 years) and timing (current, former) of use. To determine the risks of dying from breast cancer according to hormone therapy (never, any hormone therapy, E-alone, EP, and by recency of any hormone therapy use), we used life table techniques to calculate estimated cumulative incidence of death, a statistical method that accounts for the presence of competing risk (e.g., death from causes other than breast cancer; ref. 26).

Cox proportional hazards regression was used to estimate the adjusted hazard rate ratio (HRR), interpreted here as a rate ratio, and corresponding 95% confidence intervals (95% CI) for death according to categories of hormone therapy use (27). All regression models were stratified on study center, year of interview, and exact age at diagnosis. Potential confounders included in multivariate models were body mass index (BMI, kg/m^2) in quartiles, smoking status, history of regular mammography screening, time from date of diagnosis to interview, and menopausal status. Women were classified as postmenopausal if they reported

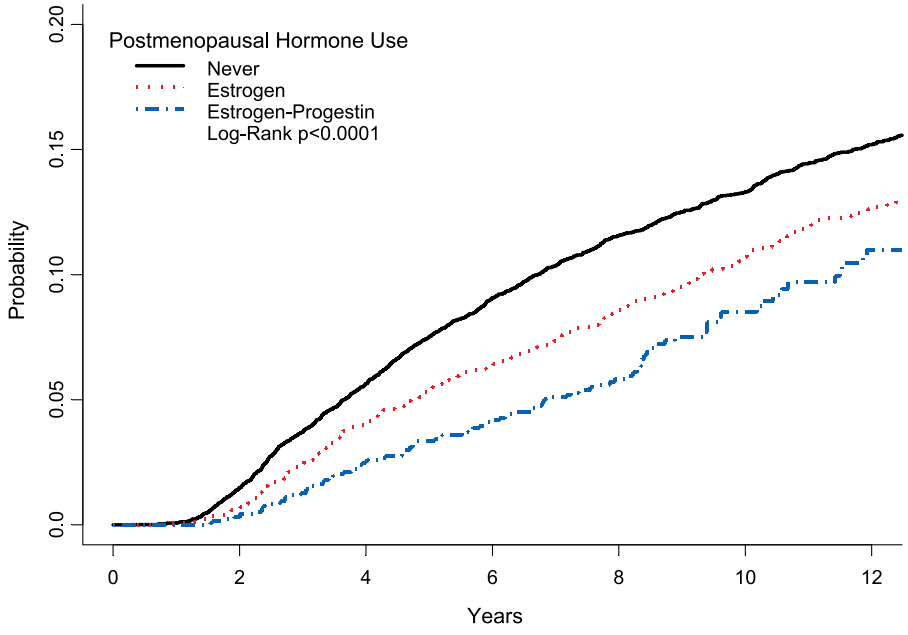

Figure 2. Kaplan-Meier cumulative incidence of breast cancer mortality by type of hormone therapy preparation.

Table 2. Breast cancer mortality of women by use of hormone therapy before breast cancer diagnosis for all women and stratified by stage of disease

Hormone therapy	All women* (N = 12,269)			Localized (n = 7,601)		Regional (n = 3,270)	
	No. deaths	Rate ratio † (95% CI)	Multivariate rate ratio †,‡ (95% CI)	No. deaths	Multivariate rate ratio †,‡ (95% CI)	No. deaths	Multivariate rate ratio †,‡ (95% CI)
Never§	1,235	1.00 (Reference)	1.00 (Reference)	362	1.00 (Reference)	623	1.00 (Reference)
Any HT use	455	0.78 (0.70-0.88)	0.87 (0.78-0.98)	176	1.14 (0.91-1.38)	219	0.84 (0.71-1.00)
Former HT use	168	0.86 (0.73-1.01)	0.92 (0.78-1.08)	62	1.05 (0.80-1.39)	85	0.97 (0.77-1.23)
Current HT use	287	0.74 (0.65-0.85)	0.85 (0.73-0.98)	114	1.21 (0.95-1.53)	134	0.76 (0.62-0.94)
Type of exclusive treatment							
Estrogen	270	0.81 (0.71-0.93)	0.89 (0.78-1.02)	108	1.17 (0.94-1.47)	131	0.90 (0.74-1.09)
EP	104	0.64 (0.52-0.79)	0.73 (0.59-0.91)	40	1.00 (0.70-1.42)	49	0.67 (0.49-0.91)
Other/unknown	81	0.91 (0.72-1.14)	1.01 (0.80-1.27)	28	1.20 (0.81-1.78)	39	0.91 (0.65-1.27)
Former or current use by type of exclusive treatment							
Estrogen, former	111	0.81 (0.67-0.99)	0.86 (0.71-1.05)	47	1.12 (0.83-1.53)	56	0.95 (0.72-1.26)
Estrogen, current	159	0.81 (0.68-0.96)	0.91 (0.77-1.09)	61	1.25 (0.94-1.67)	75	0.84 (0.65-1.08)
EP, former	20	0.90 (0.58-1.40)	0.96 (0.62-1.50)	5	0.78 (0.32-1.90)	11	0.98 (0.53-1.80)
EP, current	84	0.59 (0.47-0.75)	0.69 (0.55-0.88)	35	1.08 (0.74-1.58)	38	0.59 (0.41-0.84)
Duration by type of exclusive treatment							
Estrogen, <5 y	111	0.83 (0.69-1.01)	0.89 (0.73-1.08)	45	1.21 (0.88-1.66)	54	0.86 (0.64-1.14)
Estrogen, ≥5 y	159	0.79 (0.67-0.94)	0.89 (0.75-1.06)	63	1.17 (0.89-1.54)	77	0.91 (0.71-1.16)
EP, <5 y	64	0.74 (0.57-0.96)	0.84 (0.65-1.09)	24	1.12 (0.73-1.72)	31	0.72 (0.49-1.06)
EP, ≥5 y	40	0.51 (0.37-0.71)	0.60 (0.43-0.84)	16	0.89 (0.52-1.51)	18	0.56 (0.34-0.93)

* Includes all women with local, regional, and distant disease, and unknown extent of disease.
† Proportional hazards models stratified on state, year of interview, and age at diagnosis.
‡ Proportional hazards models adjusted for BMI, menopausal status, smoking status, mammography, and time from date of diagnosis to interview.
§ Reference category.

having a natural menopause or hysterectomy with bilateral oophorectomy before diagnosis. Women with hysterectomy without bilateral oophorectomy were considered postmenopausal if they were ≥55 years of age at diagnosis (or ≥54 years for smokers). All reported P values are two sided and statistical significance was evaluated at 0.05. All analyses were done using SAS version 9.1 (SAS Institute, Inc.).

Results

Women were followed, on average, for 10.3 years from diagnosis. A total of 3,953 deaths were documented, including 1,690 from breast cancer. Women who used hormone therapy were younger, of lower BMI, were more likely to have a history of mammographic screening, and more likely to be diagnosed with a local stage of disease than nonusers (Table 1). EP users were more likely than other hormone therapy users to be younger, to be of lower BMI, to be never smokers, to report regular mammographic screening, and to be diagnosed with local stage disease.

Cumulative breast cancer mortality differed depending on whether the woman had ever used hormone therapy, and was statistically significantly lower in current users in the year before diagnosis (Fig. 1). The lowest cumulative mortality was observed among women using EP (Fig. 2).

Overall, there was a significant inverse association between ever having used any hormone therapy and breast cancer mortality (adjusted HRR, 0.87; 95% CI, 0.78-0.98; Table 2). This multivariate HRR associated with ever use of hormone therapy was attenuated from the crude HRR of 0.78, suggesting appreciable confounding by BMI, history of mammography, and other covariates in the model. Mortality was significantly reduced in current hormone therapy users (HRR, 0.85; 95% CI, 0.73-0.98) but not former users. After additional adjustment for stage of disease, HRRs changed only slightly (HRR, 0.87), suggesting little evidence of further confounding by extent of disease. Among users of hormone therapy, breast cancer mortality was statistically significantly reduced for EP users (HRR, 0.73; 95% CI, 0.59-0.91) but not for E-alone (HRR, 0.89); however, these estimates were not statistically significantly different.

For women using EP, breast cancer mortality varied according to duration and timing of use. A significant reduction in breast cancer mortality associated with hormone therapy use was observed for current users of EP (HRR, 0.69; 95% CI, 0.55-0.88) compared with never users of hormone therapy, and the greatest benefit was observed for long-term users (≥5 years; HRR, 0.60; 95% CI, 0.43-0.84). In contrast, there was no statistically significant relation between former EP use of any duration and breast cancer mortality. For users of E-alone preparations, there were no statistically significant associations between breast cancer mortality and current use, former use, or duration of use. Increasing time since last use did not seem to be significantly associated with this inverse relation for either hormone therapy type ($P_{continuous} > 0.05$; data not shown).

Results stratified by extent of disease showed statistically significantly lower HRRs among women with breast cancer diagnosed at a regional stage of disease, but not with disease diagnosed at a local stage. Among women diagnosed at a regional stage, HRRs were strongly and significantly lower for both women currently using EP (HRR, 0.59; 95% CI, 0.41-0.84) and long-term users of EP (HRR, 0.56; 95% CI, 0.34-0.93). The difference between hormone therapy by stage was not statistically significant for any type, recency, or duration.

Table 3. All-cause mortality of women with incident breast cancer by patterns of use of hormone therapy before diagnosis

Hormone therapy	No. deaths	Rate ratio* (95% CI)	Multivariate rate ratio*,† (95% CI)
Never‡	3,009	1.00 (Reference)	1.00 (Reference)
Any HT use	944	0.74 (0.69-0.80)	0.81 (0.75-0.87)
Former HT use	436	0.82 (0.74-0.91)	0.87 (0.78-0.96)
Current HT use	507	0.68 (0.61-0.75)	0.75 (0.68-0.83)
Type of exclusive treatment			
Estrogen alone	610	0.76 (0.70-0.83)	0.82 (0.75-0.90)
EP	174	0.63 (0.53-0.73)	0.68 (0.58-0.81)
Other/unknown	160	0.83 (0.71-0.98)	0.89 (0.76-1.04)
Former or current use by type of exclusive treatment			
Estrogen, former	312	0.79 (0.70-0.89)	0.84 (0.74-0.94)
Estrogen, current	298	0.73 (0.64-0.82)	0.80 (0.71-0.91)
EP, former	44	0.97 (0.72-1.31)	1.01 (0.75-1.37)
EP, current	130	0.55 (0.45-0.66)	0.61 (0.50-0.73)
Duration by type of exclusive treatment			
Estrogen, <5 y	251	0.78 (0.69-0.89)	0.83 (0.72-0.94)
Estrogen, ≥5 y	359	0.74 (0.67-0.83)	0.82 (0.73-0.91)
EP, <5 y	105	0.74 (0.61-0.91)	0.80 (0.65-0.98)
EP, ≥5 y	69	0.49 (0.39-0.63)	0.55 (0.43-0.71)

* Proportional hazards models stratified on state, year of interview, and age at diagnosis.
† Proportional hazards models adjusted for BMI, mammography, smoking status and time from date of diagnosis to interview.
‡ Reference category.

Breast cancer cases diagnosed with lobular (n = 1,159) and nonlobular (n = 11,110) disease showed similar overall patterns in current E-alone and EP use and breast cancer mortality, with two notable exceptions (data not shown). Current users of E-alone with lobular disease experienced a halving in breast cancer mortality (HRR, 0.53; 95% CI, 0.30-0.96). In contrast, among women with lobular disease, former EP users experienced a 3-fold higher breast cancer mortality (HRR, 3.24; 95% CI, 1.05-9.99). Although few former EP users had lobular breast cancer as an underlying cause of death, this elevated risk contrasts with the low HRRs seen previously.

The associations with current hormone therapy were consistent according to age at diagnosis (<60 years, ≥60 years, P = 0.58) and BMI (<25.7 kg/m^2, ≥25.7 kg/m^2, P = 0.67). The results of analyses stratified by state (New Hampshire, Wisconsin, Massachusetts) were also similar to the combined results, with no significant heterogeneity observed. In a subanalysis of Wisconsin women, where first course of treatment was available, treatment-adjusted results were similar to results unadjusted for treatment (data not shown).

Death from all causes was significantly lower both in current users of hormone therapy (adjusted HRR, 0.75; 95% CI, 0.68-0.83) and former hormone therapy users (adjusted HRR, 0.87; 95% CI, 0.78-0.96; Table 3). All-cause mortality risks associated with type of preparation differed (P < 0.0001): Current user of E-alone was less strongly associated with risk (HRR, 0.80; 95% CI, 0.71-0.91) than that associated with EP (HRR, 0.61; 95% CI, 0.50-0.73). Inverse relations with mortality also differed by duration and type of preparation (P < 0.0001) among long-term users of EP (HRR, 0.55; 95% CI, 0.43-0.71) compared with E-alone (HRR, 0.82; 95% CI, 0.73-0.91). Hormone therapy use was not associated with mortality from other cancers besides breast cancer or from cerebrovascular diseases. However, both E-alone and EP users had reduced risks of mortality from cardiovascular disease (HRR, 0.62; 95% CI, 0.48-0.80 for E-alone and HRR, 0.27; 95% CI, 0.12-0.57 for EP).

Discussion

The extent to which specific hormone therapy use influences the risk of mortality among breast cancer cases had been largely unknown, and no prior research has investigated whether this risk varies by either patient or tumor characteristics. In this large population-based cohort of women with breast cancer, current use of hormone therapy was associated with a moderately lower breast cancer–specific mortality when compared with never use of these preparations. Mortality was lowest among current and long-term users of combined EP therapy. The present results provide the strongest evidence to date that hormone therapy use is associated with the subsequent development of less aggressive breast cancers through mechanisms that are not yet fully clear.

Evidence is limited on the relationship between hormone therapy use before breast cancer diagnosis and mortality from this disease. This and other studies evaluated self-reported hormone therapy use before the diagnosis of invasive breast cancer (3-5). Only one showed a statistically significant lower risk of the association of prediagnostic hormone therapy use with case fatality in a cohort (n = 2,614 women) with breast cancers assembled in a large breast cancer screening program (5). After adjustment for age, race, BMI, tumor size, and number of positive lymph nodes, women using hormone therapy at the time of diagnosis experienced approximately half the risk of dying of breast cancer in both node-negative and node-positive diseases, although this effect waned with increasing time since diagnosis. These authors reported that the inverse association was no longer apparent after 4 years for node-positive disease and 12 years for node-negative disease, and thus this association may reflect residual confounding due to screening for node-positive disease, but this is less likely for node-negative disease, given the prolonged protection conferred. Limitations of the study are that the results were not stratified by type of hormone therapy, and other relevant personal and tumor characteristics.

In an earlier study, Bergkvist et al. (3) compared a group of 261 cases of breast cancer that had taken E-alone before diagnosis with 6,627 breast cancer cases identified through a population cancer registry whose estrogen exposure status was unknown. After consideration of mortality attributable to competing risks of death, the relative survival rate among previous users of hormone therapy was suggestively higher when compared with the general cancer registry cases with a greater reduction in breast cancer mortality in users of EP. Other investigators have reported decreased all-cause mortality among women with breast cancer who had used hormone therapy, although these studies made no adjustment for competing risks of death, potentially leading to bias (4, 6, 11, 28).

Studies have also generally shown lower breast cancer mortality with hormone therapy use in women initially without cancer, although in one study the mortality effects observed with hormone therapy use seem to wane over time, with increased breast cancer mortality observed among women using hormone therapy for 10 years of more (29). Because studies have consistently indicated a modestly increased risk of developing breast cancer in hormone therapy users (30-33), these results suggest that breast cancers that develop in hormone therapy users may be associated with a less aggressive course than breast cancers that develop in nonusers (9, 29, 34-42). A further reason for lower case fatality may be that the cancers developing in women using hormone therapy are selected to be more hormonally responsive. Thus, with termination of the promoting factor at diagnosis (hormone therapy use) and the use of antiestrogen treatment, now standard of care, these tumors would be expected to be associated with improved prognosis.

It has been suggested that the reduction in breast cancer mortality associated with hormone therapy use is attributable to an earlier stage at diagnosis (3, 19), which may be due to a higher likelihood of screening among hormone therapy users (surveillance bias; ref. 5) or the tendency for women who develop a serious illness to stop taking hormone therapy (healthy estrogen-user effect; ref. 43), rather than a modifying effect of hormone use on tumor biology. We observed that the inverse association between hormone therapy use and breast cancer mortality was limited to women originally diagnosed with regional, but not localized, disease. It has been well documented that hormone therapy users are likely to be screened more aggressively than nonusers (44) and have cancers that are diagnosed at an earlier stage (45), despite evidence that use of postmenopausal hormones reduces both sensitivity and specificity of screening mammograms (46). However, even in analyses that adjust for screening, cancers that develop in hormone therapy users tend to be smaller (11, 19), of lower grade (47), have fewer positive axillary lymph nodes (11, 19, 48), lower tumor cell proliferation rate (49, 50), and have other clinically more favorable features (14, 48). Yet, in the Women's Health Initiative randomized trial of the combined EP regimen, the rate of incident metastatic breast cancer was similar regardless of hormone therapy assignment (2).

It may also be relevant to consider an effect of hormone therapy on tumor growth after diagnosis. Although rare, hormone therapy use initiated after diagnosis of breast cancer has been shown to have a beneficial (5, 17, 51) or neutral (18) association with survival, and there has been no observed improvement in survival associated with duration of use or route of administration (oral or vaginal cream; ref. 51).

In our study, we found better breast cancer survival among women who used combined EP therapy before diagnosis. Widespread use of combined EP preparations began in the 1980s (52) and most earlier mortality studies evaluated the use of E-alone formulations. Two previous studies have reported more favorable prognostic profiles associated with combined EP therapy relative to other types of hormone therapy. Magnusson et al. (19) found that women receiving a combined EP regimen were less likely to have tumors >20 mm in diameter, but have axillary lymph node dissemination, and poorly differentiated or aneuploid tumors at diagnosis. Daling et al. (53) observed that the tumors of users of continuous EP therapy (relative to E-alone therapy or sequential EP therapy) were more likely to be estrogen receptor and progesterone receptor positive, features that are associated with better prognosis (14). Thus, our observation of reduced mortality among users of combined hormone therapy might be expected based on the generally favorable profiles of the tumors occurring among women using hormone therapy compared with the tumors developing in nonusers or users of other regimens.

Our confidence in these study results is enhanced by the large sample size, mature follow-up, and availability of comprehensive information on tumor stage and other covariates associated with breast cancer mortality. Arising from a population-based study with high response rates, the cohort reflected the spectrum of breast cancer as it occurs in the population. However, some limitations should be considered when interpreting our results. This evaluation was based on hormone therapy use before diagnosis, ~2 years before interview. Participants were not followed-up for changes in hormone therapy practices after breast cancer diagnosis, except on a subset of the population that participated in a study of postdiagnosis diet and other factors, including hormone therapy, in relation to breast cancer survival. In this actively followed subgroup, few women (4.5%) reported use of hormone therapy, which has generally not been recommended after breast cancer diagnosis (54). Thus, the uncommon use of postdiagnostic hormone therapy is unlikely to have biased our results. However, other exposures sustained or initiated after diagnosis may affect survival. Unmeasured postdiagnosis characteristics of hormone therapy users, such as changes in weight and physical activity, could influence the observed differences in survival according to hormone therapy use. To reduce this possibility, we excluded from the analysis women whose breast cancer was diagnosed at a late stage and the results were unchanged.

Screening is a particularly important covariate affecting breast cancer survival. In our population, hormone therapy was associated with mammography; only 10% of hormone therapy users had never been screened compared with 30% of never hormone therapy users. Surprisingly, stratification by mammography screening suggested stronger inverse relations with hormone therapy, particularly with respect to EP use, among

women who were not screened compared with women who reported regular screening. Limited sample sizes made it impossible to rule out chance in these associations, but the results are generally reassuring in that characteristics as measured by screening use are unlikely to have introduced bias. The examination of cause-specific mortality may suggest some artifact of unmeasured confounders, because hormone therapy users have statistically significantly reduced cardiovascular disease. Follow-up of cases randomized to receive hormone therapy before diagnosis, such as in the Women's Health Initiative study or Heart and Estrogen/Progestin Replacement Study, will help address this limitation of observational studies.

We were unable to consider the estrogen receptor/progesterone receptor status of tumors in our analysis. As a common phenotype of breast cancer tumors, the inability to control for receptor status is unlikely to overestimate our estimates of survival by hormone therapy use; rather, the combination of all tumor types increases the heterogeneity of our sample and may attenuate our results if hormone therapy use is related to survival only among those with tumors expressing estrogen receptor/progesterone receptor. However, because estrogen receptor/progesterone receptor positivity increases with increasing age (55), and our sample was postmenopausal, most women's tumors would have been hormone receptor positive.

In summary, we found that use of hormone therapy before diagnosis in a large population-based cohort of women with breast cancer was associated with improved breast cancer survival. Survival was best among current and long-term users among women using combination regimens of EP, and seemed limited to women with regional disease. The better breast cancer survival in users of hormone therapy before diagnosis persisted after adjustment for screening, stage, and measured risk factors.

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