Prediagnostic Use of Hormone Therapy and Mortality After Breast Cancer

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ABSTRACT

Background: A few studies have observed reduced breast cancer mortality in women who used hormone therapy (HT) prior to diagnosis. Due to the high prevalence of hormone use, it is important to establish whether these preparations are related to breast cancer mortality.

Methods: To evaluate the influence of prediagnostic use of HT on breast cancer mortality, a prospective cohort of 12,269 women aged 50 years or more diagnosed with incident invasive breast cancer and residents of Wisconsin, Massachusetts, or New Hampshire, US were enrolled in three phases beginning in 1988. They were followed for death until December 31, 2004 using the National Death Index.

Results: During an average 9.6 years of follow up, 1614 deaths from breast cancer were documented. Cumulative mortality from breast cancer was lower among HT users compared to nonusers. Survival varied by type and duration of HT prior to diagnosis, a reduced risk of death from breast cancer was associated with ever use of estrogen-progestin (EP) preparations (HRR 0.71 (0.57-0.88) and with ≥5 years of EP use (0.54; 0.38-0.76) No association was observed for women former or current users of estrogen-only 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. Survival was best among recent and long-term users.

INTRODUCTION

Compelling evidence demonstrates that hormone therapy (HT) use, particularly formulations containing progestins, increases breast cancer incidence (1, 2). However, *reduced* breast cancer mortality has been observed among women using HT prior to 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 HT use and breast cancer mortality might also be explained by more favorable tumor profiles, and therefore improved prognosis, among HT users compared with non-users (11-14).

A substantial proportion of women in the U.S. have used HT in their lifetimes, including about half of postmenopausal U.S. women aged 50-69 years (15, 16). Given the large number of women with a history of HT 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 HT 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 multi-site 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 aged 20-74 years in phase 1 (1988-91), aged 50-79 years in phase 2 (1992-95) and aged 20-69 years in phase 3 (1997-2001). Approximately 81% of eligible case women participated in the case-control study.

Ascertainment of Exposure

All subjects completed a structured telephone interview that included detailed information on prediagnosis use of HT, 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 prior to diagnosis, approximately two years prior to interview. Format of the questions on HT use varied slightly depending on period of data collection; all versions after 1989 elicited a standard history of HT, including type, duration, age started and time since last use.

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 aged 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 HT questions were included in the interview; 662 had missing information on HT usage; 116 used hormones before age 40 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, 2004 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) (though 1998) (24) and ICD-10 (1999-2000) (25). We considered both death from breast cancer (ICD-9 codes 174-174.9 and ICD-10 codes C50.0-C50.9), and all-cause mortality.

Statistical Analysis

Survival time was calculated as the number of months from date of diagnosis to date of death, or December 31, 2004 for surviving women. Annual age-adjusted

mortality rates were computed according to length of HT use (26). Women were classified as ever/never having used HT; women who had ever used HT were then further classified by current use or former use of HT at the time of diagnosis, with current use defined as HT use in the year prior to breast cancer diagnosis. HT exposure by type of preparation was assessed as estrogen only ("E-only") or combined estrogen and progestin only ("EP-only") when women had used only one of these HT types; otherwise, HT was assessed as use of any preparation. We also examined the duration (<5, $\geq$ 5 years) and timing (current, former) of use. To determine the risks of dying from breast cancer according to HT (never, E-only, EP- only and by recency of 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) (27).

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 HT use (28). 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, history of mammography screening, time from date of diagnosis to interview, and menopausal status. Women were classified as postmenopausal if they reported having a natural menopause or hysterectomy with bilateral oophorectomy at the reference date. Women with hysterectomy without bilateral oophorectomy were considered postmenopausal if they had reached the age at which natural menopause occurred in 90% of the controls. All reported *P* values are two sided and statistical

significance was evaluated at 0.05. All analyses were performed using SAS version 9.1 (SAS Institute, Inc., Carey, NC).

RESULTS

Women were followed, on average, for 9.6 years from diagnosis. A total of 3,653 deaths were documented, including 1,614 from breast cancer. Women who used HT 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).

Cumulative breast cancer mortality differed depending on whether the woman had ever used HT (Figure 1), with the lowest cumulative mortality found among women using EP (Figure 2). Cumulative breast cancer mortality was also lower among long term users compared to short term users of HT, with the lowest cumulative mortality among long-term users of EP-only (data not shown).

Overall, there was a significant inverse association between ever having used any HT and breast cancer mortality (adjusted HRR 0.86, 95% CI 0.76-0.96; Table 2). This multivariate HRR associated with ever use of HT was attenuated from the crude HRR of 0.78, suggesting appreciable confounding by body mass index, history of mammography, and other covariates in the model. This reduction in mortality was found most strongly in current users of HT (adjusted HRR 0.82, 95% CI: 0.71-0.95). HRR's for current users after additional adjustment for stage of disease (HRR 0.85, 95% CI: 0.73-0.98) changed only slightly, suggesting little evidence of further

confounding by extent of disease. For ever use of HT, there was a suggestion that breast cancer specific mortality was lower for EP-only (HRR = 0.71) than for estrogen-only (HRR = 0.88), however, these were not statistically significantly different.

For women using EP-only, breast cancer mortality varied according to duration and timing of use (Table 2). A significant reduction in breast cancer mortality associated with HT use was observed for current users of EP-only (HRR: 0.65; 95% CI: 0.51-0.84) compared to never users of HT, and the greatest benefit was observed for long-term users ($\geq$5 years, HRR: 0.54; 95% CI: 0.38-0.76). In contrast, there was no statistically significant relation between former EP use and breast cancer mortality. For users of E-only preparations, there were no statistically significant associations between breast cancer mortality and current, former or duration of use. Differences between E-only and EP-only were significantly different for both current (p=0.03) and long-term users (p=0.01).

Results stratified by extent of disease showed lower HRR's among women with breast cancer diagnosed at a regional stage of disease than at a local stage (Table 2), although HRR's were not statistically different by stage. Among women diagnosed at a regional stage, HRR's were strongly and significantly lower for both long-term users of EP-only (HRR 0.46; 95% CI: 0.27-0.81) and women currently using EP-only (HRR 0.53; 95% CI: 0.37-0.78).

Breast cancer cases diagnosed with lobular disease (n=1,159) showed similar overall associations between current and EP-only HT use and breast cancer mortality, with two notable exceptions (data not shown). Current users of E-only with lobular disease experienced a halving in breast cancer mortality (HRR: 0.50; 95% CI: 0.27-

0.94). In contrast, among women with lobular disease, former EP-only users experienced a three-fold higher breast cancer mortality (95% CI: 0.93-9.32). Although few EP-only former users had breast cancer as an underlying cause of death, this elevated risk contrasts with the low HRR's seen above.

The associations with current HT 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 (NH, WI, MA) were also similar to the combined results, with no significant heterogeneity observed. In a sub-analysis 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 also significantly lower in current users of HT (adjusted HRR 0.73; 95% CI: 0.66-0.81) and former HT users (adjusted HRR 0.86; 95% CI: 0.78-0.96; Table 3). Both current users of EP-only (HRR 0.57; 95% CI: 0.47-0.70) and E-only (HRR 0.78; 95% CI: 0.69-0.89) displayed lower risks of all-cause mortality; notably the difference in HRR's was statistically significant (p=0.02). Inverse relations with mortality also differed by type of preparation (p=0.004) among long-term users of EP-only (HRR 0.50; 95% CI: 0.38-0.66) compared with E-only (HRR 0.81, 95% CI: 0.72-0.91). Former users of E-only experienced a modestly lower risk (HRR 0.84, 95% CI: 0.75-0.95). Increasing time since last use did not appear to be significantly associated with this inverse relation for either HT type ($P_{continuous}$ >0.05, data not shown).

DISCUSSION

The extent to which specific HT use influences the risk of mortality among breast cancer cases had been largely unknown, and no prior research has investigated whether or not this risk varies by either patient or tumor characteristics. In this large population-based cohort of women with breast cancer, current use of HT was associated with a moderately lower breast cancer specific mortality when compared to 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 HT 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 HT use before breast cancer diagnosis and mortality from this disease. This and other studies evaluated self-reported HT use before the diagnosis of invasive breast cancer (3-5). Only one showed a statistically significant lower risk of the association of pre-diagnostic HT 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 HT at the time of diagnosis experienced approximately half the risk of dying of breast cancer in both node-negative and node-positive disease, 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 HT,

and other relevant personal and tumor characteristics.

In an earlier study, Bergkvist et al compared a group of 261 cases of breast cancer that had taken E-only prior to diagnosis with 6627 breast cancer cases identified through a population cancer registry whose estrogen exposure status was unknown (3). After consideration of mortality attributable to competing risks of death, the relative survival rate among previous users of HT was suggestively higher when compared with the general cancer registry cases with a greater reduction in breast cancer mortality in uses of EP. Other investigators have reported decreased all-cause mortality among women with breast cancer who had used HT , though these studies made no adjustment for competing risks of death, potentially leading to bias (4, 6, 11, 29).

Studies have also generally shown lower breast cancer mortality with HT use in women initially without cancer, although in one study the mortality effects observed with HT use appear to wane over time, with *increased* breast cancer mortality observed among women using HT for 10 years of more (30). Because studies have consistently indicated a modestly increased risk of developing breast cancer in HT users (31-34), these results suggest that breast cancers that develop in HT users may be associated with a less aggressive course than breast cancers that develop in nonusers (9, 30, 35-43). A further reason for lower case-fatality may be that the cancers developing in women using HT are selected to be more hormonally responsive. Thus, with termination of the promoting factor at diagnosis (HT use) and the use of anti-estrogen treatment, now standard of care, these tumors would be expected to be particularly responsive.

It has been suggested that the reduction in breast cancer mortality associated

with HT use is attributable to an earlier stage at diagnosis (3, 19), which may be due to a higher likelihood of screening among HT users (surveillance bias) (5) or the tendency for women who develop a serious illness to stop taking HT (healthy estrogen-user effect) (44), rather than a modifying effect of hormone use on tumor biology. It has been well-documented that HT users are likely to be screened more aggressively than non-users (45) and have cancers that are diagnosed at an earlier stage (46), despite evidence that use of postmenopausal hormones reduces both sensitivity and specificity of screening mammograms (47). However, even in analyses that adjust for screening, cancers that develop in HT users tend to be smaller (11, 19), of lower grade (48), have fewer positive maxillary lymph nodes (11, 19, 49), lower tumor cell proliferation rate (50, 51), and have other clinically more favorable features (14, 49). Yet, in the Women's Health Initiative (WHI) randomized trial of the combined EP regimen, the rate of incident metastatic breast cancer was similar regardless of HT assignment (2).

It may also be relevant to consider an effect of HT's on tumor growth after diagnosis. Although rare, HT use initiated *after* diagnosis of breast cancer has been shown to have a beneficial (5, 17, 52) 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) (52).

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 1980's (53) and most earlier mortality studies evaluated the use of E-only formulations. Two previous studies have reported more favorable prognostic profiles associated with combined estrogen-progestin therapy relative to other types of HT.

Magnusson et al. found that women receiving a combined EP regimen were less likely to have tumors >20mm in diameter, but to have axillary lymph node dissemination, and poorly differentiated, or aneuploid tumors at diagnosis (19). Daling et al. observed that the tumors of users of continuous combined hormonal therapy (relative to E-only therapy or sequential combined therapy) were more likely to be estrogen receptor and, progesterone receptor positive (54), features that are associated with better prognosis. (14) Thus, our observation of reduced mortality among users of combined HT might be expected, based upon the generally favorable profiles of the tumors occurring among women using HT compared to the tumors developing in non-users, 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 upon HT use before diagnosis, approximately two years prior to interview. Participants were not followed-up for changes in HT practices after breast cancer diagnosis, except on a subset of the population that participated in a study of post-diagnosis diet and other factors, including HT, in relation to breast cancer survival. In this actively followed sub-group, few women (4.5%) reported use of HT—which has generally not been recommended after breast cancer diagnosis (55). Thus, the uncommon use of post diagnostic HT is unlikely to have biased our results. However, other exposures sustained or initiated after diagnosis

may affect survival. Unmeasured post-diagnosis characteristics of HT users, such as changes in weight and physical activity, could influence the observed differences in survival according to HT use.

Screening is a particularly important covariate affecting survival. In our population HT was strongly associated with mammography: only 10% of HT users had never been screened compared with 30% of never users. As screening history was self-reported by each woman, residual confounding by mammography is a possibility. Women who use HT, especially combined EP preparations, are more likely to have greater breast density than non-users (56). Increased breast density is a clinically significant predictor of breast cancer risk (57), and HT users with increased breast density may experience worse prognosis (58, 59). However, only about 20-35% of women initiating HT experience these changes in breast density (60).

We were unable to consider the ER/PR 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 HT use; rather, the combination of all tumor types increases the heterogeneity of our sample and may attenuate our results if HT use is related to survival only among those with tumors expressing ER/PR. However, since ER/PR positivity increases with increasing age (61); and our sample was postmenopausal, most women's tumors would have been hormone receptor positive.

In summary, we found that use of HT prior to diagnosis in a large population-based cohort of women with breast cancer was associated with improved breast cancer survival. Survival was best among recent and long-term users, and among women

using combination regimens including EP. The better breast cancer survival in users of HT prior to diagnosis is unlikely to be attributable to differences in screening, stage, or other measured characteristics related to HT use and breast cancer mortality.

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TABLE 1. Baseline characteristics of study subjects by postmenopausal hormone use.

Characteristic	HT non-users (N=8071) N (%)	HT ever users E-only (N=2258) N (%)	HT ever users E+P (N=1340) N (%)
Age at Diagnosis			
50-54	1342 (16.6)	335 (14.8)	379 (28.3)
55-59	1116 (13.8)	445 (19.7)	479 (35.8)
60-64	1586 (19.6)	497 (22.0)	324 (24.2)
65-69	2079 (25.8)	517 (22.9)	132 (9.9)
70-74	1332 (16.5)	344 (15.2)	22 (1.6)
75-79	616 (7.6)	120 (5.3)	4 (0.3)
Extent of Disease/Stage			
Local	4836 (59.9)	1470 (65.1)	914 (68.2)
Regional	2191 (27.1)	539 (23.9)	322 (24.0)
Distant	249 (3.1)	36 (1.6)	13 (1.0)
Unstaged	795 (9.9)	213 (9.4)	91 (6.8)
Histologic Type			
Lobular	729 (9.0)	219 (9.7)	155 (11.6)
Non-lobular	7342 (91.0)	2039 (90.3)	1185 (88.4)
Menopausal Status			
Postmenopausal	7109 (88.1)	2094 (92.7)	1154 (86.1)
Premenopausal	807 (10.0)	35 (1.6)	115 (8.6)
Unknown	155 (1.9)	129 (5.7)	71 (5.3)
Body Mass Index			
Less than 22.8	1724 (21.4)	577 (25.6)	409 (30.5)
22.8-25.5	1878 (23.3)	565 (25.0)	348 (26.0)
25.6-29.1	2014 (25.0)	574 (25.4)	314 (23.4)
Unknown	291 (3.6)	49 (2.2)	24 (1.8)
Regular History of Mammography Screening			
Yes	2293 (28.4)	249 (11.0)	40 (3.0)
No	5064 (62.7)	1842 (81.6)	1263 (94.3)
Unknown	714 (8.9)	167 (7.4)	37 (2.8)

TABLE 2. Breast cancer mortality of women by use of hormone therapy prior to breast cancer diagnosis for all women and stratified by stage of disease.

	All Women (n=12269)					**Localized** (n=7601)			**Regional** (n=3270)		
Hormone Therapy	Number of Deaths	Rate ratio*	(95%CI)	Multivariate rate ratio*†	(95%CI)	Number of Deaths	Multivariate rate ratio*†	(95%CI)	Number of Deaths	Multivariate rate ratio*†	(95%CI)
Never‡	1186	1.00	reference	1.00	reference	339	1.00	reference	605	1.00	reference
Ever HT	428	0.78	0.70-0.87	0.86	0.76-0.96	165	1.14	0.93-1.39	205	0.82	0.69-0.97
Former	163	0.86	0.73-1.02	0.91	0.77-1.08	57	1.03	0.77-1.37	85	1.00	0.79-1.26
Current	265	0.73	0.63-0.84	0.82	0.71-0.95	108	1.22	0.96-1.56	120	0.71	0.57-0.88
Type of Exclusive Treatment											
Estrogen	256	0.81	0.70-0.93	0.88	0.76-1.01	102	1.18	0.94-1.48	124	0.87	0.71-1.07
EP	95	0.63	0.51-0.78	0.71	0.57-0.88	37	0.99	0.69-1.43	44	0.63	0.45-0.87
Other/Unknown	77	0.90	0.72-1.14	0.99	0.79-1.26	26	1.17	0.78-1.75	37	0.89	0.63-1.26
Former or Current Use by Type of Treatment											
Estrogen, Former	107	0.81	0.66-0.98	0.86	0.70-1.05	43	1.09	0.79-1.51	56	0.97	0.73-1.28
Estrogen, Current	149	0.81	0.68-0.96	0.89	0.74-1.06	59	1.30	0.97-1.74	68	0.79	0.61-1.02
EP, Former	20	0.94	0.60-1.46	0.98	0.63-1.53	5	0.81	0.33-1.98	11	1.03	0.56-1.90
EP, Current	75	0.57	0.45-0.73	0.65	0.51-0.84	32	1.09	0.73-1.62	33	0.53	0.37-0.78
Duration by Type of Treatment											
Estrogen, < 5 years	108	0.85	0.70-1.03	0.90	0.73-1.10	43	1.23	0.89-1.70	53	0.86	0.65-1.15
Estrogen, ≥ 5 years	148	0.78	0.65-0.92	0.86	0.72-1.03	59	1.17	0.87-1.56	71	0.86	0.67-1.11
EP, < 5 years	61	0.75	0.58-0.98	0.84	0.65-1.10	22	1.13	0.72-1.77	30	0.73	0.49-1.07
EP, ≥ 5 years	34	0.47	0.33-0.67	0.54	0.38-0.76	15	0.89	0.52-1.53	14	0.46	0.27-0.81

* Proportional hazards models stratified on state, year of interview, and age at diagnosis.

† Proportional hazards models adjusted for body mass index, menopausal status mammography, and time from date of diagnosis to interview mammography, and time from date of diagnosis to interview

‡ Reference category.

** Excludes never users

TABLE 3. All-cause mortality of women with incident breast cancer by patterns of use of hormone therapy prior to diagnosis.

Hormone Therapy	Number of Deaths	Rate ratio*	(95%CI)	Multivariate rate ratio*†	(95%CI)
Never‡	2794	1.00	reference	1.00	reference
Any HT Use	859	0.74	0.69-0.80	0.79	0.73-0.86
Former HT Use	402	0.82	0.74-0.91	0.86	0.78-0.96
Current HT Use	456	0.68	0.61-0.75	0.73	0.66-0.81
Type of Exclusive Treatment					
Estrogen Only	561	0.76	0.69-0.83	0.81	0.74-0.89
EP	151	0.61	0.51-0.72	0.65	0.55-0.77
Other/Unknown	147	0.83	0.70-0.98	0.88	0.74-1.04
Former or Current Use by Type of Treatment					
Estrogen, Former	290	0.79	0.70-0.90	0.84	0.75-0.95
Estrogen, Current	271	0.73	0.64-0.83	0.78	0.69-0.89
EP, Former	39	0.93	0.68-1.28	0.96	0.70-1.32
EP, Current	112	0.53	0.44-0.65	0.57	0.47-0.70
Duration by Type of Treatment					
Estrogen, < 5 years	233	0.78	0.69-0.90	0.82	0.72-0.94
Estrogen, ≥ 5 years	328	0.75	0.66-0.84	0.81	0.72-0.91
EP, < 5 years	94	0.73	0.59-0.91	0.78	0.63-0.97
EP, ≥ 5 years	57	0.47	0.36-0.61	0.50	0.38-0.66

* Proportional hazards models stratified on state, year of interview, and age at diagnosis.

† Proportional hazards models adjusted for body mass index, mammography, and time from date of diagnosis to interview.

‡ Reference category.

Figure 1
Newcomb PA

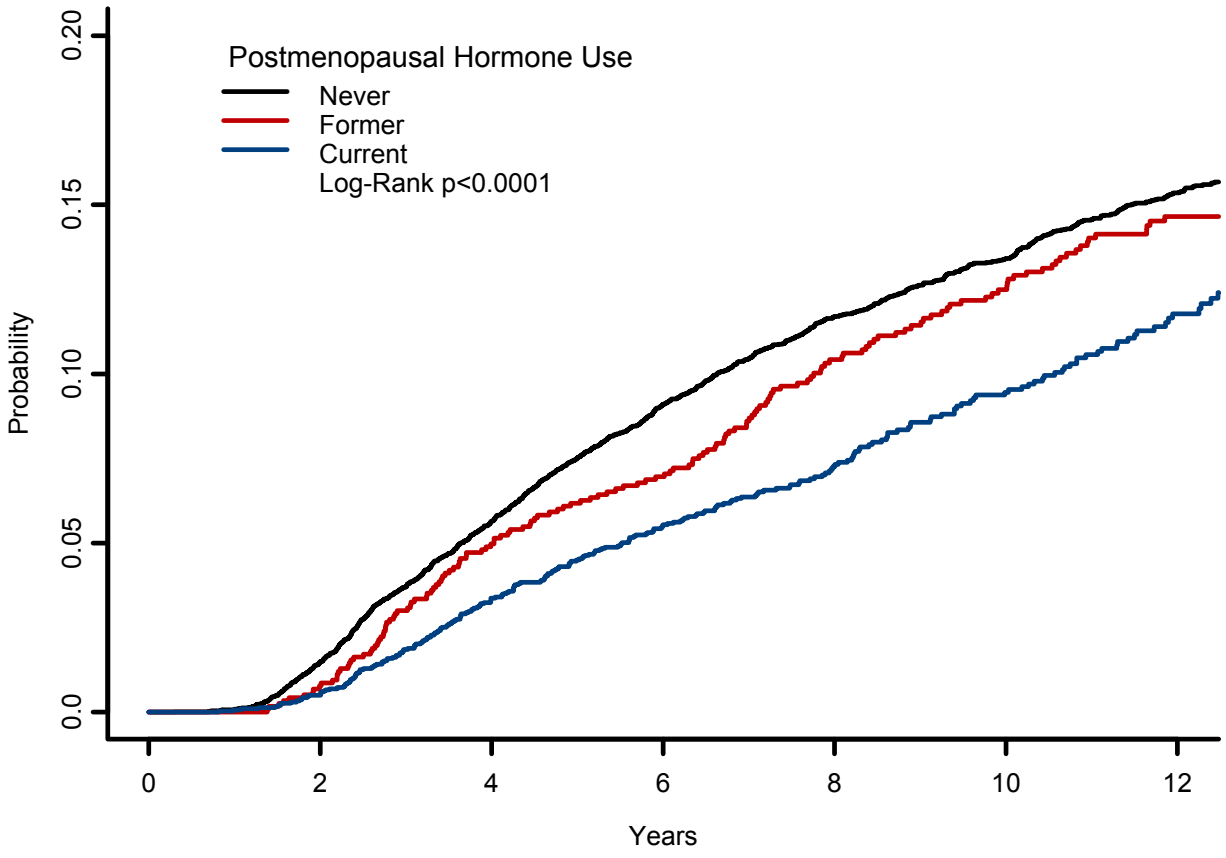

FIGURE 1. Kaplan-meier cumulative incidence of breast cancer mortality according to history of hormone use.

Figure 2
Newcomb PA

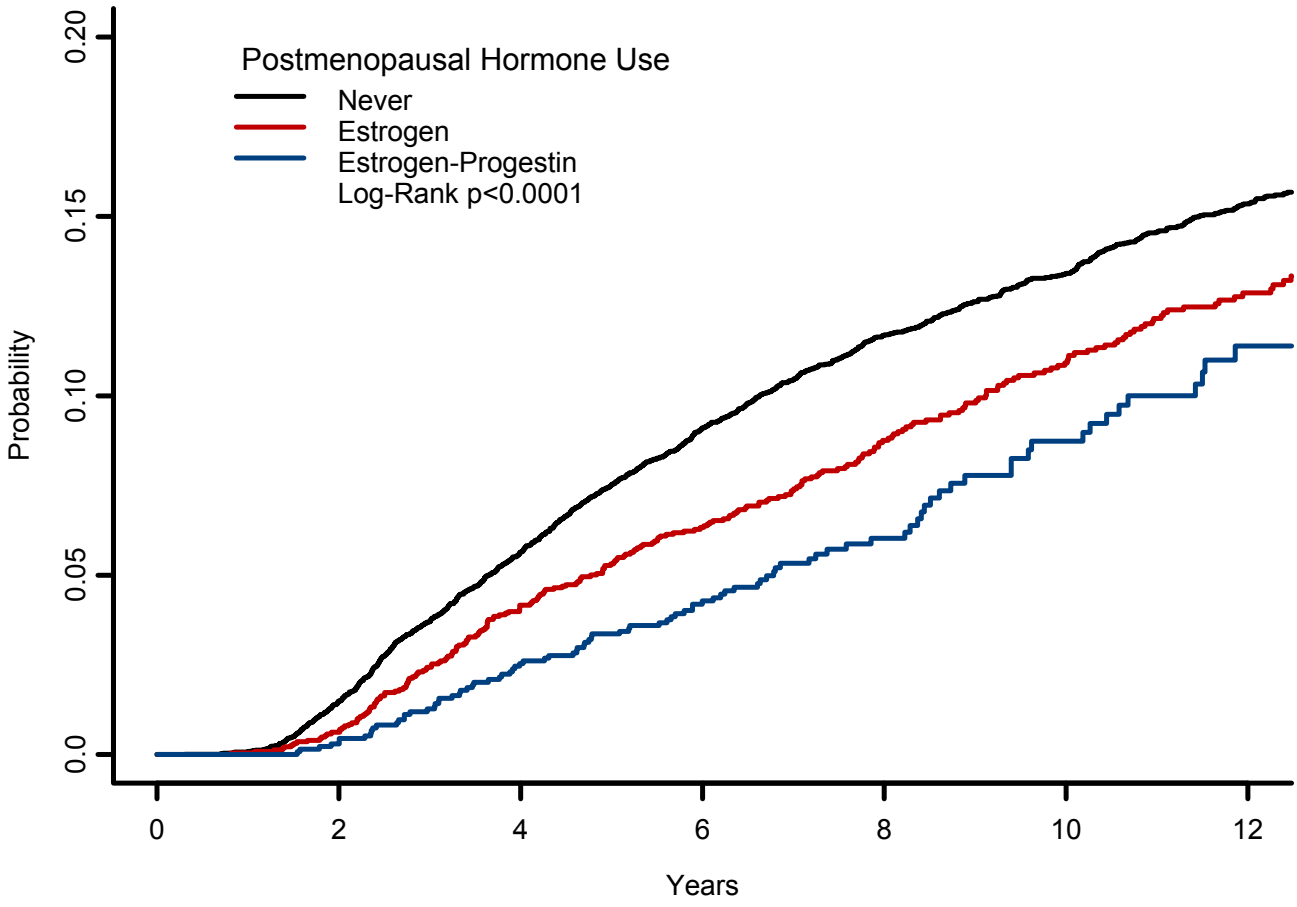

FIGURE 2. Kaplan-meier cumulative incidence of breast cancer mortality by type of hormone therapy preparation.