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Age-related variation in the relationship between menopausal hormone therapy and the risk of dying from breast cancer

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Abstract

Introduction—Multiple past studies have reported a reduced risk of breast cancer-related mortality (BCM) in relation to pre-diagnostic use of hormone therapy (HT); however, the extent to which this reduction is due to heightened screening or tumor biology is unknown.

Methods—Using a population-based cohort of 1,911 post-menopausal women diagnosed with invasive breast cancer at ages 45-79 from 1993-1999, we investigated the extent to which the reduced risk in BCM observed in relation to HRT might be explained by screening patterns or tumor features.

Results—Estrogen-progestin therapy (EPT) use was associated with a decreased risk of BCM (after adjustment for age, study, mammography, stage, and treatment), but only among older women (ever use: ≥65 years: HR = 0.45 [95% CI: 0.26-0.80]; <65 years: HR = 1.03 [95% CI: 0.60-1.79]). Estrogen-alone therapy (ET) use was not associated with risk of BCM (ever use: ≥65 years: HR= 0.76 [95% CI: 0.51-1.12]; <65 years: HR = 1.20 [95% CI: 0.71-2.02]). HT users had a much greater frequency of mammography (p-value < 0.001). EPT use was associated with tumor characteristics related to improved prognosis in older women after adjustment for screening, including an inverse association with poorly differentiated tumors (OR = 0.57 [95% CI: 0.38-0.85]) and an association with lobular tumors (OR = 1.68 [95% CI: 1.07-2.65]).

Conclusion—Beyond the influence of EPT use on screening uptake, these data indicate that the improved survival associated with pre-diagnostic EPT use may be due in part to the development of more favorable tumor characteristics.

Keywords

breast cancer; mortality; hormone therapy; prognosis

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Competing interests The author(s) declare that they have no competing interests.

Introduction

There has been long-standing interest in the possible influence of menopausal hormone therapy (HT) not only on the risk of developing breast cancer but also on the risk of dying from breast cancer. Multiple studies have investigated the association between risk of breast cancer-related mortality (BCM) and HT with the majority observing a reduced risk of death among women using HT, such as combined estrogen-progestin therapy (EPT) and estrogen-alone therapy (ET) [5,7,9,18,25,26,30,34]. Previous studies have also reported EPT use and ET use to be associated with many tumor characteristics related to a favorable prognosis [3,15,16,23] with one notable exception [6]. Specifically, the WHI trial reported EPT use to be associated with both an increased risk of advanced stage and larger tumor size [6]; however the WHI trial does not have estimates of BCM risk in relation to EPT use because insufficient follow-up time has elapsed for mortality analyses. At this point, the extent to which the reduced risk of BCM is due to differences in tumor biology or differences in health seeking behaviors between HT users and non-users remains unclear.

In addition, heterogeneity in BCM risk has been observed among postmenopausal women with middle-aged women found to have better survival than older women in some [1,17,22,35], but not all studies [8]. We thus hypothesized that age at diagnosis might also impact associations between menopausal HT use and the risk of BCM. Within a cohort of 1,911 post-menopausal breast cancer cases, our study examined the risk of death associated with pre-diagnostic use of EPT and ET, the extent to which mammography screening and/or tumor biology may explain the associations between EPT and BCM, and the presence of effect modification by age.

Materials and Methods

Study Design and Data Collection

The cohort study population, women diagnosed with invasive breast cancer between ages 45 and 79, was recruited from three previously conducted population-based case-control studies of incident breast cancer in Western Washington state. The methods for these three studies, the **E**lectro**m**agnetic **F**ields and Risk of Breast Cancer (EMF) Study [12,13] the Women's **C**ontraceptive **a**nd **R**eproductive **E**xperiences (CARE) Study [24], and the **P**uget Sound **A**rea Breast **C**ancer **E**valuation (PACE) Study [20], have been reported previously. The EMF Study included Caucasian women aged 20-74 years who were diagnosed between January 1993 and March 1995, of which all cases ages 45-74 years were eligible for the cohort (n=599); the CARE Study included African American and Caucasian women aged 35-64 years who were diagnosed between July 1994 and April 1998, of which all cases aged 45-64 years from the Seattle site of this multi-center study were eligible for the follow-up study (n=763); the PACE Study included women aged 65-79 years who were diagnosed between April 1997 through December 1999 (n=975). All cases were originally ascertained through the Cancer Surveillance System (CSS), the population-based tumor registry serving Western Washington, and a participant in the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, which captures more than 99% of incident cancer cases. The three case study populations were mutually exclusive of one another. Cases were required to have had histologic confirmation of their breast cancer, be English speaking, and have had no previous breast cancer diagnosis. In summary, the study cohort is comprised of 2,337 women diagnosed with invasive breast cancer at ages 45-79 in the years 1993-1999 while residing within the three county Seattle metropolitan area. Because this analysis focused on menopausal hormone therapy, we restricted the study population to women who were post-menopausal at diagnosis, resulting in 1,911 breast cancer cases for analysis.

As part of their participation in the previous case-control studies, women completed detailed in-person interviews which included histories of their lifetime use of HTs, including drug name, start and stop dates of use, separate and combined uses of estrogen and progestin, strength, and monthly pattern of pill use prior to diagnosis. In addition, trained abstractors reviewed medical records to obtain information on all courses of treatment for breast cancer, including radiotherapy, chemotherapy, and hormonal treatment. Study interviewers and abstractors were not aware of the study hypotheses. Informed consent was obtained from participants in the parent studies, as well as within the follow-up study prior to the interview (for interviewed participants) or prior to medical record review. This study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center.

Information on ER and PR status came from our centralized pathology review and the CSS. In the relatively small number of discordant instances (3.5% for ER and 12.0% for PR), hormone receptor status was classified as positive due to the possibility of tumor heterogeneity leading to accurate but discordant results from two sources.

Follow-up

The primary source of information on follow-up and vital status was the CSS, which uses both active surveillance, primarily consisting of contact with physicians and tumor registrars at the last hospital reporting follow-up, and passive surveillance, which includes monitoring national and local databases such as the National Death Index, Washington State death certificates, the Health Care Finance Administration, and the Department of Motor Vehicles. CSS follows cases even after they move out of the CSS catchment area. Cause of death information was obtained from CSS, death certificate reviews, and medical records with primary importance placed on classifying whether the death was due to breast cancer. A 2003 validation study looking at cancer deaths observed 80% agreement between the cause of death from pathologists and from death certificate reviews [36].

Participants underwent follow-up until the earliest of the date of death, the date last known to be alive, or the end date of follow-up (October 31, 2009). The 1,911 women eligible for this analysis were followed for a mean duration of 12.4 years. As of 10/09, 98.8% of QUILT living cases had been successfully followed up by CSS in the last 12 months. The primary mortality end point was breast cancer-related mortality. Of the 718 deaths observed to date, 283 (39.4%) were known to be due to breast carcinoma, 116 (16.2%) were due to cardiovascular disease, 73 (10.2%) were due to cancers other than breast cancer, 128 (17.8%) were due to other causes, and 118 (16.4%) were coded as unknown causes of death.

Statistical Methods

Primary mortality analyses examined associations between pre-diagnostic HT use and the risk of breast cancer-related mortality. The Cox proportional hazards model was used to estimate hazard ratios of risk factors for BCM and all-cause mortality. The failure times were left-truncated to account for the time lag between diagnosis and original interview. Censoring occurred at either the date of last known follow-up or the end date of follow-up (October 2009) if death had not occurred prior to this. Interaction terms were investigated using the likelihood ratio test (LRT).

Both duration and recency of pre-diagnostic HT use were examined as categorical variables. HT users of ≥ 60 months of use were classified as long-term users; those who used between 6 and 59 months of HT were classified as short-term users. Recency of use was categorized as current or former use (≥ 0.5 months since last use). Users of less than 6 months of HT use were excluded from our analyses. Never use of any HT served as the referent category.

We assessed the following factors for their potential confounding or modifying effects in analyses of the association between HT use and mortality: age at diagnosis, mammogram history (defined as having a screening mammogram in the five years prior to diagnosis), time since last screening mammogram (prior to diagnosis), SEER stage (local, regional/distant), histology (lobular, ductal, and other), estrogen receptor (ER) and progesterone receptor (PR) status (positive, negative), chemotherapy (ever, never), radiation (ever, never), hormone treatment (ever, never), type of hormone treatment (tamoxifen only, any aromatase inhibitors [AI], or none), mastectomy (yes, no), tumor size (< 1 cm, 1-1.9 cm, ≥ 2.0 cm), smoking history (never, former, current), body mass index at the time of diagnosis (< 25.0, 25-29.9, ≥ 30.0), education (some high school, graduated high school, some college, graduated college), income (<$15,000/year, $15,000 to $24,999, $25000 to $49,999/year, ≥ $50,000/year), race (white and non-white), age at menopause (< 45, 45-49, ≥ 50), parity (nulliparous, 1-2, 3-5, ≥ 6), age at 1st full-term pregnancy, (< 30, ≥ 30), age at menarche (≤ 12, > 12), oral contraceptive use (ever, never), and breast cancer family history (1^{st} degree relative[s] with breast cancer, no affected 1^{st} degree relative[s]). The Mantel-Haenszel Chi-Square test was used for bivariate analyses involving categorical variables.

Factors which were associated with both exposure and outcome and altered the HR by 10% or more were retained in the model. The exception to this was the inclusion of breast cancer treatment variables (regardless of association with exposure) in each survival model investigating the risk of BCM associated with HT use due to the strong association between breast cancer treatments and breast cancer-related survival.

In the investigation of effect modification by age at diagnosis, the age categories were set *a priori* at < 65 and ≥ 65 years (for ease, henceforth referred to as middle-aged and older women, respectively). The time interval between menopause and HT use was calculated using a woman's age at menopause and age at first use of HT. For this variable, use within 5 years of menopause also includes women who began HT use peri-menopausally (up to 2 years before menopause) for whom determination of age at menopause has been described previously (24).

In order to calculate the odds ratio (OR) and corresponding 95% CIs of developing a tumor with certain characteristics (many of which are known to affect prognosis) based on history of HT use, we used a logistic regression model adjusted for age at diagnosis, study, and mammography history. Stata (version 11.0) was used to conduct the analysis.

Results

The impact of demographic and tumor characteristics on risk of breast cancer-related death and all-cause death are shown in Table 1. Tumor characteristics known to be associated with poor prognosis, including regional/distant stage, advanced grade, larger tumor size, PR-negative, and ER-negative tumors, were associated with an increased risk of death. Additionally, a strong reduction in risk of dying was associated with a history of a screening mammogram in the past five years, with a greater reduction in risk observed for those with less time since their last mammogram. The association between history of mammography and BCM was attenuated after adjusting for ER and PR status, stage, and tumor size (HR = 0.75 [95% CI: 0.55-1.02]).

Compared to never users, users of HT were more likely to have a history of OC use, lower body mass index (BMI), higher incomes and more education than never users (Supplemental Table 1). EPT users were also more likely to have an older age at menopause while ET users had a younger age at menopause. With respect to breast cancer treatment, users of HT were

also more likely to use hormone treatments, including tamoxifen and AIs, after taking into account age and study.

Mammography screening in the five years before diagnosis was strongly associated with HT use (Table 2), and this association did not differ between older and middle-aged women. Overall, the proportions of women with a mammogram were very high among users of EPT and ET (on average 94.7% and 93.5%, respectively, compared to 69.8% in never users). Additionally, the mean time between diagnosis and a woman's last mammogram differed significantly between HT users and non-users with a mean of 21.3 months for non-users, 5.3 months for former EPT users, 2.6 months for current EPT users, 6.7 months for former ET users, and 3.4 months for current ET users.

To further examine the potential for mammography to impact the association between HT and BCM, we investigated how a woman's breast cancer was detected within a subset of the study population (from the EMF Study cases) on which this information was collected (n=461). We observed no association between use of EPT or ET and the manner in which breast cancer was detected (comparing EPT use to never use: p-value = 0.14; comparing ET use to never use: p-value = 0.30). Specifically, breast cancer was found by the study participant 40.9% of the time for ever users of EPT, 33.3% of the time for ever users of ET, and 40.2% for never users; found by a health professional 14.4%, 13.0%, 8.0% of the time, respectively for EPT users, ET users, and never users; found by a screening mammogram 41.7%, 52.6%, 51.8% of the time, respectively; or by another means 2.3%, 0.5%, and 0.0% of the time, respectively. There was also no association between HT and method of detection when investigated by recency of HT use, recency of mammogram, age, or stage.

There was the suggestion of a reduced risk of BCM associated with ever use of EPT in women overall (HR = 0.72 [95% CI: 0.50-1.03]; Table 3). We observed the risk of BCM associated with use of EPT to differ by age at diagnosis ($p_{heterogeneity} = 0.04$) with a 55% reduction in the risk of BCM associated with ever use of pre-diagnostic EPT among older women (95% CI: 0.26-0.80) and no association among middle-aged women (HR = 1.03 [95% CI: 0.60-1.79]) after controlling for age, study, stage, treatment, and mammography history. There was little additional variation in the risk estimates when examined in the context of duration and recency of EPT use. Adjustment for history of screening mammography substantially altered the risk of BCM associated with EPT use, as did adjustment for time since last mammogram. When mammography was not controlled for (i.e. removed from the above described model), ever use of EPT was associated with a 39% risk reduction of BCM (95% CI: 0.44-0.84) in all women, a 59% risk reduction (95% CI: 0.25-0.68) in older women, and a non-significant 20% risk reduction (95% CI: 0.51-1.27) in middle-aged women.

With respect to pre-diagnostic ET use, we observed no reduction in BCM risk overall, (ever use: HR = 0.93 [95% CI: 0.68-1.27]) and associations did not differ by age at diagnosis ($p_{heterogeneity} = 0.18$). While the point estimates were generally in opposite directions for all categories of ET use within middle-aged and older women, we did not observe statistically significant associations between ET use and BCM risk in either age group (ever use of pre-diagnostic ET among older women: HR = 0.76 [95% CI: 0.51-1.12]; middle-aged women: HR = 1.20 [95% CI: 0.71-2.02]).

We did not detect evidence of effect modification in the relationships between EPT use and risk of BCM by ER status, PR status, stage, tumor size, BMI, smoking or race, although our sample size was constrained in the numbers of women of non-white race. Additionally, we did not detect differences in BCM risk according to type of EPT used (e.g. continuous versus sequential EPT).

In response to a recent report of differing breast cancer risk in relation to the time interval between EPT initiation and menopause [28], we investigated whether risk of BCM differed according to this interval. Among middle-aged women, we observed BCM risk to differ by the length of time between menopause and initiation of EPT use ($p_{heterogeneity}$ <0.001; Table 4). No association with BCM risk was observed for EPT initiated within 5 years of menopause (HR=0.86 [95% CI: 0.47-1.56) whereas a 3.8-fold increased risk (95% CI: 1.76-8.36) of BCM was observed for EPT use initiated 5 or more years after menopause among middle-aged women. Differences were not observed in the risk of BCM for older women by the interval between menopause and EPT initiation ($p_{heterogeneity}$ =0.30), nor in either age group with respect to time interval between menopause and ET initiation.

We also investigated the impact of HT use on tumor characteristics (Table 5). EPT use was inversely associated with poorly differentiated tumors overall (OR = 0.67 [95% CI: 0.49-0.91]) and among older women (OR = 0.57 [95% CI: 0.38-0.85]). A similar association was not observed among middle-aged women (OR = 0.90 [95% CI: 0.55-1.48]) but this difference by age did not achieve statistical significance ($p_{heterogeneity}$ =0.15). Also, among older women, use of EPT was associated with the more favorable lobular histology (OR = 1.68 [95% CI: 1.07-2.65]) whereas no association was observed between lobular histology and EPT use in middle-aged women (OR = 0.93 [95% CI: 0.52-1.64]), although this difference did not reach statistical significance ($p_{heterogeneity}$ = 0.11). In contrast to this, we observed in middle-aged women a marginal inverse association with ET use and lobular histology (OR = 0.56 [95% CI: 0.30-1.03) and among older women a marginal association with tumor size (OR = 1.28 [95% CI: 0.94-1.74] for larger tumors), but the relationship between ET use and tumor size was substantially impacted by history of screening mammography (i.e without adjustment for screening, the association was attenuated [OR = 1.05 (95% CI: 0.79-1.39) for larger tumors]).

We did not observe variation in the associations with tumor characteristics when examined by duration of HT use with the possible exception of short-term EPT use and stage. Among older women, short-term EPT use was associated with a nearly significant increased risk of advanced stage (OR = 1.71 [95% CI: 0.95-3.07]) but not among long-term users (OR = 0.78 [95% CI: 0.47-1.29]; $p_{heterogeneity}$ = 0.05). In addition, we did not detect evidence of effect modification by history of mammography screening in the relationships between EPT use and tumor characteristics.

Discussion

Our study did not observe an association between pre-diagnostic ET use and risk of breast cancer-related mortality in the aggregate of all women ages 45 to 79 years nor within middle-aged or older women. Among the two larger studies reporting results for ever use of ET in relation to mortality, one study observed a modestly increased risk (OR = 1.23 [95% CI: 0.72-2.10]) of BCM among stage I breast cancers and the second reported an 11% reduction (95% CI: 0.78-1.02) of BCM overall among women aged 50 to 79 years [5,26]. Newcomb, et al, reported that the risk of BCM did not differ by recency or duration of ET use. One study reporting on age modification observed past and current users of ET less than 60 years of age at diagnosis to be at a 40% (95% CI: 0.4-1.0) and 60% (95% CI: 0.2-0.6) reduced risk of BCM, respectively, while older past and current users of ET had no reduction (95% CI: 0.6-1.8) and a 30% (95% CI: 0.4-1.4) reduction in the risk of BCM, respectively, in comparison to non-users [30]. Our study observed a modest, non-significant increased risk of BCM generally among middle-aged women and a non-significant decreased risk of BCM among older women in relation to ET use, but did not detect evidence of effect modification by age. Our findings, along with the prior reports for ET use

overall with BCM indicate that there is at most a modest association between ET use and death related to breast cancer.

Our study observed a reduced risk of dying from breast cancer associated with ever use of pre-diagnostic EPT (in women overall: HR = 0.72 [95% CI: 0.50-1.03]) that was largely confined to older women (HR = 0.45 [95% CI: 0.26-0.80]). These findings are consistent with the majority of previous studies reporting a reduction in risk of BCM associated with pre-diagnostic EPT use [5,7,9,18,25,26,30,34]. Among the two larger studies (n ≥ 1500) investigating this research question, the reduction in risk of BCM associated with ever use of pre-diagnostic EPT was 48% (95% CI: 0.26-1.04) and 27% (95% CI: 0.59-0.91) [5,26]. While the first study did not report on differences by duration or recency [5], the second study observed the risk to vary by duration and recency of EPT use with the greatest reduction in risk reported among long-term EPT users (HR = 0.60 [95% CI: 0.43-0.84]) and among current users (HR = 0.69 [95% CI: 0.55-0.88]) [26]. In our analyses we observed rather consistent risk estimates associated with ever use, recency and duration of EPT use overall and within the two age groups.

With respect to effect modification by age, the two previous studies that have considered this relationship have not similarly observed age to modify the effect of EPT use, although their age cutpoints differed from our cutpoint of 65 years (< 55 and < 60, respectively; refs: [5,26]). In addition to the consistent associations observed for duration and recency of EPT use within the separate age groups in our study, we also observed EPT use to be associated with favorable prognostic features only among older women, including a 43% risk reduction of poorly differentiated tumors and a 1.7-fold increased risk of lobular tumors in older women. Because the associations between EPT and favorable tumor characteristics were not similarly observed among middle-aged women, this may explain in part the differences in risks of BCM observed among the two age groups. It is also possible that with middle-aged women experiencing a lower baseline risk of BCM compared to older women, the reduction in risk associated with EPT use was more readily observed in older women.

A recent report using data from the WHI trial and observational study suggests that initiation of EPT soon after menopause led to greater risks of breast cancer incidence (HR = 1.77 [95% CI: 1.07-2.93]) whereas initiation of EPT use more than 5 years after menopause was not associated with breast cancer risk (HR = 0.99 [95% CI: 0.74-1.31]; ref: [28]). These authors also reported that the time interval between menopause and EPT initiation did not modify the association between EPT and overall mortality (HR for < 5 years = 0.73 [95% CI: 0.38-1.39]; HR for ≥5 years= 1.05 [95%CI: 0.84-1.33]; p-value = 0.36), although they did not report on breast cancer-related mortality. In our data we observed among middle-aged women a 3.8-fold increased risk of BCM for women initiating EPT use 5 or more years after menopause and no association among women who began use within 5 years of menopause. Taken together with the report by the WHI authors, these data suggest that middle-aged women initiating use of EPT 5 years after menopause do not experience an increased risk of breast cancer but if they develop breast cancer do not benefit from the improved survival associated with EPT use. Because this pattern was not similarly observed in older women (and because the proportions of women who initiated use 5 years after menopause differs substantially between older and middle-aged women), it may in part account for difference in BCM risk by age observed in our dataset. Clearly, replication of these findings would be needed before any firm conclusion can be drawn.

Studies to date have been unclear as to whether a reduction in BCM associated with EPT use is attributable in part to differences in health seeking behavior between EPT users and non-users (particularly as it impacts screening practices) and/or to the impact of EPT use on tumor biology. In our investigation of the impact of HT use on tumor characteristics, we

observed that ever use of EPT was associated with favorable prognostic features, including less aggressive grade among all women and among older women with lobular histology, after adjustment for screening.

The literature is currently mixed on whether HT use is related to favorable prognostic features in tumors. Initially, HT use was thought to lead to improved prognosis with most of the observational studies reporting favorable associations between HT use and tumor features. These reports included associations between HT use and smaller tumor size [3,16,23,32], less aggressive grade [5,29,31] decreased nodal involvement [14,23,31,32], less advanced stage [11,14], higher percentage of ER+ [5,11,14,16,29,32], and favorable histology [15,29], including *in situ* tumors [21,30]. However, some studies have either found no association between HT use and all favorable prognostic factors [19] or with some but not all favorable prognostic factors investigated [3,5,11,23,29,30,32,33]. Most notably, the WHI trial reported findings in opposition to the bulk of the observational studies with the report that tumors of (essentially by definition short-term) EPT users were larger in size (P=0.04) and more advanced in stage (P = 0.04; ref: [6]). Interestingly, we observed some suggestion of increased risk of advanced stage disease among older women in relation to short-term EPT use. With respect to the conflicting reports in the literature, it is possible that publication bias plays a role [2]. However, there are important differences between the WHI trial and observational studies. Among them is the difference in mammography rates for non-users (in WHI, non-users had yearly mammograms whereas in our study only 69.8% of never users had had a mammogram in the past 5 years). As such, non-users may have had smaller tumors detected in the WHI trial as opposed to our study in which non-users would be less likely to have smaller tumors detected because mammographic screening was undertaken less frequently.

We observed in several instances the impact of mammography on the associations between HT use and tumor characteristics to be substantial, including a nearly significant association between ET use and increased tumor size after adjustment for mammogram history. In addition we observed that HT users were receiving screening mammograms more regularly and with less time between mammogram and diagnosis compared to non-users in both age groups (an aspect that was not supported by another recent study investigating this research question; ref: [27]). However, we also found in a subset of cases with this information available that HT users were no more likely to have had their cancer detected by a mammogram or health practitioner than never users of HT. In addition, screening was associated with EPT use to a similar degree in middle-aged and older women; in middle-aged women, however, despite the increased screening in EPT users relative to non-users, EPT users were not observed to be at a reduced risk of BCM in relation to EPT use, suggesting that perhaps other factors contributed to the reduced BCM risk in older women. We did, however, observe that a recent mammogram reduced the risk of all-cause mortality by 50%. These findings taken together indicate that although the majority of EPT users' breast cancers were not detected by mammograms, mammograms may well serve as an important marker of health seeking behavior.

We investigated the potential for unmeasured health seeking behaviors to confound our associations by investigating the association between HT use and multiple mortality endpoints in our analyses. We observed the risk of all-cause mortality to be reduced among HT users (HR = 0.71 [95% CI: 0.60-0.83]), a non-significant reduction in all cancer-related deaths (HR = 0.87 [95% CI: 0.68-1.11]), and a reduction in risk of deaths due to CVD (HR = 0.51 [95% CI: 0.35-0.74]). These associations were similarly observed in a previous report by another group investigating the role of pre-diagnostic HT use on breast cancer mortality [26].

Within an observational study, such as this, a potential limitation is the possibility that unmeasured confounding factors play a role in the findings. Despite the breadth of data available to us for assessing potential confounding influences, including reproductive variables, BMI, screening, and breast cancer treatments, we could not exclude the possibility that unmeasured confounders accounted in part for our findings of a reduced risk of breast cancer death associated with EPT use. An additional limitation of the current study is that the ascertainment of hormone therapy use relied on self-reports. However, a prior validation study conducted within the subset of women in our study who were originally recruited into the PACE Study (and who constitute the oldest age categories in this report) observed the agreement between self-reported medication use and pharmacy records overall to be good [4]. In addition, because the parent case-control studies observed breast cancer risks in relation to HT use that are consistent with those in the literature [10,20], we are fairly confident in the participant's reports of HT use. Lastly, a potential study limitation is the omission of a portion of breast cancer cases who were eligible but did not participate in the parent case-control studies. The primary reason a woman did not participate in the parent studies was that death from breast cancer occurred before she could be enrolled; thus, our study's findings may only be generalizable to women who have survived at least one year. Strengths of our study include the generous sample of women older than 65 years in whom we can investigate associations between HT use and BCM.

Conclusions

The results from this study suggest that the reduction in risk of BCM associated with EPT use prior to diagnosis is strongest among women who are 65 years of age and older at the time of diagnosis. In our investigation of the impact of screening mammography and tumor characteristics on this reduction in mortality, we observed HT use overall to be strongly associated with a history of mammography similarly in both age groups and EPT use to be associated additionally with favorable histology and grade among older women. The associations with tumor characteristics persisted beyond adjustment for screening, which provides support for the hypothesis that biologic mechanisms underlie the relationship between EPT use and BCM. In addition, we observed that the time interval between menopause and initiation of EPT use may contribute to the differences in risk of breast cancer-related death by age, but this would need to be confirmed by future studies. While our study cannot exclude the possibility that unmeasured confounders may affect our findings, our study adds to the growing literature indicating that pre-diagnostic EPT use is associated with a decreased risk of death among breast cancer patients, at least among older women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Adami HO, Malker B, Holmberg L, Persson I, Stone B. The relation between survival and age at diagnosis in breast cancer. N Engl J Med. 1986; 315(9):559–63. [PubMed: 3736639]

2. Antoine C, Liebens F, Carly B, Pastijn A, Rozenberg S. Influence of HRT on prognostic factors for breast cancer: a systematic review after the Women's Health Initiative trial. Hum Reprod. 2004; 19(3):741–756. [PubMed: 14998980]
3. Biglia N, Sgro L, Defabiani E, De R G, Ponzone R, Marenco D, Sismondi P. The influence of hormone replacement therapy on the pathology of breast cancer. Eur J Surg Oncol. 2005; 31(5): 467–472. [PubMed: 15922881]
4. Boudreau DM, Daling JR, Malone KE, Gardner JS, Blough DK, Heckbert SR. A validation study of patient interview data and pharmacy records for antihypertensive, statin, and antidepressant medication use among older women. Am J Epidemiol. 2004; 159(3):308–17. [PubMed: 14742292]
5. Chen W, Petitti DB, Geiger AM. Mortality following development of breast cancer while using oestrogen or oestrogen plus progestin: a computer record-linkage study. Br J Cancer. 2005; 93(4): 392–398. [PubMed: 16106246]
6. Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, Rodabough RJ, Gilligan MA, Cyr MG, Thomson CA, Khandekar J, Petrovitch H, McTiernan A. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA. 2003; 289(24):3243–3253. [PubMed: 12824205]
7. Christante D, Pommier S, Garreau J, Muller P, LaFleur B, Pommier R. Improved breast cancer survival among hormone replacement therapy users is durable after 5 years of additional follow-up. Am J Surg. 2008; 196(4):505–511. [PubMed: 18809052]
8. Cluze C, Colonna M, Remontet L, Poncet F, Sellier E, Seigneurin A, Delafosse P, Bossard N. Analysis of the effect of age on the prognosis of breast cancer. Breast Cancer Res Treat. 2009; 117(1):121–129. [PubMed: 18931908]
9. Colditz GA, Hankinson SE, Hunter DJ, Willett WC, Manson JE, Stampfer MJ, Hennekens C, Rosner B, Speizer FE. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med. 1995; 332(24):1589–93. [PubMed: 7753136]
10. Daling JR, Malone KE, Doody DR, Voigt LF, Bernstein L, Coates RJ, Marchbanks PA, Norman SA, Weiss LK, Ursin G, Berlin JA, Burkman RT, Deapen D, Folger SG, McDonald JA, Simon MS, Strom BL, Wingo PA, Spirtas R. Relation of regimens of combined hormone replacement therapy to lobular, ductal, and other histologic types of breast carcinoma. Cancer. 2002; 95(12): 2455–2464. [PubMed: 12467057]
11. Daling JR, Malone KE, Doody DR, Voigt LF, Bernstein L, Marchbanks PA, Coates RJ, Norman SA, Weiss LK, Ursin G, Burkman RT, Deapen D, Folger SG, McDonald JA, Simon MS, Strom BL, Spirtas R. Association of regimens of hormone replacement therapy to prognostic factors among women diagnosed with breast cancer aged 50-64 years. Cancer Epidemiol Biomarkers Prev. 2003; 12(11 Pt 1):1175–1181. [PubMed: 14652277]
12. Davis S, Mirick DK, Stevens RG. Night shift work, light at night, and risk of breast cancer. J Natl Cancer Inst. 2001; 93(20):1557–1662. [PubMed: 11604479]
13. Davis S, Mirick DK, Stevens RG. Residential magnetic fields and the risk of breast cancer. Am J Epidemiol. 2002; 155(5):446–54. [PubMed: 11867356]
14. Delgado RC, Lubian Lopez DM. Prognosis of breast cancers detected in women receiving hormone replacement therapy. Maturitas. 2001; 38(2):147–156. [PubMed: 11306203]
15. Gapstur SM, Morrow M, Sellers TA. Hormone replacement therapy and risk of breast cancer with a favorable histology: results of the Iowa Women's Health Study. JAMA. 1999; 281(22):2091–2097. [PubMed: 10367819]
16. Hall P, Ploner A, Bjohle J, Huang F, Lin CY, Liu ET, Miller LD, Nordgren H, Pawitan Y, Shaw P, Skoog L, Smeds J, Wedren S, Ohd J, Bergh J. Hormone-replacement therapy influences gene expression profiles and is associated with breast-cancer prognosis: a cohort study. BMC Med. 2006; 4:16. [PubMed: 16813654]
17. Holli K, Isola J. Effect of age on the survival of breast cancer patients. Eur J Cancer. 1997; 33(3): 425–428. [PubMed: 9155527]
18. Jernstrom H, Frenander J, Ferno M, Olsson H. Hormone replacement therapy before breast cancer diagnosis significantly reduces the overall death rate compared with never-use among 984 breast cancer patients. Br J Cancer. 1999; 80(9):1453–1458. [PubMed: 10424750]

19. Khan HN, Bendall S, Bates T. Is hormone replacement therapy-related breast cancer more favorable? A case-control study. Breast J. 2007; 13(5):496–500. [PubMed: 17760672]
20. Li CI, Malone KE, Porter PL, Weiss NS, Tang MT, Cushing-Haugen KL, Daling JR. Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. JAMA. 2003; 289(24):3254–3263. [PubMed: 12824206]
21. Longnecker MP, Bernstein L, Paganini-Hill A, Enger SM, Ross RK. Risk factors for in situ breast cancer. Cancer Epidemiol Biomarkers Prev. 1996; 5(12):961–965. [PubMed: 8959317]
22. Louwman WJ, Voogd AC, van Dijck JA, Nieuwenhuijzen GA, Ribot J, Pruijt JF, Coebergh JW. On the rising trends of incidence and prognosis for breast cancer patients diagnosed 1975-2004: a long-term population-based study in southeastern Netherlands. Cancer Causes Control. 2008; 19(1):97–106. [PubMed: 18038250]
23. Magnusson C, Holmberg L, Norden T, Lindgren A, Persson I. Prognostic characteristics in breast cancers after hormone replacement therapy. Breast Cancer Res Treat. 1996; 38(3):325–334. [PubMed: 8739086]
24. Marchbanks PA, McDonald JA, Wilson HG, Burnett NM, Daling JR, Bernstein L, Malone KE, Strom BL, Norman SA, Weiss LK, Liff JM, Wingo PA, Burkman RT, Folger SG, Berlin JA, Deapen DM, Ursin G, Coates RJ, Simon MS, Press MF, Spirtas R. The NICHD Women's Contraceptive and Reproductive Experiences Study: methods and operational results. Ann Epidemiol. 2002; 12(4):213–221. [PubMed: 11988408]
25. Nanda K, Bastian LA, Schulz K. Hormone replacement therapy and the risk of death from breast cancer: a systematic review. Am J Obstet Gynecol. 2002; 186(2):325–334. [PubMed: 11854659]
26. Newcomb PA, Egan KM, Trentham-Dietz A, Titus-Ernstoff L, Baron JA, Hampton JM, Stampfer MJ, Willett WC. Prediagnostic use of hormone therapy and mortality after breast cancer. Cancer Epidemiol Biomarkers Prev. 2008; 17(4):864–871. [PubMed: 18381475]
27. Onega T, MacKenzie T, Weiss J, Goodrich M, Titus-Ernstoff L. Screening mammography intervals among postmenopausal hormone therapy users and nonusers. Cancer Causes Control. 2010; 21(1):147–152. [PubMed: 19844798]
28. Prentice RL, Manson JE, Langer RD, Anderson GL, Pettinger M, Jackson RD, Johnson KC, Kuller LH, Lane DS, Wactawski-Wende J, Brzyski R, Allison M, Ockene J, Sarto G, Rossouw JE. Benefits and Risks of Postmenopausal Hormone Therapy When It Is Initiated Soon After Menopause. Am J Epidemiol. 2009
29. Rosenberg LU, Granath F, Dickman PW, Einarsdottir K, Wedren S, Persson I, Hall P. Menopausal hormone therapy in relation to breast cancer characteristics and prognosis: a cohort study. Breast Cancer Res. 2008; 10(5):R78. [PubMed: 18803850]
30. Schairer C, Gail M, Byrne C, Rosenberg PS, Sturgeon SR, Brinton LA, Hoover RN. Estrogen replacement therapy and breast cancer survival in a large screening study. J Natl Cancer Inst. 1999; 91(3):264–270. [PubMed: 10037105]
31. Sener SF, Winchester DJ, Winchester DP, Du H, Barrera E, Bilimoria M, Krantz S, Rabbitt S. The effects of hormone replacement therapy on postmenopausal breast cancer biology and survival. Am J Surg. 2009; 197(3):403–407. [PubMed: 19245923]
32. Slanger TE, Chang-Claude JC, Obi N, Kropp S, Berger J, Vettorazzi E, Braendle W, Bastert G, Hentschel S, Flesch-Janys D. Menopausal hormone therapy and risk of clinical breast cancer subtypes. Cancer Epidemiol Biomarkers Prev. 2009; 18(4):1188–1196. [PubMed: 19336542]
33. Stanford JL, Weiss NS, Voigt LF, Daling JR, Habel LA, Rossing MA. Combined estrogen and progestin hormone replacement therapy in relation to risk of breast cancer in middle-aged women. JAMA. 1995; 274(2):137–142. [PubMed: 7596001]
34. Strickland DM, Gambrell RD, Butzin CA, Strickland K. The relationship between breast cancer survival and prior postmenopausal estrogen use. Obstet Gynecol. 1992; 80(3 Pt 1):400–404. [PubMed: 1495695]
35. Ugnat AM, Xie L, Morriss J, Semenciw R, Mao Y. Survival of women with breast cancer in Ottawa, Canada: variation with age, stage, histology, grade and treatment. Br J Cancer. 2004; 90(6):1138–1143. [PubMed: 15026792]
36. Ziogas A, nton-Culver H. Validation of family history data in cancer family registries. Am J Prev Med. 2003; 24(2):190–198. [PubMed: 12568826]

List of abbreviations

BMI	body mass index
BCM	breast cancer-related mortality
CI	confidence interval
CVD	cardiovascular disease
ET	estrogen-alone therapy
EPT	estrogen-progestin therapy
ER	estrogen receptor
HR	hazards ratio
HT	menopausal hormone therapy
OR	odds ratio
PR	progesterone receptor

Table 1

Relationship of demographic, treatment, and tumor characteristics to the risk of dying

	Alive (n=1193)		BC-related (n=283)		Non-BC related (n=435)		BC-related death		All-cause death	
	n	%	n	%	n	%	HR[1]	95% CI	HR[1]	95% CI
Age at diagnosis[2]										
45-54	109	(9.1)	31	(11.0)	7	(1.6)	1.00	(ref)	1.00	(ref)
55-64	417	(35.0)	93	(32.9)	69	(15.9)	0.76	(0.50-1.14)	1.07	(0.75-1.52)
65-74	532	(44.6)	123	(43.5)	236	(54.3)	1.02	(0.60-1.74)	**2.04**	(1.35-3.08)
75-79	135	(11.3)	36	(12.7)	123	(28.3)	1.14	(0.58-2.22)	**3.38**	(2.13-5.35)
Age at menopause										
<45	250	(22.5)	70	(26.3)	115	(29.2)	1.00	(ref)	1.00	(ref)
45-49	356	(32.0)	84	(31.6)	115	(29.2)	1.02	(0.73-1.42)	0.89	(0.73-1.10)
50+	507	(45.6)	112	(42.1)	164	(41.6)	0.97	(0.71-1.32)	**0.79**	(0.66-0.96)
Missing	80		17		41					
Family history										
No 1st degree	868	(77.7)	199	(76.8)	322	(78.3)	1.00	(ref)	1.00	(ref)
1st degree	249	(22.3)	60	(23.2)	89	(21.7)	1.08	(0.80-1.45)	1.04	(0.86-1.26)
Missing	76		24		24					
Mammography[3,4]										
No	110	(9.5)	68	(24.9)	77	(18.4)	1.00	(ref)	1.00	(ref)
Yes	1054	(90.5)	205	(75.1)	341	(81.6)	**0.42**	(0.32-0.56)	**0.50**	(0.42-0.60)
Missing	29		10		17					
Time since last mammogram[4]										
None	59	(5.1)	48	(17.5)	48	(11.3)	1.00	(ref)	1.00	(ref)
<2 yrs	845	(72.3)	142	(51.6)	268	(63.1)	**0.30**	(0.22-0.42)	**0.44**	(0.35-0.55)
2 yrs	157	(13.4)	42	(15.3)	53	(12.5)	**0.45**	(0.30-0.68)	**0.51**	(0.38-0.67)
3+ yrs	107	(9.2)	43	(15.6)	56	(13.2)	**0.59**	(0.39-0.90)	**0.73**	(0.55-0.96)
Missing	25		8		10					
Stage										
Local	950	(79.9)	95	(34.1)	331	(77.3)	1.00	(ref)	1.00	(ref)

	Alive (n=1193)		BC-related (n=283)		Non-BC related (n=435)		BC-related death		All-cause death	
	n	%	n	%	n	%	HR[1]	95% CI	HR[1]	95% CI
Regional/Distant	239	(20.1)	184	(65.9)	97	(22.7)	**5.69**	(4.41-7.35)	**2.23**	(1.91-2.61)
Missing	4		4		7					
Histology										
Ductal	830	(69.6)	196	(69.3)	290	(66.7)	1.00	(ref)	1.00	(ref)
Any Lobular[5]	200	(16.8)	60	(21.2)	87	(20.0)	1.21	(0.90-1.63)	1.10	(0.91-1.33)
Other	163	(13.7)	27	(9.5)	58	(13.3)	0.72	(0.48-1.10)	0.94	(0.74-1.19)
ER status										
ER+	995	(83.4)	208	(73.5)	371	(85.3)	1.00	(ref)	1.00	(ref)
ER-	132	(11.1)	61	(21.6)	49	(11.3)	**2.09**	(1.55-2.82)	**1.70**	(1.38-2.10)
Borderline/Unknown	66	(5.5)	14	(4.9)	15	(3.4)	1.10	(0.64-1.89)	0.87	(0.59-1.27)
PR status										
PR+	904	(75.8)	175	(61.8)	322	(74.0)	1.00	(ref)	1.00	(ref)
PR-	226	(18.9)	94	(33.2)	98	(22.5)	**1.91**	(1.48-2.48)	**1.58**	(1.33-1.88)
Borderline/Unknown	63	(5.3)	14	(4.9)	15	(3.4)	1.24	(0.72-2.15)	0.93	(0.63-1.37)
Grade										
Well	248	(23.7)	15	(6.2)	83	(21.8)	1.00	(ref)	1.00	(ref)
Moderate	446	(42.6)	72	(29.6)	158	(41.6)	**2.35**	(1.35-4.11)	1.25	(0.98-1.59)
Poor	302	(28.8)	129	(53.1)	121	(31.8)	**5.42**	(3.16-9.31)	**1.98**	(1.56-2.52)
Undifferentiated	51	(4.9)	27	(11.1)	18	(4.7)	**6.49**	(3.41-12.34)	**2.10**	(1.46-3.02)
Missing	146		40		55					
Tumor size										
<1 cm	330	(28.2)	21	(8.3)	112	(26.5)	1.00	(ref)	1.00	(ref)
1-<2 cm	545	(46.6)	55	(21.7)	180	(42.6)	1.47	(0.88-2.44)	1.09	(0.88-1.35)
2+ cm	294	(25.1)	178	(70.1)	131	(31.0)	**7.17**	(4.54-11.31)	**2.19**	(1.78-2.69)
Missing	24		29		12					

[1] Models adjusted for age (continuous), study, and mammography history, except where noted

[2] Models not adjusted for age

[3] History of mammography in the 5 years prior to diagnosis

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[4] Models not adjusted for mammography history

[5] Lobular includes mixed lobular

Table 2

Distribution of mammography screening among categories of pre-diagnostic hormone therapy use stratified by age

	Mammography History [1]											
	All women				Age <65				Age 65+			
	No (n=255)		Yes (n=1600)		No (n=102)		Yes (n=619)		No (n=153)		Yes (n=981)	
	n	%	n	%	n	%	n	%	n	%	n	%
EPT use[2,3]												
Never use	154	(30.2)	356	(69.8)	58	(38.4)	93	(61.6)	96	(26.7)	263	(73.3)
Short term use	15	(6.9)	202	(93.1)	10	(7.0)	133	(93.0)	5	(6.8)	69	(93.2)
Current	6	(4.5)	127	(95.5)	6	(6.1)	93	(93.9)	0	(0.0)	34	(100.0)
Former	9	(10.7)	75	(89.3)	4	(9.1)	40	(90.9)	5	(12.5)	35	(87.5)
Long-term use	15	(4.2)	343	(95.8)	9	(5.1)	166	(94.9)	6	(3.3)	177	(96.7)
Current	12	(3.7)	313	(96.3)	7	(4.3)	156	(95.7)	5	(3.1)	157	(96.9)
Former	3	(9.4)	29	(90.6)	2	(18.2)	9	(81.8)	1	(4.8)	20	(95.2)
<6 months EPT[4]	8		49		6		29		2		20	
Other HRT[4]	63		650		19		198		44		452	
Missing[4]	0		1		0		1		0		0	
p-value[5]			<0.001									
ET use[2,3]												
Never use	154	(30.2)	356	(69.8)	58	(38.4)	93	(61.6)	96	(26.7)	263	(73.3)
Short term use	12	(5.6)	202	(94.4)	9	(10.2)	79	(89.8)	3	(2.4)	123	(97.6)
Current	3	(3.8)	75	(96.2)	3	(6.0)	47	(94.0)	0	(0.0)	28	(100.0)
Former	9	(6.6)	127	(93.4)	6	(15.8)	32	(84.2)	3	(3.1)	95	(96.9)
Long-term use	40	(6.8)	549	(93.2)	7	(3.9)	173	(96.1)	33	(8.1)	376	(91.9)
Current	24	(5.6)	407	(94.4)	7	(4.7)	141	(95.3)	17	(6.0)	266	(94.0)
Former	16	(10.1)	142	(89.9)	0	(0.0)	32	(100.0)	16	(12.7)	110	(87.3)
<6 months ET[4]	15		91		7		28		8		63	
Other HRT[4]	34		402		21		246		13		156	
p-value[5]			<0.001									

[1] Defined as having had a screening mammogram in the 5 years prior to diagnosis; row percentages are presented here

[2] Short-term use is defined as use lasting from 6 months to <5 years

[3] Long-term use is defined as use lasting ≥5 years

[4] Excluded from this and subsequent analyses

[5] Testing the association between pre-diagnostic HT ever use and mammography in all women

Table 3

Risk of dying from breast cancer in relation to pre-diagnostic hormone therapy use, stratified by age

	All women		< 65 years				≥ 65 years							
			Alive/cens. (n=602)		BC death (n=124)				Alive/cens. (n=1026)		BC death (n=159)			
	HR[1]	95% CI	n	%	n	%	HR[1]	95% CI	n	%	n	%	HR[1]	95% CI	p-value
EPT use															
Never use	1.00	(ref)	121	(79.6)	31	(20.4)	1.00	(ref)	317	(83.9)	61	(16.1)	1.00	(ref)	
Ever use	0.72	(0.50-1.03)	269	(84.1)	51	(15.9)	1.03	(0.60-1.79)	245	(91.4)	23	(8.6)	**0.45**	(0.26-0.80)	0.04
Short term use[2]	0.65	(0.40-1.05)	124	(85.5)	21	(14.5)	0.90	(0.47-1.72)	70	(89.7)	8	(10.3)	**0.42**	(0.18-0.97)	
Current	0.62	(0.34-1.13)	87	(87.0)	13	(13.0)	0.80	(0.38-1.70)	32	(88.9)	4	(11.1)	0.44	(0.13-1.47)	
Former	0.69	(0.37-1.29)	37	(82.2)	8	(17.8)	1.10	(0.48-2.54)	38	(90.5)	4	(9.5)	0.42	(0.15-1.19)	
Long-term use[3]	0.76	(0.51-1.14)	145	(82.9)	30	(17.1)	1.15	(0.63-2.12)	175	(92.1)	15	(7.9)	**0.47**	(0.25-0.90)	
Current	0.72	(0.47-1.10)	137	(84.0)	26	(16.0)	1.09	(0.58-2.05)	156	(92.9)	12	(7.1)	**0.44**	(0.22-0.88)	
Former	0.95	(0.40-2.22)	8	(72.7)	3	(27.3)	1.25	(0.36-4.33)	19	(86.4)	3	(13.6)	0.67	(0.20-2.27)	
ET use															
Never use	1.00	(ref)	121	(79.6)	31	(20.4)	1.00	(ref)	317	(83.9)	61	(16.1)	1.00	(ref)	
Ever use	0.93	(0.68-1.27)	219	(80.8)	52	(19.2)	1.20	(0.71-2.02)	481	(86.7)	74	(13.3)	0.76	(0.51-1.12)	0.18
Short term use[2]	0.96	(0.63-1.47)	66	(73.3)	24	(26.7)	1.36	(0.75-2.47)	119	(90.8)	12	(9.2)	0.59	(0.30-1.16)	
Current	1.01	(0.57-1.80)	37	(72.5)	14	(27.5)	1.22	(0.60-2.49)	26	(92.9)	2	(7.1)	0.37	(0.09-1.58)	
Former	0.92	(0.55-1.56)	29	(74.4)	10	(25.6)	1.58	(0.72-3.45)	93	(90.3)	10	(9.7)	0.70	(0.34-1.44)	
Long-term use[3]	0.92	(0.66-1.28)	153	(84.5)	28	(15.5)	1.07	(0.59-1.94)	362	(85.4)	62	(14.6)	0.80	(0.54-1.20)	
Current	0.92	(0.64-1.32)	129	(86.6)	20	(13.4)	0.90	(0.48-1.71)	248	(84.4)	46	(15.6)	0.92	(0.59-1.43)	
Former	0.91	(0.56-1.49)	24	(75.0)	8	(25.0)	2.07	(0.88-4.89)	114	(87.7)	16	(12.3)	0.60	(0.32-1.11)	

[1] Adjusted for age (continuous), study, history of screening mammography, stage, chemotherapy, radiation, and hormone treatment

[2] Short-term use is defined as use lasting from 6 months to <5 years

[3] Long-term use is defined as use lasting ≥5 years

Table 4

Risk of dying from breast cancer jn relation to pre-diagnostic hormone therapy use, stratified by the interval between menopause and HT use

	< 65 years						≥ 65 years					
	Alive/cens. (n=602)		BC death (n=124)				Alive/cens. (n=1026)		BC death (n=159)			
	n	%	n	%	HR[1]	95% CI	n	%	n	%	HR[1]	95% CI
EPT use												
Never use	121	(79.6)	31	(20.4)	1.00	(ref)	317	(83.9)	61	(16.1)	1.00	(ref)
Ever use began within 5 yrs of menopause	224	(86.2)	36	(13.8)	0.86	(0.47-1.56)	89	(93.7)	6	(6.3)	**0.33**	(0.14-0.82)
Short term use[2]	104	(87.4)	15	(12.6)	0.73	(0.35-1.50)	12	(92.3)	1	(7.7)	0.28	(0.04-2.12)
Long-term use[3]	120	(85.1)	21	(14.9)	1.00	(0.51-1.95)	77	(93.9)	5	(6.1)	**0.34**	(0.13-0.91)
Ever use began ≥5 yrs of menopause	38	(73.1)	14	(26.9)	**3.83**	(1.76-8.36)	123	(89.8)	14	(10.2)	0.56	(0.28-1.12)
Short term use[2]	16	(72.7)	6	(27.3)	**3.87**	(1.43-10.48)	50	(90.9)	5	(9.1)	0.41	(0.14-1.21)
Long-term use[3]	22	(73.3)	8	(26.7)	**4.00**	(1.60-9.96)	73	(89.0)	9	(11.0)	0.68	(0.31-1.50)
p-value[4]						<0.001						0.30
ET use												
Never use	121	(79.6)	31	(20.4)	1.00	(ref)	317	(83.9)	61	(16.1)	1.00	(ref)
Ever use began within 5 yrs of menopause	197	(81.7)	44	(18.3)	1.16	(0.68-1.98)	291	(87.9)	40	(12.1)	0.77	(0.49-1.21)
Short term use[2]	57	(76.0)	18	(24.0)	1.25	(0.66-2.39)	67	(93.1)	5	(6.9)	0.63	(0.25-1.62)
Long-term use[3]	140	(84.3)	26	(15.7)	1.08	(0.59-1.98)	224	(86.5)	35	(13.5)	0.80	(0.50-1.27)
Ever use began ≥5 yrs of menopause	11	(61.1)	7	(38.9)	1.68	(0.69-4.05)	76	(80.0)	19	(20.0)	1.03	(0.56-1.89)
Short term use[2]	8	(57.1)	6	(42.9)	1.89	(0.75-4.78)	33	(86.8)	5	(13.2)	0.73	(0.28-1.88)
Long-term use[3]	3	(75.0)	1	(25.0)	0.97	(0.12-7.56)	43	(75.4)	14	(24.6)	1.27	(0.63-2.56)
p-value[4]						0.37						0.35

[1] Adjusted for age (continuous), study, history of screening mammography, stage, chemotherapy, radiation, and hormone treatment

[2] Short-term use is defined as use lasting from 6 months to <5 years

[3] Long-term use is defined as use lasting ≥5 years

[4] Testing the difference between initiation of HT use of <5 and ≥5 years after menopause for ever users

Table 5

Relationship between pre-diagnostic hormone therapy use and breast cancer characteristics[1]

	All Women						< 65 years						≥ 65 years					
	n	%	n	%	OR[2]	95% CI	n	%	n	%	OR[2]	95% CI	n	%	n	%	OR[2]	95% CI
	***ER*+ (n=1559)**		***ER*- (n=234)**				***ER*+ (n=557)**		***ER*- (n=118)**				***ER*+ (n=1002)**		***ER*- (n=116)**			
EPT																		
Never	439	(47.0)	62	(49.6)	1.00	(ref)	115	(30.7)	21	(32.8)	1.00	(ref)	324	(57.9)	41	(67.2)	1.00	(ref)
Ever	496	(53.0)	63	(50.4)	0.67	(0.44-1.04)	260	(69.3)	43	(67.2)	0.74	(0.40-1.36)	236	(42.1)	20	(32.8)	0.54	(0.28-1.03)
ET																		
Never	439	(39.1)	62	(36.0)	1.00	(ref)	115	(35.5)	21	(27.6)	1.00	(ref)	324	(40.6)	41	(42.7)	1.00	(ref)
Ever	683	(60.9)	110	(64.0)	1.02	(0.71-1.48)	209	(64.5)	55	(72.4)	1.21	(0.66-2.22)	474	(59.4)	55	(57.3)	0.90	(0.56-1.45)
	***PR*+ (n=1389)**		***PR*- (n=400)**				***PR*+ (n=502)**		***PR*- (n=176)**				***PR*+ (n=887)**		***PR*- (n=224)**			
EPT																		
Never	382	(46.0)	122	(52.4)	1.00	(ref)	103	(30.3)	36	(35.0)	1.00	(ref)	279	(56.8)	86	(66.2)	1.00	(ref)
Ever	449	(54.0)	111	(47.6)	0.80	(0.57-1.11)	237	(69.7)	67	(65.0)	0.73	(0.44-1.23)	212	(43.2)	44	(33.8)	0.81	(0.51-1.27)
ET																		
Never	382	(38.7)	122	(39.5)	1.00	(ref)	103	(36.1)	36	(30.8)	1.00	(ref)	279	(39.8)	86	(44.8)	1.00	(ref)
Ever	604	(61.3)	187	(60.5)	1.00	(0.75-1.34)	182	(63.9)	81	(69.2)	1.29	(0.77-2.15)	422	(60.2)	106	(55.2)	0.88	(0.62-1.24)
	***Ductal* (n=1316)**		***Lob/Mix* (n=347)**				***Ductal* (n=516)**		***Lob/Mix* (n=115)**				***Ductal* (n=800)**		***Lob/Mix* (n=232)**			
EPT																		
Never	372	(48.4)	84	(42.0)	1.00	(ref)	106	(32.2)	25	(31.6)	1.00	(ref)	266	(60.5)	59	(48.8)	1.00	(ref)
Ever	397	(51.6)	116	(58.0)	1.37	(0.96-1.96)	223	(67.8)	54	(68.4)	0.93	(0.52-1.64)	174	(39.5)	62	(51.2)	**1.68**	(1.07-2.65)
ET																		
Never	372	(39.5)	84	(34.7)	1.00	(ref)	106	(34.1)	25	(43.1)	1.00	(ref)	266	(42.2)	59	(32.1)	1.00	(ref)
Ever	570	(60.5)	158	(65.3)	1.14	(0.83-1.57)	205	(65.9)	33	(56.9)	0.56	(0.30-1.03)	365	(57.8)	125	(67.9)	1.46	(1.00-2.11)
	***Local* (n=1376)**		***Reg/Dist* (n=520)**				***Local* (n=485)**		***Reg/Dist* (n=237)**				***Local* (n=891)**		***Reg/Dist* (n=283)**			
EPT																		
Never	373	(46.2)	151	(49.7)	1.00	(ref)	91	(29.0)	59	(38.1)	1.00	(ref)	282	(57.2)	92	(61.7)	1.00	(ref)
Ever	434	(53.8)	153	(50.3)	0.96	(0.70-1.31)	223	(71.0)	96	(61.9)	0.85	(0.54-1.34)	211	(42.8)	57	(38.3)	1.02	(0.66-1.58)
ET																		
Never	373	(38.7)	151	(39.7)	1.00	(ref)	91	(33.6)	59	(39.6)	1.00	(ref)	282	(40.8)	92	(39.8)	1.00	(ref)

	All Women						< 65 years						≥ 65 years					
	n	**%**	**n**	**%**	**OR[2]**	**95% CI**	**n**	**%**	**n**	**%**	**OR[2]**	**95% CI**	**n**	**%**	**n**	**%**	**OR[2]**	**95% CI**
Ever	590	(61.3)	229	(60.3)	1.17	(0.89-1.53)	180	(66.4)	90	(60.4)	1.01	(0.63-1.61)	410	(59.2)	139	(60.2)	1.25	(0.89-1.75)
	***Well/Mod* (n=1022)**		***Poor/Undiff* (n=648)**				***Well/Mod* (n=319)**		***Poor/Undiff* (n=275)**				***Well/Mod* (n=703)**		***Poor/Undiff* (n=373)**			
EPT																		
Never	280	(45.1)	185	(51.4)	1.00	(ref)	61	(28.1)	53	(32.3)	1.00	(ref)	219	(54.2)	132	(67.3)	1.00	(ref)
Ever	341	(54.9)	175	(48.6)	**0.67**	(0.49-0.91)	156	(71.9)	111	(67.7)	0.90	(0.55-1.48)	185	(45.8)	64	(32.7)	**0.57**	(0.38-0.85)
ET																		
Never	280	(38.9)	185	(39.2)	1.00	(ref)	61	(34.1)	53	(32.3)	1.00	(ref)	219	(40.6)	132	(42.9)	1.00	(ref)
Ever	439	(61.1)	287	(60.8)	1.06	(0.81-1.38)	118	(65.9)	111	(67.7)	1.31	(0.79-2.18)	321	(59.4)	176	(57.1)	0.99	(0.73-1.34)
	***<2cm* (n=1243)**		***≥2cm* (n=603)**				***<2cm* (n=463)**		***≥2 cm* (n=238)**				***<2cm* (n=780)**		***≥2 cm* (n=365)**			
EPT																		
Never	338	(45.9)	176	(51.0)	1.00	(ref)	87	(29.3)	57	(36.8)	1.00	(ref)	251	(57.2)	119	(62.6)	1.00	(ref)
Ever	398	(54.1)	169	(49.0)	0.92	(0.69-1.24)	210	(70.7)	98	(63.2)	0.80	(0.51-1.26)	188	(42.8)	71	(37.4)	1.04	(0.70-1.56)
ET																		
Never	338	(38.7)	176	(40.1)	1.00	(ref)	87	(32.5)	57	(39.9)	1.00	(ref)	251	(41.4)	119	(40.2)	1.00	(ref)
Ever	536	(61.3)	263	(59.9)	1.16	(0.89-1.50)	181	(67.5)	86	(60.1)	0.92	(0.58-1.47)	355	(58.6)	177	(59.8)	1.28	(0.94-1.74)

[1]Table abbreviations: Lob/Mixed: Lobular and mixed lobular histology; Well/Mod: well and moderately differentiated; Reg/Dist: regional and distant stage; Poor/Undiff: poorly differentiated and undifferentiated

[2]Adjusted for age at diagnosis (continuous), study, and history of screening mammography