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Contralateral Prophylactic Mastectomy and its Association with Reduced Mortality: Evidence for Selection Bias

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Abstract

Background—Contralateral prophylactic mastectomy (CPM) refers to removal of the opposite uninvolved breast in women with unilateral breast cancer, and rates are increasing worldwide. In observational studies, CPM is often associated with reductions in breast cancer-specific and all-cause mortality, but this may reflect the selection of a healthier cohort of women for CPM (selection bias). To further explore this possibility, we examined the association between CPM and non-cancer mortality, an indicator of selection bias.

Methods—We identified 449,178 adult women diagnosed with unilateral, primary American Joint Committee on Cancer (AJCC) stage I–III ductal or lobular breast cancer, utilizing the 1998–2010 Surveillance, Epidemiology, and End Results (SEER) dataset. Of these, 5.8% (n=25,961) underwent CPM as their first course of treatment. We examined associations between CPM and breast cancer-specific, all-cause, and non-cancer mortality utilizing multivariate logistic regression, adjusting for age, race, AJCC stage, estrogen receptor status, progesterone receptor status, and histologic grade of the tumor.

Results—Among all patients receiving CPM as first course of treatment, CPM was associated with lower breast cancer-specific (HR: 0.84 (95% CI: 0.79–0.89)), all-cause (HR: 0.83 (95% CI: 0.80–0.88)), and non-cancer (HR: 0.71 (95% CI: 0.64–0.80)) 5-year hazard of death.

Conclusion—Although our results are consistent with other observational studies showing associations between CPM and reductions in breast cancer-specific and all-cause mortality, we demonstrate an even stronger association between CPM and reduced non-cancer mortality. Thus, the reported associations between CPM and reductions in mortality might at least partly be attributable to selection bias.

Background

Contralateral prophylactic mastectomy (CPM) refers to the removal of the opposite uninvolved breast in women with unilateral breast cancer, and rates are dramatically

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increasing worldwide^{1–6}. Moreover, there is now a large body of evidence, derived entirely from observational studies, suggesting that CPM is associated with reductions in breast cancer-specific and all-cause mortality, even after adjusting for measured confounding variables^{7–13}. This association has been demonstrated not only in women with early stage unilateral breast cancer with an increased risk of developing contralateral breast cancer (such as BRCA1/BRCA2 mutation carriers and those with estrogen receptor negative tumors), but also in patients at average risk for developing contralateral breast cancer.

Yet, observational studies rely on datasets that often omit important covariates linked to outcomes, thereby producing biased estimates of treatment effects¹⁴. For instance, healthier women (who are better able to withstand a longer surgical procedure) and those from higher socioeconomic backgrounds (with better healthcare access), might be preferentially selected for CPM, but such confounders are generally not measured and recorded in datasets. Thus, the results of observational studies demonstrating an association between CPM and lower breast cancer-specific and all-cause mortality might, at least in part, be attributable to unmeasured confounders (selection bias).

To further explore this possibility, we examined associations between CPM and breast cancer-specific, all-cause, and non-cancer mortality, utilizing SEER (Surveillance, Epidemiology, and End Results), a large population-based dataset. If CPM was having the intended treatment effect, it should lower breast cancer-specific and all-cause mortality, but not lower non-cancer mortality as it is not expected to reduce non-cancer risk factors for death (e.g. heart disease, stroke). Therefore, an association between CPM and reduced non-cancer mortality would suggest a selection bias favoring women who undergo CPM and indicate that there may be unmeasured factors contributing to the previously identified associations between CPM and lower breast cancer-specific and all-cause mortality.

A previous study utilized an earlier version of the SEER dataset and evaluated associations between CPM and breast cancer-specific and non-cancer mortality in age-stratified cohorts, but not across all age groups⁹. CPM was associated with significant reductions in non-cancer deaths in older but not younger women. The authors concluded that a bias exists for selecting healthier older women for CPM, but that such a bias could not account for the association between CPM and lower breast-cancer specific mortality in younger women. Yet, the results of this study might be event-driven. As older women are much more likely to experience non-cancer deaths than younger women, a significant association between CPM and non-cancer mortality is more likely to be detected in older women. We have therefore utilized a more recent and expanded version of the SEER dataset to examine associations between CPM and breast-cancer specific, overall, and non-cancer mortality across all age groups. In our opinion, the overall association between CPM and non-cancer mortality should be a more reliable indicator of selection bias, irrespective of age.

As it is highly unlikely that there will ever be a randomized trial addressing the effect of CPM on breast cancer mortality, the validity of observational studies addressing this issue remains an important consideration.

Methods

Data source

We used the 1998–2010 Surveillance, Epidemiology, and End Results (SEER) data for our study¹⁵. SEER collects cancer incidence and survival data from population-based cancer registries representing approximately 26% of the US population including patient characteristics, primary tumor site, tumor stage and grade, first course of treatment (including surgery and irradiation, with information on contralateral prophylactic mastectomy beginning in 1998), lymph node status and survival. First course of treatment includes all methods of treatment recorded in the treatment plan and administered to the patient before disease progression or recurrence.

Patients

We included women diagnosed between 18 and 90 years of age with their first invasive, non-metastatic, ductal or lobular carcinoma of the breast from January 1, 1998 through December 31, 2010. Patients were excluded if they had unknown microscopic confirmation of the tumor (n=52); were diagnosed with bilateral breast cancer (n=49); had an unknown length of survival (n=0); or had their cancer first diagnosed in a nursing home, on autopsy or first cited on the death certificate (as these patients would unlikely undergo treatment for their cancer) (n=16). Our final study sample included 449,178 adult women diagnosed with unilateral, primary American Joint Committee on Cancer (AJCC) stage I–III ductal or lobular breast cancer.

Variable Definitions

CPM—CPM was defined in SEER as the removal of an uninvolved contralateral breast in women with unilateral breast cancer using total (simple), radical or modified radical mastectomy, as part of the first course of treatment.

Mortality—Five-year, cause-specific mortality was defined using a combination of the SEER-reported survival time, in months, combined with the cause of death cited on the death certificate. Mortality was further classified as all-cause mortality (i.e., death from any cause), breast cancer-specific mortality (i.e. death from breast cancer), and non-cancer mortality (i.e., death from a cause other than cancer).

Patient Demographics

Each patient was classified according to reported demographics available in SEER, which included age and race. Age was evaluated as a continuous variable, while race was categorized as: White, Black, or Other.

Cancer Characteristics

Patient tumor characteristics reported in the SEER data included: American Joint Commission on Cancer (AJCC) Stage (I, II, and III), estrogen receptor status (negative, positive, and unknown), progesterone receptor status (negative, positive, and unknown), and histologic grade (grade I & II, grade III & IV, and unknown grade).

Statistical Analysis

We first examined the unadjusted association between patient and tumor characteristics and receipt of CPM using chi-square tests for categorical variables and t-tests for continuous variables. Next, we used multivariate logistic regression to examine the adjusted association between patient and tumor characteristics and receipt of CPM, after adjusting for age, race, AJCC stage, estrogen receptor status, progesterone receptor status and histologic grade. Finally, multivariate Cox proportional hazards modeling was used to assess the association between the use of CPM and the 5-year relative hazard of 1) all-cause, 2) breast cancer specific and 3) non-cancer hazard of death, after adjusting for age, race, AJCC stage, estrogen receptor status, progesterone receptor status and histologic grade. Data retrieval, cleaning and statistical analysis were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). P-values ≤ 0.05 were considered statistically significant. This study was approved by the University of Texas Health Science Center at San Antonio Institutional Review Board.

Results

In our study of 449,178 adult women diagnosed with unilateral, primary American Joint Committee on Cancer (AJCC) stage I–III ductal or lobular breast cancer in the SEER cancer registries, we found that 5.8% ($n=25,961$) of patients received CPM as part of their first course of treatment (Table 1). Overall, the mean age at diagnosis in our cohort was 59.5. The majority of the study population was White (82.2%), AJCC stage I (48.8%), estrogen receptor positive (72.2%), progesterone receptor positive (60.8%), and had low grade disease (59.2% with histologic grades I–II) (Table 1).

Patient Demographic and Cancer Characteristics Associated with Receiving CPM

In univariate analysis, CPM was more common in women who were younger at diagnosis (mean age: CPM, 51.1 years vs. No CPM, 60.0 years), White, estrogen receptor positive, progesterone receptor positive, and higher grade ($p<0.05$ for all, Table 1). Multivariate analyses further demonstrated that younger, White patients (Odds Ratio (OR), 95% Confidence Interval (CI): 0.43 (0.41, 0.46) for Black vs. White), those with higher AJCC stage (OR, 95% CI: 1.87 (1.80, 1.94), AJCC Stage III vs. I), low-grade disease (OR, 95% CI: 0.92 (0.89, 0.95), histologic grade III/IV vs. I/II), and estrogen receptor positive tumors (OR, 95% CI: 1.08 (1.03, 1.13), positive vs. negative) were all more likely to undergo CPM (Table 2); although progesterone receptor status was no longer associated with receiving CPM.

Association between Receiving CPM and Mortality

Among all patients, the all-cause 5-year mortality rate was 14.3%, while the 5-year breast cancer mortality rate and non-cancer mortality rates were 7.9% and 5.7% respectively (Table 3). Five-year all-cause and breast-cancer specific mortality increased with more advanced stage at diagnosis, while non-cancer mortality was relatively consistent across AJCC stage at diagnosis. Multivariate Cox Proportional hazards models demonstrated that, among all patients, receiving a CPM as part of first course of treatment was associated with lower all-cause (HR: 0.83 (0.80, 0.88)), breast cancer-specific (HR: 0.84 (0.79, 0.89)) and

non-cancer (HR: 0.71 (0.64, 0.80)) 5-year hazard of death; however the relationship between CPM and non-cancer mortality was stronger than either all-cause or breast cancer-specific mortality (Table 3). This relationship was consistent when stratified by AJCC stage.

Discussion

In our multivariate analysis of non-metastatic breast cancer patients diagnosed in the SEER cancer registries between 1998–2010, we found that first course of treatment with CPM was associated with significant reductions in breast cancer-specific, all-cause, and non-cancer mortality. However, the significant association between CPM and reduced non-cancer mortality, coupled with the stronger association between CPM and reduced non-cancer mortality relative to both breast cancer-specific and all-cause mortality, suggests an underlying selection bias for treating potentially healthier women with CPM. As a result, the previously reported associations between CPM and reductions in breast cancer-specific and all-cause mortality may partly be attributed to unmeasured factors (i.e., confounders).

Contralateral breast cancers are generally regarded as new primary cancers, and not metastases from the opposite breast¹⁶. If contralateral breast cancers were simply a manifestation of distant metastases, then CPM should not have an effect in reducing mortality. Among women with unilateral early stage breast cancer, the risk of developing a contralateral cancer varies according to patient and tumor characteristics. Thus, for BRCA1/BRCA2 mutation carriers with early stage breast cancer, that risk is about 2% per year or approximately 20% over a 10-year period, while for non-mutation carriers that risk is less than 5% over the same period^{17, 18}. As the majority of women can be effectively treated following diagnosis of a contralateral breast cancer then, at least in theory, the absolute benefit of CPM on breast cancer mortality should not exceed 4% for the BRCA mutation carrier or 1% for the average risk patient over a 10-year period¹⁷. Yet, observational studies generally show much larger benefits, which call into question the validity of such studies.

Worldwide, CPM rates are increasing, and several factors may account for this trend¹⁹. First, there has been greater use of genetic testing, and CPM is often recommended for women who harbor mutations (such as BRCA 1 and BRCA 2) that increase risk for contralateral breast cancer²⁰. Yet, many women who undergo CPM appear to be at low-to-moderate risk for developing contralateral breast cancer, so the wider use of genetic testing can only partly account for the trend towards greater utilization of CPM²¹. Secondly, some patients may overestimate their risk of developing contralateral breast cancer, and experience considerable anxiety over this issue^{21, 22}. In this regard, it is somewhat ironic that CPM rates are increasing during a period when contralateral breast cancer rates are decreasing due to better adjuvant systemic therapies¹⁹. Thirdly, wider use of pre-operative breast MRI has increased the likelihood of detecting potentially suspicious lesions in the opposite breast, and this may prompt CPM²³. Indeed, there is evidence that women who have a pre-operative breast MRI are twice as likely to choose CPM²⁴. Fourthly, there have been improvements in breast reconstruction techniques, and some women may prefer the better symmetry associated with bilateral mastectomy and reconstruction versus unilateral mastectomy with reconstruction¹⁹.

Finally, several observational studies have demonstrated associations between CPM and reductions in breast cancer-specific and all-cause mortality, and these reports may influence treatment decisions^{7–13}. These associations are evident not only in women with early stage breast cancer who harbor the BRCA1/BRCA2 mutations and those with ER-negative tumors, but also breast cancer patients in the general population. Our study is consistent with such previous reports, but we also demonstrate an even stronger association between CPM and reduced non-cancer deaths, which cannot be attributed to CPM. The strong and consistent association with lower non-cancer mortality, even after adjusting for potential confounders, suggests that unmeasured confounders (rather than CPM itself) are at least partly responsible for the associations between CPM and reduced breast cancer-specific and overall mortality.

In our multivariate regression model, we have adjusted for covariates included in the dataset, specifically age, race, and tumor characteristics (AJCC stage, ER/PR status, and histologic grade). Some reports suggest that women with advanced stage disease (stage III, with shorter lifespan), are less likely to undergo CPM than those with earlier stage disease (stage I or II, with longer lifespan), and one might therefore speculate that the associations between CPM and reductions in breast cancer-specific and all-cause mortality are partly attributable to the confounding effect of stage at diagnosis^{21, 25}. Yet, in our study, women with higher AJCC stage disease were more likely to undergo CPM, and the association between CPM and lower breast-cancer specific, overall, and non-cancer mortality persists even after adjusting for stage. We have not included patients who initially present with metastatic disease (stage IV) in our analyses, as these patients are generally treated with systemic therapy alone, and recent trials indicate that local therapy does not reduce mortality in these patients²⁶.

Other potential confounders, not included in our multivariate model, should also be considered. Specifically, one might wonder whether the type of surgery performed on the ipsilateral breast (for the primary cancer) influences the decision to undergo CPM and mortality. However, women who choose CPM will almost invariably undergo an ipsilateral mastectomy (and not lumpectomy), and the extent of axillary surgery is unlikely to have an effect on the decision to undergo CPM or on mortality. Also, it has been pointed out that women may undergo CPM any time after a diagnosis of unilateral breast cancer, and therefore long-term survivors of unilateral breast cancer are more likely to undergo CPM than short-term survivors (survivor bias)¹⁷. Yet, survivor bias is unlikely to have confounded the results of our study because the SEER dataset generally only includes treatments during the first year following diagnosis. Finally, other covariates not measured in our dataset, such as socioeconomic status, general health, and access to health care, are potential confounders that may partly account for the association between CPM and lower mortality.

Systematic biases are common in all observational studies, but often difficult to discern²⁷. Selection bias implies a lack of comparability between study groups, and are attributable to a wide range of measured as well as unmeasured variables²⁸. Such confounders create imbalances between two groups in a study, and produce biased estimates of treatment effects. In this observational study, we provide evidence for a selection bias favoring women

who undergo CPM. The persistence of an association between CPM and non-cancer mortality, even in our multivariate regression model (where we account for potential measured confounders in our dataset), suggests that unmeasured confounders are at least partly responsible for associations between CPM and reduced breast cancer-specific and all-cause mortality²⁹.

There are limitations to our study, and our results should be interpreted with some caution. Evidence of selection bias does not exclude the possibility of CPM having a real benefit in lowering breast cancer-specific and all-cause mortality. Moreover, we have examined the effect of CPM in a single large population-based dataset, and there might be other datasets where the association between CPM and non-cancer mortality is lacking (and therefore evidence of the beneficial effect of CPM is more compelling). For instance, the incidence of contralateral breast cancer is much higher in women who harbor the BRCA1/BRCA2 mutations, and CPM may have a real benefit in reducing mortality in these patients.

A randomized prospective trial would be required to minimize the effect of selection bias and determine whether CPM has a real benefit on cause-specific and all-cause mortality. Such a trial is unlikely, as women would probably not agree to randomization, so the true effect of CPM on breast cancer-specific and all-cause mortality will likely never be completely understood. Yet, our study suggests that observational studies produce biased estimates of the effect of CPM. Faced with the diagnosis of unilateral breast cancer, a woman may choose CPM for a variety of reasons, but she should not do so simply on the basis of observational studies demonstrating associations with reduced breast-cancer specific and all-cause mortality.

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Table 1

Differences in Patient Demographic and Tumor Characteristics by Receipt of Contralateral Prophylactic Mastectomy (CPM) among Female AJCC stages I–III Breast Cancer Patients in the 1998–2010 Surveillance, Epidemiology and End Results Cancer Registries

	All Patients, N (%)	Did Not Receive CPM, N (%)	Received CPM, N (%)	P-Value
Number of Patients	449,178	423,217	25,961	-
Age at Diagnosis, mean(std)	59.5 (13.5)	60.0 (13.5)	51.1 (11.7)	<0.001
Race				<0.001
White	369,204 (82.2)	346,187 (81.8)	23,017 (88.6)	
Black	43,576 (9.7)	42,048 (9.9)	1,528 (5.9)	
Other	36,398 (8.1)	34,982 (8.3)	1,416 (5.5)	
AJCC Stage				<0.001
I	219,154 (48.8)	209,157 (49.4)	9,997 (38.5)	
II	179,442 (39.9)	168,193 (39.7)	11,249 (43.3)	
III	50,582 (11.3)	45,867 (10.9)	4,715 (18.2)	
Estrogen Receptor Status				<0.001
Positive	324,257 (72.2)	305,438 (72.2)	18,819 (72.5)	
Negative	86,583 (19.3)	80,985 (19.1)	5,598 (21.5)	
Unknown/Other	38,338 (8.5)	36,794 (8.7)	1,544 (6.0)	
Progesterone Receptor Status				<0.001
Positive	272,897 (60.8)	256,685 (60.7)	16,212 (62.5)	
Negative	130,443 (29.0)	122,528 (28.9)	7,915 (30.5)	
Unknown/Other	45,838 (10.2)	44,004 (10.4)	1,834 (7.0)	
Histologic Grade				<0.001
I/II	265,868 (59.2)	251,598 (59.5)	14,270 (55.0)	
III/IV	157,930 (35.2)	147,873 (34.9)	10,057 (38.7)	
Unknown	25,380 (5.6)	23,746 (5.6)	1,634 (6.3)	

Table 2

Association between Patient Demographic and Tumor Characteristics and Receipt of Contralateral Prophylactic Mastectomy among Female AJCC stages I–III Breast Cancer Patients in the 1998–2010 Surveillance, Epidemiology and End Results Cancer Registries, Multivariate Logistic Regression

	N (%)	OR (95% CIs)
All Patients	449,178 (100)	-
CPM		
Yes	25,961 (5.8)	-
No	423,217 (94.2)	-
Age at Diagnosis, mean(std)	59.5 (13.5)	0.95 (0.94, 0.95)
Race		
White	369,204 (82.2)	Ref.
Black	43,576 (9.7)	0.43 (0.41, 0.46)
Other	36,398 (8.1)	0.49 (0.47, 0.52)
AJCC Stage		
I	219,154 (48.8)	Ref.
II	179,442 (39.9)	1.23 (1.19, 1.26)
III	50,582 (11.3)	1.87 (1.80, 1.94)
Estrogen Receptor Status		
Positive	324,257 (72.2)	1.08 (1.03, 1.13)
Negative	86,583 (19.3)	Ref.
Unknown/Other	38,338 (8.5)	0.98 (0.87, 1.11)
Progesterone Receptor Status		
Positive	272,897 (60.8)	0.99 (0.95, 1.03)
Negative	130,443 (29.0)	Ref.
Unknown/Other	45,838 (10.2)	0.73 (0.65, 0.81)
Histologic Grade		
I/II	265,868 (59.2)	Ref.
III/IV	157,930 (35.2)	0.92 (0.89, 0.95)
Unknown	25,380 (5.6)	1.22 (1.15, 1.29)

ORs: Odds Ratios; CIs: Confidence Intervals; Note: OR>1 indicates higher likelihood of receiving CPM.

Association between Contralateral Prophylactic Mastectomy and 5-Year Relative Hazard of Death, Multivariate Cox Proportional Hazards Models, Hazard Ratios, 95% Confidence Intervals (N=449,178)

Table 3

	All Patients, AJCC Stage I–III				AJCC Stage I (n=219,154)				AJCC Stage II (n=179,442)				AJCC Stage III (n=50,582)			
	All-Cause Mortality	Breast Cancer Mortality	Non-Cancer Mortality	AHR (95% CI)	All-Cause Mortality	Breast Cancer Mortality	Non-Cancer Mortality	AHR (95% CI)	All-Cause Mortality	Breast Cancer Mortality	Non-Cancer Mortality	AHR (95% CI)	All-Cause Mortality	Breast Cancer Mortality	Non-Cancer Mortality	AHR (95% CI)
5-year Mortality (%)	14.3%	7.9%	5.7%		8.5%	2.3%	5.2%		15.9%	9.5%	5.9%		35.4%	28.7%	7.9%	
	AHR (95% CI)	AHR (95% CI)	AHR (95% CI)		AHR (95% CI)	AHR (95% CI)	AHR (95% CI)		AHR (95% CI)	AHR (95% CI)	AHR (95% CI)		AHR (95% CI)	AHR (95% CI)	AHR (95% CI)	
CPM																
Yes	0.83 (0.80, 0.88)	0.84 (0.79, 0.89)	0.71 (0.64, 0.80)		0.93 (0.82, 1.06)	1.02 (0.84, 1.24)	0.80 (0.66, 0.98)		0.81 (0.75, 0.88)	0.83 (0.76, 0.92)	0.70 (0.59, 0.83)		0.78 (0.72, 0.84)	0.81 (0.74, 0.88)	0.61 (0.47, 0.78)	
No	Ref.	Ref.	Ref.		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.	
Age at Diagnosis, years	1.05 (1.05, 1.05)	1.02 (1.02, 1.02)	1.10 (1.09, 1.10)		1.08 (1.08, 1.08)	1.03 (1.02, 1.03)	1.11 (1.11, 1.11)		1.05 (1.05, 1.05)	1.02 (1.02, 1.02)	1.10 (1.10, 1.10)		1.03 (1.03, 1.03)	1.02 (1.02, 1.02)	1.08 (1.08, 1.09)	
Race																
White	Ref.	Ref.	Ref.		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.	
Black	1.51 (1.47, 1.55)	1.47 (1.42, 1.52)	1.55 (1.48, 1.63)		1.52 (1.44, 1.61)	1.52 (1.37, 1.68)	1.54 (1.43, 1.67)		1.48 (1.42, 1.53)	1.46 (1.39, 1.53)	1.52 (1.42, 1.62)		1.51 (1.44, 1.57)	1.47 (1.40, 1.55)	1.64 (1.47, 1.82)	
Other	0.81 (0.78, 0.85)	0.84 (0.79, 0.88)	0.84 (0.79, 0.90)		0.77 (0.71, 0.84)	0.75 (0.65, 0.88)	0.78 (0.70, 0.87)		0.80 (0.75, 0.84)	0.81 (0.76, 0.88)	0.87 (0.78, 0.96)		0.88 (0.82, 0.95)	0.90 (0.83, 0.97)	0.95 (0.80, 1.14)	
AJCC Stage																
I	Ref.	Ref.	Ref.													
II	1.99 (1.95, 2.04)	3.82 (3.68, 3.97)	1.40 (1.35, 1.45)													
III	5.11 (4.99, 5.24)	12.71 (12.22, 13.22)	2.06 (1.96, 2.15)													
Estrogen Receptor Status																
Positive	0.62 (0.60, 0.64)	0.54 (0.52, 0.56)	0.92 (0.87, 0.97)		0.69 (0.65, 0.73)	0.50 (0.45, 0.56)	0.94 (0.86, 1.03)		0.65 (0.62, 0.67)	0.57 (0.54, 0.60)	0.95 (0.88, 1.02)		0.56 (0.53, 0.59)	0.52 (0.48, 0.55)	0.82 (0.72, 0.94)	
Negative	Ref.	Ref.	Ref.		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.	
Unknown/Other	0.92 (0.86, 0.98)	0.86 (0.78, 0.95)	1.18 (1.05, 1.32)		0.91 (0.80, 1.03)	0.74 (0.57, 0.97)	1.12 (0.95, 1.33)		0.96 (0.87, 1.07)	0.88 (0.77, 1.02)	1.34 (1.13, 1.59)		0.90 (0.78, 1.03)	0.89 (0.76, 1.05)	0.95 (0.70, 1.28)	
Progesterone Receptor Status																
Positive	0.81 (0.78, 0.83)	0.67 (0.65, 0.70)	0.96 (0.92, 1.00)		0.89 (0.85, 0.94)	0.69 (0.62, 0.76)	0.97 (0.91, 1.04)		0.76 (0.73, 0.79)	0.64 (0.61, 0.68)	0.91 (0.85, 0.97)		0.78 (0.74, 0.82)	0.71 (0.67, 0.76)	1.08 (0.96, 1.21)	
Negative	Ref.	Ref.	Ref.		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.	
Unknown/Other	0.88 (0.83, 0.94)	0.83 (0.76, 0.91)	0.99 (0.90, 1.10)		0.92 (0.82, 1.03)	0.75 (0.58, 0.96)	1.04 (0.90, 1.20)		0.83 (0.75, 0.92)	0.79 (0.70, 0.91)	0.87 (0.74, 1.02)		0.96 (0.84, 1.10)	0.91 (0.78, 1.07)	1.32 (1.00, 1.75)	
Histologic Grade																
I/II	Ref.	Ref.	Ref.		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.		Ref.	Ref.	Ref.	
III/IV	1.52 (1.48, 1.55)	2.04 (1.98, 2.10)	1.12 (1.09, 1.16)		1.38 (1.33, 1.44)	2.45 (2.26, 2.65)	1.06 (1.00, 1.13)		1.62 (1.57, 1.67)	2.18 (2.09, 2.28)	1.14 (1.08, 1.20)		1.57 (1.51, 1.64)	1.71 (1.64, 1.81)	1.22 (1.11, 1.33)	
Unknown	1.20 (1.16, 1.25)	1.51 (1.43, 1.60)	1.08 (1.02, 1.14)		1.07 (0.99, 1.14)	1.35 (1.17, 1.56)	1.04 (0.95, 1.13)		1.18 (1.11, 1.25)	1.34 (1.22, 1.46)	1.08 (0.99, 1.19)		1.52 (1.41, 1.62)	1.66 (1.53, 1.79)	1.22 (1.05, 1.41)	

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AHR: Adjusted Hazard Ratio; CI: Confidence Interval

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