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Preoperative breast MRI and mortality in older women with breast cancer

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Abstract

Purpose—The survival benefit from detecting additional breast cancers by preoperative magnetic resonance imaging (MRI) continues to be controversial.

Methods—We followed a cohort of 4,454 women diagnosed with non-metastatic breast cancer (stage 0 – III) from 2/2005 – 6/2010 in five registries of the Breast Cancer Surveillance

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AVAILABILITY OF DATA AND MATERIALS

Information regarding data acquisition and materials for this study is available at the Breast Cancer Surveillance Consortium (<http://www.bsc-research.org>)

AUTHORS' CONTRIBUTIONS

TO, WZ, JW, MG, AT, WD, BV, LH, DB, KW, KK, and RH conceived of the study. TO, WZ, JW and RH analyzed and interpreted the data. TO, JW, and MG helped to draft the manuscript. TO, WZ, JW, MG, AT, WD, BV, LH, DB, KW, KK, and RH participated in the study design and coordination, and helped to interpret the data. TO, WZ, JW, MG, AT, WD, BV, LH, DB, KW, KK, and RH helped with editing the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All participating registry sites within the BCSC received institutional review board approval for either active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analytic studies. All procedures are Health Insurance Portability and Accountability Act compliant and all registries and the SCC have received a Federal Certificate of Confidentiality and other protections for the identities of women, physicians, and facilities involved in this research.

Consortium (BCSC). BCSC clinical and registry data were linked to Medicare claims and enrollment data. We estimated the cumulative probability of breast cancer-specific and all-cause mortality. We tested the association of preoperative MRI with all-cause mortality using a Cox proportional hazards model.

Results—917 (20.6%) women underwent preoperative MRI. No significant difference in the cumulative probability of breast cancer-specific mortality was found. We observed no significant difference in the hazard of all-cause mortality during the follow-up period after adjusting for sociodemographic and clinical factors among women with MRI (HR 0.90; 95% CI: 0.72 – 1.12) compared to those without MRI.

Conclusion—Our findings of no breast cancer-specific or all-cause mortality benefit supplements prior results that indicate a lack of improvement in surgical outcomes associated with use of preoperative MRI. In combination with other reports, the results of this analysis highlight the importance of exploring the benefit of preoperative MRI in patient reported outcomes such as women's decision quality and confidence levels with decisions involving treatment choices.

Keywords

breast cancer; breast cancer mortality; pre-operative breast MRI; breast cancer treatment

Purpose

Over the past two decades (1988-2009), deaths from breast cancer have declined significantly, from 33 to 21 per 100,000 women annually.(1) Because randomized trials of breast conserving surgery (BCS) and mastectomy have demonstrated nearly equivalent mortality,(2–5) critics of routine preoperative magnetic resonance imaging (MRI) assert that the additional cancers detected are either biologically inert or adequately treated with radiation.(6, 7) In addition, studies in recent years have provided evidence that preoperative MRI does not improve surgical margins or reoperation rates(8) and may increase the invasiveness of surgery from BCS to mastectomy or even bilateral mastectomy.(9) (10) Therefore, controversy exists over whether detecting additional cancers by breast MRI has yielded any benefit for survival or contributed to the decline in deaths from breast cancer.

The Early Breast Cancer Trialists' Collaborative Group(11) overview established that there is an important relationship between local control (stopping cancer at the site of origin) and survival in patients with breast cancer. However, there are little data available on the impact of preoperative breast MRI on recurrence rates. The only evidence available is from the short term follow up from the comparative effectiveness of MRI in breast cancer (COMICE) randomized controlled trial, which included assessment of local recurrence as a secondary endpoint.(12) Findings from the COMICE trial indicated that at three years recurrence-free rates were similar with 94% and 96% for the breast MRI and no MRI groups.(13) Mortality outcomes from trials of preoperative MRI are not yet available.

In this study, we compared mortality outcomes for women with preoperative breast MRI and those without, specifically examining crude and adjusted mortality rates, and time to death between these two groups of women with a breast cancer diagnosis. We hypothesized that

there would be no difference in mortality rates by receipt of breast MRI when adjusting for important confounders.(Appendix A)

Methods

Data Source

We conducted this study at six Breast Cancer Surveillance Consortium (BCSC) breast screening registries sponsored by the National Cancer Institute (BCSC; <http://bcsc-research.org/>): in New Hampshire, New Mexico, North Carolina, San Francisco, Vermont, and Western Washington State (Kaiser Permanente Washington Registry), which send data to the Statistical Coordinating Center (SCC) for pooling and analysis.(14) The BCSC collects risk factor, clinical history, and sociodemographic data for women receiving breast imaging exams within the registries, which are further linked to both benign and malignant breast pathology outcomes, cancer registry data, and vital status.

For this study, we linked BCSC registries to Medicare claims data or electronic health records from 1998-2010.(15) Specifically, the Medicare MedPAR, Outpatient and Carrier files allowed us to capture all preoperative MRI, to quantify comorbidities, and to determine women received breast conserving surgery or mastectomy (Appendix B). For women within the Kaiser Permanente Washington registry, electronic health records, rather than claims, were used to ascertain preoperative MRI.

Study Population

BCSC women aged 66 and older with an initial non-metastatic breast cancer (stage 0-III) diagnosed from February, 2005 through June, 2010 were included. We required women in this study to have received either breast conserving surgery (with or without radiation) or mastectomy within 6 months of their diagnosis. Women were required to have been enrolled in Medicare Parts A and B or Kaiser Permanente Washington continuously in the 12 months prior to diagnosis. Follow-up continued from time of breast cancer diagnosis through the end of 2014.

Outcome

Mortality was determined by a combination of BCSC vital status records obtained from state death tapes and Medicare records from 1998 to 2010 to determine date of death and only from BCSC records for 2011-2014. If BCSC and Medicare death dates differed by more than 30 days the earlier of the two death dates was chosen. Cases were excluded when a date of death was found in the BCSC before 2011 but not in Medicare. Time-to-death was defined as the interval between date of breast cancer diagnosis and date of death. Date of diagnosis was derived from BCSC pathology (breast biopsy) and cancer registry data. Deaths were considered breast cancer related if cause of death from state death tapes were coded as breast cancer. The maximum follow up time was 8.3 years with median 4.6 years (IQR: 3.2, 6.1).

Exposure

Our main exposure was receipt of preoperative breast MRI, defined as a breast MRI occurring 30 days prior to breast cancer diagnosis or within 6 months after diagnosis and prior to the initial breast cancer surgery. Codes used to identify breast MRI from MedPAR, Outpatient, and Carrier files are given in Appendix B.

Covariates

We included covariates that may be related to MRI receipt, which we hypothesized could confound the relationship between preoperative MRI and mortality. Covariates obtained from the BCSC database included age at diagnosis, race/ethnicity, educational attainment, first degree family history of breast cancer, breast cancer histology (*in situ*, invasive, ductal, lobular), breast density, comorbidities, and type of breast cancer surgery (BCS vs. mastectomy). Charlson comorbidity index score was based on data from the 12 months before diagnosis and was calculated using Medicare claims.(16)

Analyses

Women with and without preoperative MRI were characterized by sociodemographic, breast history, and breast cancer-related factors. Cell counts of < 11 were annotated and footnoted as required by our data use agreement with the Center for Medicare and Medicaid Services. We calculated raw all-cause mortality rates (per 1,000 person-years) and 5-year cumulative probabilities of death by preoperative MRI and woman, tumor, and treatment characteristics. We plotted unadjusted cumulative probabilities for both breast cancer-specific mortality and other-cause mortality over time since diagnosis stratified by receipt of preoperative MRI. Using Cox proportional hazards models for time to all-cause mortality, we estimated the association between preoperative MRI and death, while adjusting for BCSC registry site, age, education, race/ethnicity, first degree family history of breast cancer, comorbidity, breast density, histology and breast cancer surgical treatment type. We did not estimate adjusted proportional hazards models for breast cancer-specific mortality due to the small number of events (n=169).

For the multivariable analysis, we imputed unknown/missing data (% missing) for the women's characteristics of race (12.8%), education (23.9%), breast density (19.8%), family history (8.4%) and histology (< 2%). We created 5 complete data sets using the multiple imputation via chained equations (MICE) algorithm (17) To impute missing observations, MICE proceeds by estimating a regression model for each variable with missing data conditional on all other variables in the dataset. Multiple imputation preserves statistical efficiency by including all observations in the multivariable analysis while allowing for uncertainty in the imputed data by incorporating variability in results across imputations. Sensitivity analyses were conducted to evaluate the robustness of results across analyses with and without imputation. Analyses were performed in R version 3.4.0 with results reported as hazard ratios (HR) and 95% confidence intervals (CI). Imputation using MICE was carried out using the mice package in R (18)

Results

Of the 4,454 women meeting inclusion criteria, 917 (20.6%) underwent preoperative MRI. The majority of women with preoperative MRI were less than 75 years of age (69%), compared to 48% <75 years among women without preoperative MRI. A greater proportion of women in the preoperative MRI group were white compared to the group without MRI. (Table 1) Women with preoperative MRI were also more likely to have at least a college education compared to women not receiving preoperative MRI (29% versus 21%). First-degree family history of breast cancer was similar among women with and without preoperative MRI. Women with preoperative MRI also tended to have dense breasts, fewer comorbidities, lobular histology and breast conserving surgery with radiation compared to women not receiving preoperative MRI. (Table 1)

Of the 917 women with preoperative MRI, 100 (10.9%) died during 4,016 person years of follow-up. (Table 2) The crude mortality rate for women with preoperative MRI was 24.90 (95% CI: 20.30 – 30.20) per 1000 person years compared to 38.41 (95% CI: 35.55 – 41.44) per 1000 person years for women without preoperative MRI. The unadjusted 5-year cumulative probability of death was 0.12 for women with MRI and 0.17 for those without. Crude all-cause mortality rates showed the expected increase with increasing age and were higher for women who were Black compared to White or Hispanic, did not graduate from high school and had more comorbidities. (Table 2)

In a multivariable Cox proportional hazards model, there was no significant difference in the hazard of all-cause mortality during the follow-up period comparing women with preoperative MRI to those without after adjusting for age, sociodemographic and clinical factors (HR 0.90; 95%CI: 0.72 – 1.12). (Table 3) Similarly, cumulative probability plots over time since diagnosis for other-cause mortality (Fig. 1a) and breast cancer-specific mortality (Fig. 1b) did not reveal significant differences between women with and without preoperative MRI, although cumulative probability plots of other-cause mortality suggested lower mortality among women with preoperative MRI (Fig. 1a).

Sensitivity analyses yielded markedly similar results with and without missing observations included in the analysis. (Data not shown) Models with and without multiple imputation resulted in similar point estimates for the hazard ratio and 95% CI for pre-operative MRI, with the expected narrower confidence intervals with imputation (without imputation: HR 0.82; 95% CI 0.59-1.14).

Discussion

This study, based on a large, population-based observational cohort, supports the hypothesis that receipt of preoperative breast MRI is not associated with a significant difference in breast cancer-specific mortality, or all-cause mortality after adjusting for patient, cancer, and treatment characteristics. In crude analyses, mortality rates were significantly lower among women receiving preoperative MRI, but this difference did not persist after accounting for confounding factors such as age. Similarly, when examining the probability of mortality over time, breast cancer-specific mortality showed no differences by preoperative MRI

status. These results indicate that preoperative MRI does not improve mortality overall or mortality due to breast cancer.

Controversy exists over whether detecting additional cancers by breast MRI yields any benefit for survival. Because randomized trials of breast conserving surgery and mastectomy have demonstrated nearly equivalent mortality,(2–5) critics of routine preoperative MRI assert that the additional cancers detected are either biologically inert or adequately treated with radiation. (6, 7) Further, until recently, subsequent tumor events (second primaries and recurrences), which occur in 10-20% of women, were not thought to impact survival. However, recent published studies indicate that local recurrences have a negative impact on overall survival.(2–5) While breast MRI has been shown to be associated with excision of more tumor in initial treatment, a reasonable hypothesis is that breast MRI could decrease mortality via this early control. In a meta-analysis of preoperative MRI and 8-year local recurrence- and distant recurrence-free survival, the MRI and no MRI groups were not significantly different. (19) In theory, any causal effect of preoperative MRI on overall mortality should influence breast-cancer specific mortality but not mortality from other causes. Our findings from the cumulative probability analysis support a lack of effect of preoperative MRI influence on mortality. Even unadjusted cumulative probability of death was not significantly different for breast cancer-specific mortality, but plots for other-cause mortality suggested notably lower mortality among women with preoperative MRI. We would not expect MRI to affect mortality from other causes; thus our findings reinforce the lack of MRI effect on mortality. In fact, the difference in other-cause mortality appears similar or greater in magnitude to the effect on breast cancer-specific mortality, suggesting that this difference represents confounding.

Together, these findings point to a putative effect of confounding among women with preoperative MRI (unadjusted analysis). Our findings suggest that both sociodemographic and clinical factors confound the relation between preoperative MRI and all-cause mortality, as predicted in our conceptual model. (Appendix A) Specifically, older age, black race, more comorbidities, invasive histology, and mastectomy or breast conserving surgery without radiation, all were associated with both preoperative MRI and mortality. For observational studies, such as this one, inclusion of these hypothesized confounders is critical to evaluating the effectiveness of preoperative MRI in a valid manner. Currently, only observational data are available to assess preoperative MRI and mortality, although experimental evidence will be available in the future.

There are four randomized controlled trials of preoperative MRI, but to date, none have reported mortality outcomes.(12, 20–22) In fact, only the Alliance A11104 Clinical Trial from the American College of Radiology Imaging Network (ACRIN) has a primary endpoint possibly related to mortality, specifically local-regional recurrence rates at 5 years. (22) Small observational studies have reported the effect of preoperative MRI on disease-free survival. In a study of 174 women with early stage breast cancer with a median follow-up time of 8 years (range 0-13), no association of disease-free survival with preoperative MRI was found. (23) Because local recurrence risk and breast-cancer-specific risk is low among women with early stage breast cancer, large observational studies are needed with adequate data to control for confounding and with sufficient longitudinal follow-up.

As in any observational study, confounding due to unobserved factors may occur, which in this study may reflect systematic differences between women who received preoperative MRI and those who did not. While we controlled for sociodemographic factors, comorbidities, cancer characteristics, and initial treatment, we were unable to account for subsequent treatment beyond initial therapy, comorbidity severity, or longitudinal patterns of care. We were able to account for registry-specific differences in practice patterns and/or population characteristics by accounting for potential correlation among/between observations.

This study lends support to the growing consensus that preoperative breast MRI is not associated with a mortality benefit among women with breast cancer. If confirmed by the ongoing randomized control trials when sufficient follow-up has accrued, the role of preoperative breast MRI must be questioned. If it does not improve surgical outcomes or diminish breast cancer-specific mortality, its role may be more qualitative by providing information to women regarding the presence or absence of additional breast cancer following an initial diagnosis. Patient-centered outcomes may be important to examine regarding use of preoperative breast MRI, such as whether it improves decision quality related to surgical choices vis-a'-vis women's preferences and knowledge of outcomes associated with various surgical approaches. (23, 24) Although a modest increase in cost has been reported with preoperative MRI, (25) the tradeoffs of that cost with the potential for improved patient-centered outcomes should be explored.

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Appendix A. Conceptual model for the relation between preoperative MRI and mortality

Appendix B. Procedure codes used in this analysis

Procedure	ICD ^I -9 Procedure Codes	CPT/HCPCS ^I Codes
MRI		76093, 76094, 76498, 77058, 77059, 0159T, C8903-C8908
Breast Conserving Surgery	85.22, 85.23	19120, 19160, 19162, 19301, 19302
Mastectomy	85.33-85.36, 85.4, 85.41-85.48, V51.0	19180, 19182, 19200, 19220, 19240, 19303-19306

^I Abbreviations: CPT – Current Procedural Terminology; ICD9-Internationsl Classification of Diseases, 9th Edition; HCPCS – Healthcare Common Procedure Coding System

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Figure 1.

(a and b) cumulative incidence plots of women with a breast cancer diagnosis in the Breast Cancer Surveillance Consortium (BCSC) in 2005-2010, by receipt of preoperative breast MRI

(a) Cumulative incidence (95% confidence intervals) for death from causes other than breast cancer.

(b) Cumulative incidence (95% confidence intervals) for death from breast cancer

Table 1

Characteristics by preoperative MRI among 4,454 women aged 66 and older with non-metastatic breast cancer (stage 0-III) diagnosed 2/2005 – 6/2010

	Preoperative MRI	
	MRI N=917 (20.6%)	Non – MRI N=3,37 (79.4%) s
Characteristics*	N (%)	N (%)
Diagnosis Year		
2005	86 (9.4)	675 (19.1)
2006	114 (12.4)	800 (22.6)
2007	175 (19.1)	600 (17)
2008	221 (24.1)	613 (17.3)
2009	223 (24.3)	553 (15.6)
2010	98 (10.7)	296 (8.4)
Age		
66-69	322 (35.1)	831 (23.5)
70-74	313 (34.1)	890 (25.2)
75-79	167 (18.2)	843 (23.8)
80-84	86 (9.4)	592 (16.7)
85+	29 (3.2)	381 (10.8)
Race/Ethnicity		
White	756 (91.6)	2710 (88.6)
Black	39 (4.7)	183 (6.0)
Other	30 (3.6)	165 (5.4)
Education		
Less than high school	34 (5)	304 (11.2)
High school or GED	202 (29.6)	888 (32.8)
Some college or technical	185 (27.1)	747 (27.6)
College or post-graduate	261 (38.3)	767 (28.3)
Breast density		
Almost entirely fat	29 (3.9)	246 (8.7)
Scattered fibro glandular	360 (48.1)	1,461 (51.7)
Heterogeneously dense	325 (43.4)	1025 (36.3)
Extremely dense	35 (4.7)	92 (3.3)
First degree Family history		
No	641 (76.7)	2,505 (77.2)
Yes	195 (23.3)	741 (22.8)
Comorbidity index score		
0	668 (72.8)	2,312 (65.4)
1	181 (19.7)	809 (22.9)

	Preoperative MRI	
	MRI N=917 (20.6%)	Non – MRI N=3, 37 (79.4%) s
Characteristics*	N (%)	N (%)
2	43 (4.7)	249 (7)
>=3	25 (2.7)	167 (4.7)
Histology		
DCIS	136 (14.9)	624 (17.9)
Invasive ductal	515 (56.5)	2,257 (64.8)
Invasive lobular	128 (14.1)	245 (7.0)
Invasive Ductal and Lobular	102 (11.2)	211 (6.1)
Invasive Other	\$	148 (4.2)
Definitive surgery		
BCS, no radiation	190 (21.1)	876 (25.0)
BCS + radiation	434 (48.1)	1,453 (41.5)
Mastectomy	278 (30.8)	1173 (33.5)

* Missing (N): race/ethnicity (571), education (1,066), breast density (881), first degree family history (372), histology (\$), definitive surgery (50);

\$ cell value hidden so that cell sizes <11 cannot be calculated.

Table 2

Mortality and 5 year cumulative probability rates among 4,454 women aged 66 and older with non-metastatic breast cancer (stage 0-III) diagnosed 2/2005 – 6/2010

Characteristic	Death (N)	Follow up (person years)	Mortality Rate (per 1000 person years) (95% CI)	5 Year Cumulative Probability of Death
Preoperative MRI				
No	641	16,688	38.41 (35.55 - 41.44)	0.17 (0.16, 0.18)
Yes	100	4,016	24.90 (20.30 - 30.20)	0.12 (0.10, 0.15)
Age at diagnosis				
66-69	97	5,593	17.34 (14.09 - 21.12)	0.08 (0.07, 0.10)
70-74	153	5,682	26.93 (22.88 - 31.48)	0.12 (0.10, 0.14)
75-79	157	4,747	33.07 (28.17 - 38.56)	0.15 (0.13, 0.18)
80-84	180	3,026	59.49 (51.33 - 68.52)	0.25 (0.22, 0.29)
85+	154	1,657	92.94 (79.39 - 107.95)	0.36 (0.30, 0.41)
Race/Ethnicity				
White	544	16,102	33.78 (31.05 - 36.69)	0.15 (0.14, 0.17)
Black	52	1,027	50.62 (38.03 - 65.85)	0.2 (0.14, 0.26)
Hispanic/Asian/Other	31	912	34.01 (23.22 - 47.93)	0.17 (0.11, 0.23)
Unknown	114	2,663	42.80 (35.43 - 51.19)	0.19 (0.16, 0.23)
Education				
Less than high school	87	1,608	54.11 (43.56 - 66.32)	0.24 (0.19, 0.29)
High school or GED	184	5,125	35.9 (30.98 - 41.37)	0.16 (0.14, 0.19)
Some college or technical	144	4,416	32.61 (27.57 - 38.28)	0.15 (0.12, 0.17)
College or post-graduate	124	4,637	26.74 (22.29 - 31.80)	0.13 (0.10, 0.15)
Breast density				
Almost entirely fat	53	1,189	44.58 (33.57 - 57.91)	0.22 (0.16, 0.27)
Scattered fibro glandular	294	8,610	34.15 (30.41 - 38.20)	0.15 (0.13, 0.17)
Heterogeneously dense	217	6,378	34.02 (29.71 - 38.77)	0.16 (0.14, 0.18)
Extremely dense	19	536	35.42 (21.46 - 54.77)	0.16 (0.08, 0.22)
Unknown	158	3,991	39.59 (33.76 - 46.12)	0.17 (0.14, 0.20)
First degree Family history				
No	540	14,682	36.78 (33.79 - 39.95)	0.17 (0.15, 0.18)
Yes	140	4,291	32.63 (27.52 - 38.39)	0.15 (0.12, 0.17)
Unknown	61	1,732	35.22 (27.05 - 45.02)	0.16 (0.12, 0.20)
Comorbidity index score *				
0	389	14,176	27.44 (24.81 - 30.26)	0.12 (0.11, 0.14)
1	193	4,553	42.39 (36.72 - 48.65)	0.2 (0.17, 0.22)
2	92	1,224	75.15 (61.01 - 91.37)	0.3 (0.24, 0.35)
3	67	751	89.24 (69.83 - 111.95)	0.35 (0.27, 0.42)
Histology				

Characteristic	Death (N)	Follow up (person years)	Mortality Rate (per 1000 person years) (95% CI)	5 Year Cumulative Probability of Death
DCIS	76	3,652	20.81 (16.43 - 25.98)	0.1 (0.07, 0.12)
Invasive ductal	497	12,818	38.77 (35.50 - 42.26)	0.17 (0.16, 0.19)
Invasive lobular	78	1,663	46.92 (37.26 - 58.21)	0.2 (0.15, 0.24)
Invasive Ductal and Lobular	78	2,303	33.87 (26.86 - 42.09)	0.16 (0.13, 0.20)
Definitive surgery				
BCS, no radiation	203	4,855	41.81 (36.36 - 47.83)	0.19 (0.16, 0.21)
BCS + radiation	196	8,903	22.01 (19.07 - 25.28)	0.1 (0.08, 0.12)
Mastectomy	336	6,694	50.20 (45.09 - 55.70)	0.22 (0.20, 0.25)

* Charlson Comorbidity Index (26)

Table 3

Multivariable Cox Proportional Hazards Model* for the association between preoperative MRI and all-cause mortality among 4,454 women aged 66 and older with non-metastatic breast cancer (stage 0-III) diagnosed 2/2005 – 6/2010

Characteristic	HR (95% CI)
Preoperative MRI	Unadjusted
No	Reference
Yes	0.67 (0.54, 0.82)
Preoperative MRI	Adjusted
No	Reference
Yes	0.91 (0.73 - 1.13)
Age at diagnosis	
66-69	Reference
70-74	1.55 (1.2, 2.01)
75-79	1.73 (1.34, 2.23)
80-84	2.96 (2.30, 3.80)
85+	4.45 (3.41, 5.81)
Race/Ethnicity	
White	Reference
Black	1.47 (1.06, 2.06)
Hispanic/Asian/Other	1.05 (0.73, 1.52)
First degree Family history	
No	Reference
Yes	0.86 (0.71, 1.05)
Density	
Almost entirely fat	Reference
Scattered fibro glandular	0.78 (0.59, 1.03)
Heterogeneously dense	0.74 (0.54, 1.00)
Extremely dense	0.79 (0.47, 1.32)
Education	
Less than high school	1.28 (0.96, 1.71)
High school or GED	Reference
Some college or technical	0.95 (0.78, 1.17)
College or post-graduate	0.91 (0.66, 1.26)
Comorbidity index score	
0	Reference
1	1.42 (1.19, 1.69)
2	2.31 (1.82, 2.93)
>=3	2.77 (2.12, 3.62)
Histology	

Characteristic	HR (95% CI)
DCIS	Reference
Invasive ductal	1.65 (1.29, 2.11)
Invasive lobular	1.9 (1.38, 2.63)
Invasive Ductal and Lobular	1.48 (1.07, 2.05)
Definitive Surgery	
BCS, no radiation	1.58 (1.29, 1.95)
BCS + radiation	Reference
Mastectomy	1.91 (1.59, 2.3)

*
Additionally adjusted for registry site