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The association between mammographic calcifications and breast cancer prognostic factors in a population-based registry cohort

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Abstract

Background—Mammographic calcifications can be a marker of malignancy, but their association with prognosis is less well-established. We examined the relationship between calcifications and breast cancer prognostic factors in the population-based Carolina Mammography Registry (CMR).

Methods—This study included 8,472 invasive breast cancers diagnosed in the CMR between 1996-2011 where information regarding calcifications occurring within two years of diagnosis was reported. Calcification-specific Breast Imaging-Reporting and Data System (BI-RADS) assessments were reported prospectively by a radiologist. Tumor characteristic data were obtained from the North Carolina Central Cancer Registry and/or pathology reports. Multivariable-adjusted associations between the presence of calcifications in the breast affected by cancer and tumor characteristics were estimated using logistic regression. Statistical tests were two-sided.

Results—The presence of calcifications was positively associated with tumors that were high grade (vs. low, odds ratio (OR)=1.43, 95% confidence interval (CI) 1.10-1.88) or had an *in situ* component (vs. without, OR=2.15, 95%CI 1.81-2.55). Calcifications were inversely associated with hormone receptor-negative (vs. positive, OR=0.73, 95%CI 0.57-0.93), >35mm (vs. 8mm, OR=0.47, 95%CI 0.37-0.61), and lobular (vs. ductal, OR=0.39, 95%CI 0.22-0.69) tumors. The association between the presence of calcifications and an *in situ* component was limited to BI-

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RADS 4 and 5 calcifications and was absent for BI-RADS 2 or 3 (P-heterogeneity<0.01). The association with tumor size was strongest for BI-RADS 3 and 4 (P-heterogeneity<0.01).

Conclusion—Calcifications were associated with both unfavorable (high grade) and favorable (small size, hormone receptor-positive) prognostic factors. Detailed analysis of calcification biological features is necessary to understand the mechanisms driving these associations.

Graphical Abstract

Precis: Mammographic calcifications were associated with both favorable and unfavorable prognostic factors in invasive breast cancer. Associations varied according to the calcification-specific BI-RADS, suggesting that the link between calcifications and prognosis depends on calcification type.

Keywords

breast cancer; mammography; physiologic calcification; disease attributes; prognostic factors

Introduction

Calcifications are calcium deposits within the breast that appear as white, opaque markings on mammograms. Currently, the major role of calcifications in breast imaging is in the diagnosis of cancer, where they can be observed in association with invasive breast cancer and/or ductal carcinoma *in situ* (DCIS).^{1, 2} Calcifications can appear in an array of morphologic patterns and distributions that may or may not be suspicious for cancer; positive predictive values have been published previously.³⁻⁷ The American College of Radiology's Breast Imaging-Reporting and Data System (BI-RADS) provides standard terms for describing these morphologic patterns and distributions.¹ In addition, the BI-RADS lexicon defines a classification scheme to convey a radiologist's level of suspicion that a finding is associated with cancer. Using this semi-quantitative BI-RADS scale, calcifications can be categorized using a range from benign (BI-RADS 2) to highly suggestive of malignancy (BI-RADS 5).

In addition to their important role in breast cancer detection, there is evidence that calcifications may also have prognostic value. Calcifications have been associated with higher grade,⁸⁻¹³ smaller size,^{9, 11, 14} lymph node positive,¹⁰ hormone receptor-negative,^{12, 13, 15} and human epidermal growth factor receptor 2 (HER2)-positive¹²⁻¹⁴ tumors. Many of these studies were conducted among women with tumors <15mm in size.^{8-10, 13} Of those studies that did not select patients according to tumor size, all were single-institution patient series with fewer than 1,000 subjects studied.¹⁴⁻¹⁷ Moreover, in some studies, the associations were reported with respect to particular calcification types, such as casting, comedo, and crushed stone morphologies, which typically correspond to BI-RADS 4 and 5 calcifications.^{8-13, 16} Other studies^{14, 15, 17} did not distinguish between calcification types. Thus, it is unclear how associations with prognosis differ for benign-appearing *versus* suspicious calcifications.

We sought to determine the relationship between mammographic calcifications and breast cancer prognostic factors in a large, population-based breast imaging registry where tumors

were unselected for size, with the rationale that a greater understanding of the relationship between calcifications and prognostic factors may provide a more complete understanding of long-term prognosis and may inform treatment approaches. We examined (1) associations between the presence of any calcifications and breast cancer prognostic factors, and (2) associations between specific BI-RADS classifications of calcifications and prognostic factors. We hypothesized that BI-RADS 4 (suspicious) and 5 (highly suggestive of malignancy) calcifications would be more strongly associated with poor prognostic factors compared with BI-RADS 2 (benign) or 3 (probably benign) calcifications.

Materials and Methods

This study used data from the Carolina Mammography Registry (CMR), which has been described previously.¹⁸ Briefly, the CMR is a population-based breast imaging registry that operates in partnership with imaging facilities across North Carolina. Health, lifestyle, and imaging information are collected prospectively through administration of patient and radiologist questionnaires. Cancer outcomes are determined through linkage with the North Carolina Central Cancer Registry (NCCCR) and pathology reports obtained from the University of North Carolina Lineberger Comprehensive Cancer Center rapid case ascertainment program and CMR facilities. This study was approved by the UNC-Chapel Hill Institutional Review Board.

Population

This analysis included female CMR participants diagnosed with unilateral invasive breast cancer between 1996 and 2011 (Figure 1). Women diagnosed with *in situ* disease only were excluded. Inclusion required at least one screening or diagnostic mammogram of the affected breast performed within two years of diagnosis and with non-missing data on the presence of calcifications. Women who used tamoxifen or raloxifene, or reported a history of breast augmentation or reduction were excluded. A total of 12,480 mammograms among 8,472 breast cancer cases were identified.

Mammographic data

Mammographic information was collected prospectively. Participants were asked the reason for the mammogram (routine screening or symptoms), screening history, and prior history of breast cancer. The radiologist recorded the mammogram indication, exam findings, BI-RADS assessments, and recommendation for follow-up.

For each mammogram, the interpreting radiologist categorized the appearance of calcifications using BI-RADS criteria.¹⁹ BI-RADS were assigned separately for each breast if the mammogram was bilateral. The calcification-specific BI-RADS was a separate assessment from the BI-RADS assigned for the overall exam. If there were multiple mammograms of the breast affected by cancer in the two years preceding diagnosis, calcification information for use in this analysis was obtained from the mammogram closest in time to diagnosis. The median time between the mammogram selected for study and breast cancer diagnosis was 14 days (interquartile range: 5 – 31). For the purposes of this study, exams with calcification-specific BI-RADS of 2, 3, 4, or 5 were considered positive

for the presence of calcifications and exams with calcifications-specific BI-RADS 0 (incomplete) or 1 (negative) were considered negative. We did not have information regarding the location of calcifications relative to the tumor beyond breast laterality.

Pathologic data

Tumor characteristics were obtained from the NCCCR or abstracted from pathology reports. Stage at diagnosis was coded according to SEER summary stage rules.²⁰ Estrogen and progesterone receptor (ER, PR) positivity and tumor grade were reported according to the standards of the diagnosing institution. Tumor size (mm) was the total size of the invasive tumor, and was categorized into quintiles. Histology was classified according to the International Classification of Diseases for Oncology.²¹ Histologic types present at <1% were grouped together as “other.” Whether the tumor had an *in situ* component was determined based on Collaborative Stage Site-Specific Factor 6²² for data obtained from the NCCCR, or the reporting of any type of *in situ* lesion for data abstracted from pathology reports. We were unable to distinguish DCIS from lobular carcinoma *in situ* (LCIS) for 1,140 cases due to the fact that Site Specific Factor 6 does not distinguish the histologic type of the *in situ* component for invasive cancers. Therefore, the *in situ* component variable was coded as “yes” if any *in situ* was reported.

Covariates

Age, menopausal status, race, history of a previous mammogram, first degree family history of breast cancer, history of a previous breast biopsy, and current hormone use were self-reported at the time of the mammogram. Women were classified as postmenopausal if they reported that their periods had stopped for any reason. Current hormone use was based on reported use of menopausal hormone therapy or hormonal contraceptives. Mammogram type (digital vs. film-screen) and BI-RADS mammographic density¹⁹ were reported by the radiologist. Tumors were categorized as ‘screen-detected’ if there was a positive screening mammogram within 12 months of diagnosis, ‘interval-detected’ if there was a negative screening mammogram within 12 months of diagnosis, and ‘other’ if there was no screening mammogram within 12 months of diagnosis, based on criteria used by the Breast Cancer Surveillance Consortium.²³

Statistical analysis

Variables were categorized as shown in Table 1 and Supplementary Table S1, unless otherwise specified. Differences in patient characteristics according to the presence of calcifications were evaluated using the chi-square or the Mann-Whitney test. The relationship between the presence of calcifications in the affected breast and tumor characteristics was evaluated by estimating odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional binary logistic regression. Initially, each tumor characteristic was examined in a univariable model. A multivariable-adjusted model was developed by including all tumor characteristics and sequentially eliminating variables with P-values >0.05 using backwards selection (Multivariable Model 1). To determine the potential confounding effects of patient characteristics on the association between calcifications and tumor characteristics, we estimated a second multivariable model that additionally adjusted for patient characteristics (Supplementary Table S1) associated with the presence of

calcifications (Multivariable Model 2). Observations with missing data were excluded from models. Family history of breast cancer was not routinely collected before 2001, so analyses using this variable were restricted to cases from 2001 or later.

We explored whether the association between the presence of calcifications in the affected breast and tumor characteristics was modified by tumor size (<15mm, ≥15mm), mammogram type, or presence of an *in situ* component in stratified analyses. Statistical differences were evaluated by comparing models with and without a cross-product interaction term using the likelihood ratio test. Additionally, we estimated associations for calcification-specific BI-RADS using multinomial logistic regression to determine whether tumor characteristics were associated with the calcification perceived suspicion of malignancy.

In sensitivity analyses we excluded cases where women had a history of breast biopsy (N=2,755) and where the calcification assessment was BI-RADS 0 (N=81), as this indicates further imaging was needed. We also evaluated associations excluding cases that were not screen-detected (N=4,360) or where women were younger than 40 years or older than 75 years (N=1,816) to determine whether the results were influenced by screening.

Statistical analyses were performed using SAS v9.4 (Cary, NC). All statistical tests were two-sided. P-values ≤0.05 were considered statistically significant.

Results

Any calcifications in the affected breast

Calcifications in the affected breast were reported for 1,288 of the 8,472 breast cancer patients (15%). Women with calcifications were slightly younger than women without calcifications (median age: with calcifications - 60 years; without calcifications - 61 years; $P<0.01$), and were more likely to have a prior mammogram, family history of breast cancer, previous breast biopsy, heterogeneously dense or extremely dense breasts, and to not use hormones (Supplementary Table S1).

The presence of calcifications was positively associated with an earlier stage at diagnosis, lymph node negativity, hormone receptor positivity, smaller tumor size, tubular histology, and the presence of an *in situ* component in univariable analyses (Table 1). The presence of calcifications was inversely associated with lobular and mucinous histologies. In multivariable models, hormone receptor status, tumor grade, tumor size, histology, and presence of an *in situ* component remained statistically significantly associated with calcifications (Table 1). Further adjustment for patient characteristics did not change the associations between calcifications and tumor characteristics, with the exception of attenuation of the association between calcifications and tubular breast cancer (Table 1). Therefore, patient characteristics were not included in remaining analyses due to the overall lack of impact on tumor characteristic associations.

Associations between calcifications and prognostic factors were similar for tumors <15mm and ≥15mm in size, with the following exceptions: (1) calcifications were positively

associated with intermediate tumor grade among ≥ 15 mm tumors but not <15 mm tumors and (2) calcifications showed an inverse association with mixed ductal-lobular histology among <15 mm tumors but a positive association among ≥ 15 mm tumors (Figure 2). However, differences in association comparing <15 mm and ≥ 15 mm tumors were not statistically significant for any factors examined, including grade and histology (P-interaction >0.05). Associations were also similar when stratified by film-screen or digital mammography and by the presence of an *in situ* component (P-interaction >0.05 ; Supplementary Tables S2 and S3). When we excluded non-screen detected cancers, the association between calcifications and ER-/PR+ tumors (vs. ER+/PR+) was strengthened, whereas the inverse association with mucinous tumors was attenuated (Supplementary Table S4). Associations were unaffected by excluding cases where women reported a previous biopsy, were younger than 40 years or older than 75 years, or where calcifications were classified as BI-RADS '0' (Supplementary Table S4).

Calcification BI-RADS

There were some differences in association according to calcification-specific BI-RADS for tumor grade, size, and presence of an *in situ* component (Table 2). BI-RADS 4 and 5 calcifications were strongly associated with the presence of an *in situ* component, whereas there was no association for BI-RADS 2 or 3 calcifications (P-heterogeneity <0.01). Other associations did not follow a clear pattern. For example, there was a more than two-fold association between the presence of BI-RADS 2, 3, and 5 calcifications and intermediate or high tumor grade (vs. low grade), but the association between BI-RADS 4 and intermediate or high grade was closer to the null. The inverse association between calcifications and larger tumor size seen in the overall analysis was only observed for BI-RADS 3 and 4 calcifications (Table 2). Comparisons according to histology could not be made across BI-RADS groups due to the low prevalence of non-ductal histologies.

Discussion

In this study, we examined the relationship between mammographic calcifications and prognostic factors among women diagnosed with invasive breast cancer. Prior studies have reported associations between calcifications and poor prognostic features as well as poorer survival.^{8-13, 15, 17, 24} We conducted this study to determine whether those findings are generalizable to a population-based setting where patients are unselected for tumor size or calcification type. We found that tumors diagnosed among women with mammographic calcifications were more likely to have both favorable (hormone receptor positive, small size) and unfavorable (high grade) prognostic features. Associations varied when cases were examined according to the calcification-specific BI-RADS, particularly with respect to tumor size, tumor grade, and the presence of an *in situ* component. Together, these data suggest that the presence of calcifications is associated with breast cancer prognostic factors in the general patient population and that the link with some factors depends on calcification type.

Our findings are in agreement with previous studies reporting that calcifications are associated with the presence of carcinoma *in situ*,¹⁴⁻¹⁶ smaller tumor size,^{9, 11, 14} and higher

tumor grade.⁸⁻¹³ However, our results differed from previously-reported associations between calcifications and hormone receptor-negativity^{12, 13, 15} and lymph node positivity.¹⁰ Several prior studies of calcifications and prognostic factors were conducted among women with tumors ≤ 15 mm in size,^{8-10, 13} raising questions as to the consistency of previously reported associations among women with larger tumors. We did not find strong evidence of differences in association for tumors that were <15 mm *versus* ≥ 15 mm, which suggests that previous findings among women with smaller tumors are likely applicable to women with larger tumors.

We hypothesized that the association between the presence of calcifications and prognostic factors would be strongest for calcifications that were suspicious or highly suggestive of malignancy (BIRADS 4 and 5). In this population, the association between the presence of calcifications and an *in situ* component was consistent with our hypothesis, but associations with hormone receptor status, tumor size, and grade were not. This raises questions as to what biological mechanisms may be associated with the relationship between calcifications and prognostic factors. There are multiple potential causes of calcifications, including development of scar tissue after a biopsy or surgery, fluid accumulation, epithelial proliferation, tissue necrosis, and inflammation.¹ Inflammation has been linked previously with poor breast cancer prognosis and disease progression, possibly due to recruitment of macrophages that promote tumor growth and proteinases that degrade the extracellular matrix.²⁵ Our finding of an association between calcifications and ER-positivity is consistent with an inflammation hypothesis, as a greater number of ER-positive tumors could result from the induction of aromatase by insulin, tumor necrosis factor- α , interleukin-6, and prostaglandin E2 under chronic inflammation.²⁶ Evaluation of tissue-based markers of inflammation among women with and without calcifications is needed to determine whether inflammation is an important link between calcifications and prognosis.

The association between BI-RADS 4 and 5 calcifications and the presence of an *in situ* component in addition to the invasive tumor was one of the strongest we observed. This was expected, given that approximately 95% of DCIS are detected due to mammographic abnormalities, of which calcifications are the most common (76%).²⁷ Calcifications are less commonly associated with LCIS, but do occur.^{28, 29} The link between this finding and breast cancer prognosis is unclear. On one hand, studies suggest that the presence of DCIS or LCIS with an invasive tumor either has no effect on recurrence or is a predictor of good prognosis.³⁰⁻³³ Other studies suggest recurrence-free survival may be lower if there is extensive DCIS within surrounding normal tissue or the DCIS is high-grade.^{34, 35} We were unable to evaluate the grade of the *in situ* component or *in situ* extent in this study. Data addressing the impact of these factors are needed to clarify the contributions of calcifications with *in situ* components to invasive breast cancer prognosis. Women with only *in situ* disease (no invasion) were excluded from this study; the impact of calcifications on prognostic factors in *in situ* disease without invasive cancer may differ from the findings reported here.

This study was limited by missing data for some tumor characteristics, particularly ER and grade. Data missingness decreased over the course of the study period, due to structural patterns in how data was reported to the NCCCR over time. Any related missing data bias is

most likely to be non-differential and would lead to bias of associations towards the null. Thus, we believe that the results reported in this study are unlikely to be false-positive associations due to missingness. Additionally, we did not have information regarding the location of the calcifications within the affected breast relative to the invasive tumor. Other limitations were related specifically to the analysis of calcification BI-RADS. Both the fact that the assignment of BI-RADS can vary among radiologists and the publication of new editions of the BI-RADS Atlas in 1998 and 2003 may have contributed to variability in the way that calcification-specific BI-RADS were assigned over the study period. A *post hoc* analysis of our data suggests that variability over time was likely low, with slightly more calcifications reported as BI-RADS 4 and fewer reported as BI-RADS 3 in 2003 or later when compared with 1998 or earlier. A single-institution study evaluating interobserver reproducibility of the BI-RADS lexicon reported almost perfect agreement for the presence of calcifications but only fair agreement for the descriptive classification.³⁶ As such, validation of these results in an environment where all films are assessed by a group of uniformly-instructed radiologists is necessary to rule out the possibility that the BI-RADS-specific results were affected by differences among radiologists.

The strengths of this analysis are the large population size, prospective assessment of calcifications, and detailed assessment of calcifications at the BI-RADS level. To our knowledge, this study is the largest to date to examine the association between mammographic calcifications and tumor characteristics, and one of only two on this subject conducted in the US. US-based results may differ from previous studies conducted in Europe due to differences in recommended screening intervals. Furthermore, the CMR is population-based, increasing the likelihood that the results of this study will be generalizable to the general population of breast cancer patients in the US. Administration of a patient questionnaire allowed us to rule out the possibility of confounding by patient characteristics.

In summary, we found that the presence of mammographic calcifications in the same breast where invasive cancer was diagnosed was positively associated with higher tumor grade and the presence of an *in situ* tumor component, and inversely associated with hormone receptor negativity, larger tumor size, and lobular histology. Some associations varied according to calcification BI-RADS, suggesting that qualitative evaluation of calcifications may be a useful adjunct to understanding prognosis at the time of diagnosis. As more is learned about the consistency of the relationship between calcification types and prognosis, it is possible that the presence of calcifications could be considered alongside other major prognostic factors to help determine breast cancer treatment. Additionally, greater knowledge of the biological mechanisms underlying relationships between the presence of calcifications and prognosis may identify new treatment targets, such as inflammation (discussed above). Both of these hypotheses for the added value of detecting and characterizing calcifications in invasive breast cancer are currently unproven and require additional evidence. We hope that our study provides motivation for continued research along these lines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Study population inclusion criteria

We analyzed data from Carolina Mammography Registry participants who were diagnosed with invasive breast cancer between 1996 and 2011. Women must have had non-missing data on the presence or absence of mammographic calcifications within two years before diagnosis.

Figure 2. Association between the presence of calcifications and selected tumor characteristics, stratified by tumor size - <15mm (left panel) versus ≥15mm (right panel)

Referent categories are ER+/PR+ (hormone receptor status), low grade (tumor grade), ductal (histology), and no (*in situ* component). Odds ratios are not shown among ≥15mm tumors for mucinous, ductal with other types, or tubular histologies due to small sample sizes. Tests for interaction were not statistically significant for any of the factors (hormone receptor status – P=0.84; tumor grade – P=0.08; histology – P=0.09; *in situ* component – P=0.50).

Table 1
Associations between mammographic calcifications and breast tumor characteristics in the Carolina Mammography Registry.

	Calcifications in the affected breast				OR (95% CI)	
	Yes N	No N	%	Univariable	Multivariable model 1 [*]	Multivariable model 2 ^{*,†}
Total	1288	7184				
Stage at Diagnosis						
Localized	722	4271	65	Referent		
Regional spread	278	2075	32	0.79 (0.68-0.92)		
Distant metastases	23	195	3	0.70 (0.45-1.08)		
Missing	265	643				
<i>P-value</i>				<0.01		
Lymph node positivity [§]						
Negative	674	4015	64	Referent		
Positive	299	2225	36	0.80 (0.69-0.93)		
Missing	9	46				
<i>P-value</i>				<0.01		
Hormone receptors						
ER+/PR+	499	3235	61	Referent	Referent	Referent
ER+/PR-	124	671	13	1.20 (0.97-1.48)	1.17 (0.92-1.49)	1.17 (0.90-1.52)
ER-/PR+	25	148	3	1.10 (0.71-1.69)	1.19 (0.74-1.94)	1.33 (0.80-2.21)
ER-/PR-	150	1225	23	0.79 (0.65-0.96)	0.73 (0.57-0.93)	0.75 (0.58-0.97)
Missing	490	1905				
<i>P-value</i>				0.01	0.01	0.02
Tumor grade						
Low	158	1117	19	Referent	Referent	Referent
Intermediate	391	2326	39	1.19 (0.97-1.45)	1.38 (1.08-1.77)	1.48 (1.14-1.94)
High	390	2550	43	1.08 (0.89-1.32)	1.43 (1.10-1.88)	1.47 (1.10-1.96)
Missing	349	1191				
<i>P-value</i>				0.19	0.02	0.01
Tumor size (mm)						

Calculations in the affected breast					OR (95% CI)		
	Yes		No		Univariable	Multivariable model 1 *	Multivariable model 2 **†
	N	%	N	%			
8	428	38	1238	18	Referent	Referent	Referent
9 - 15	209	18	1717	16	0.35 (0.29-0.42)	0.46 (0.36-0.58)	0.43 (0.33-0.56)
16 - 21	137	12	1028	15	0.39 (0.31-0.48)	0.38 (0.29-0.51)	0.37 (0.27-0.51)
22 - 35	146	13	14720	21	0.30 (0.24-0.36)	0.33 (0.25-0.43)	0.32 (0.24-0.44)
>35	215	19	1327	20	0.47 (0.39-0.56)	0.47 (0.37-0.61)	0.44 (0.33-0.58)
Missing	153		454				
<i>P-value</i>					<0.01	<0.01	<0.01
Histology							
Ductal, NOS	1056	83	5511	78	Referent	Referent	Referent
Lobular	49	4	478	7	0.54 (0.40-0.72)	0.39 (0.22-0.69)	0.42 (0.23-0.77)
Mixed ductal-lobular	79	6	453	6	0.91 (0.71-1.17)	0.96 (0.68-1.34)	0.92 (0.64-1.31)
Mucinous	14	1	175	2	0.42 (0.24-0.72)	0.49 (0.21-1.13)	0.56 (0.24-1.33)
Ductular	21	2	127	2	0.86 (0.54-1.38)	1.45 (0.70-3.01)	1.19 (0.55-2.60)
Ductal mixed with other types	11	1	86	1	0.67 (0.36-1.26)	0.88 (0.44-1.74)	0.89 (0.44-1.80)
Tubular	20	2	71	1	1.47 (0.89-2.43)	1.94 (0.93-4.05)	1.39 (0.61-3.15)
Other	30	2	168	2	0.93 (0.63-1.38)	1.14 (0.69-1.87)	1.14 (0.57-2.27)
Missing	8		115				
<i>P-value</i>					<0.01	0.01	0.15
<i>In situ</i> component							
No	760	59	5320	74	Referent	Referent	Referent
Yes	528	41	1864	26	1.98 (1.75-2.24)	2.15 (1.81-2.55)	2.10 (1.75-2.52)
<i>P-value</i>					<0.01	<0.01	<0.01

Abbreviations: CI – confidence interval, ER – estrogen receptor, OR – odds ratio, PR – progesterone receptor

* Adjusted for other tumor characteristics in this column

† Additionally adjusted for age at mammogram (continuous), history of prior mammogram, detection method, history of previous biopsy, current hormone use, and mammographic density

§ Among women where regional lymph nodes were examined

Table 2
Association between calcification BI-RADS assessments and tumor characteristics in the Carolina Mammography Registry.

	Calcifications BI-RADS Category									
	No calcifications		2		3		4		5	
	N		N	OR (95% CI) *	N	OR (95% CI) *	N	OR (95% CI) *	N	P-value †
Total	7,184		86		73		877		252	
Hormone receptors										
ER+/PR+	3235		40	Referent	34	Referent	329	Referent	96	0.76
ER+/PR-	671		8	0.88 (0.37-2.14)	2	§	87	1.21 (0.90-1.61)	27	1.39 (0.87-2.21)
ER-/PR+	148		2	§	0	§	17	1.33 (0.75-2.36)	6	1.19 (0.46-3.05)
ER-/PR-	1225		12	0.83 (0.39-1.75)	8	0.66 (0.24-1.80)	92	0.73 (0.54-0.99)	38	0.72 (0.45-1.15)
Missing	1905		24		29		352		85	
P-value				0.92		0.35		0.03		0.14
Tumor grade										
Low	1117		10	Referent	10	Referent	121	Referent	17	Referent
Intermediate	2326		29	2.53 (0.93-6.92)	23	3.45 (1.09-10.87)	256	1.10 (0.83-1.46)	83	2.22 (1.18-4.19)
High	2550		31	2.48 (0.85-7.18)	16	2.05 (0.55-7.67)	243	1.20 (0.87-1.63)	100	2.34 (1.22-4.51)
Missing	1191		16		24		257		52	
P-value				0.18		0.08		0.53		0.03
Tumor size, mm										
8	1238		12	Referent	26	Referent	332	Referent	58	<0.01
9 - 15	1717		16	1.05 (0.39-2.83)	13	0.41 (0.17-1.00)	151	0.43 (0.32-0.56)	29	0.51 (0.28-0.95)
16 - 21	1028		11	0.76 (0.24-2.41)	9	0.42 (0.15-1.18)	87	0.30 (0.21-0.43)	30	0.76 (0.41-1.42)
22 - 35	14720		23	1.36 (0.51-3.61)	3	§	73	0.21 (0.15-0.30)	47	0.81 (0.46-1.44)
>35	1327		17	1.22 (0.45-3.30)	5	0.21 (0.06-0.68)	126	0.35 (0.25-0.47)	67	1.19 (0.69-2.04)
Missing	454		7		17		108		21	
P-value				0.81		0.01		<0.01		0.03
Histology										
Ductal, NOS	5511		60	Referent	54	Referent	726	Referent	216	Referent
										0.54

	Calcifications BI-RADS Category										P-value [†]
	No calcifications		2		3		4		5		
	N		N	OR (95% CI)*	N	OR (95% CI)*	N	OR (95% CI)*	N	OR (95% CI)*	
Lobular	478	9	1.12 (0.34-3.74)	5	1.34 (0.31-5.85)	32	0.34 (0.16-0.73)	3	---	---	
Mixed ductal-lobular	453	7	1.30 (0.45-3.70)	1	---	53	0.99 (0.66-1.49)	18	0.84 (0.42-1.69)		
Mucinous	175	3	---	1	---	8	0.59 (0.23-1.48)	2	---	---	
Ductular	127	0	---	2	---	16	1.74 (0.77-3.96)	3	---	---	
Ductal mixed with other types	86	2	---	3	---	6	0.72 (0.30-1.70)	0	---	---	
Tubular	71	1	---	2	---	17	1.98 (0.88-4.46)	0	---	---	
Other	168	3	---	3	---	14	0.60 (0.21-1.68)	10	0.70 (0.17-2.94)		
Missing	115	1		2		5					
P-value			0.61		0.20		0.04		0.62		
In situ component											
No	5320	67	Referent	54	Referent	487	Referent	152	Referent	<0.01	
Yes	1864	19	0.95 (0.52-1.72)	19	0.97 (0.46-2.08)	390	2.62 (2.13-3.22)	100	1.98 (1.41-2.80)		
P-value			0.86		0.95		<0.01		<0.01		

Abbreviations: BI-RADS – breast imaging-reporting and data system, CI – confidence interval, ER – estrogen receptor, OR – odds ratio, PR – progesterone receptor

^{*} Adjusted for all other factors shown in Table

[†] Wald P-value testing the null hypothesis that effect estimates for BI-RADS 2, 3, 4, and 5 calcifications are equal

[§] Not estimated due to small numbers