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Dense and Non-dense Mammographic Area and Risk of Breast Cancer by Age and Tumor Characteristics

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Abstract

Background—Mammographic density (MD) is a strong breast cancer risk factor. We previously reported associations of percent MD with larger and node-positive tumors across all ages, and

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estrogen receptor (ER)-negative status among women ages <55 years. To provide insight into these associations, we examined the components of percent MD (dense area (DA) and non-dense area (NDA) with breast cancer subtypes.

Methods—Data were pooled from six studies including 4095 breast cancers and 8558 controls. DA and NDA were assessed from digitized film-screen mammograms and standardized across studies. Breast cancer odds by density phenotypes and age according to histopathological characteristics and receptor status were calculated using polytomous logistic regression.

Results—DA was associated with increased breast cancer risk [odds ratios (OR) for quartiles: 0.65, 1.00(Ref), 1.22, 1.55; p-trend <0.001] and NDA was associated with decreased risk [ORs for quartiles: 1.39, 1.00(Ref), 0.88, 0.72; p-trend <0.001] across all ages and invasive tumor characteristics. There were significant trends in the magnitude of associations of both DA and NDA with breast cancer by increasing tumor size (p-trend<0.001) but no differences by nodal status. Among women <55 years, DA was more strongly associated with increased risk of ER+ vs. ER− tumors [p-heterogeneity (het) = 0.02] while NDA was more strongly associated with decreased risk of ER− vs. ER+ tumors [p-het = 0.03].

Conclusions—DA and NDA have differential associations with ER+ vs. ER− tumors that vary by age.

Impact—DA and NDA are important to consider when developing age- and subtype-specific risk models.

Keywords

Mammographic density; Breast density; Breast cancer; Tumor subtypes; Mammography; Epidemiology

Introduction

Mammographic density (MD) represents the variability of breast tissue composition on the mammogram image. Radiographically, there are two main components of breast tissue: fat, which appears dark on a mammogram and is considered “non-dense”, and fibroglandular tissue (i.e., epithelial cells and connective tissue), which appears white and is defined as “dense” tissue (1). Women in the highest quartile of percent MD (i.e., proportion of dense fibroglandular tissue within the total area of the breast) have about 4 times the risk of developing breast cancer compared to women in the lowest quartile, even after adjusting for other known breast cancer risk factors (2). The biological mechanism by which MD increases breast cancer risk, however, remains largely unknown.

We reported percent MD to be a breast cancer risk factor across tumor characteristics and age groups (3). We noted stronger associations for tumors of large size and positive lymph nodes across all ages, and ER-negative status among women ages <55 years, suggesting high MD may play an important role in tumor aggressiveness, especially in younger women. Recent evidence from a large meta-analysis suggests that dense and non-dense area may be independently associated with breast cancer risk (4–7). Few previous studies have evaluated the possible differential associations of dense and non-dense breast area by breast cancer

subtype or tumor characteristics. Therefore, we investigated the underlying associations of dense (fibroglandular) or non-dense (adipose) area, or both, with tumor characteristics. Understanding these differential associations could provide insight into the mechanism by which percent density influences risk.

Materials and Methods

Study populations

Participating studies included the Mayo Mammography Health Study (MMHS) (8, 9), Mayo Clinic Breast Cancer Study (MCBCS) (10, 11), Nurses' Health Study (NHS) and NHSII (12–14), Mayo Clinic Mammography Study (MCMAM) (15), and the San Francisco Bay Area Breast Cancer SPORE and San Francisco Mammography Registry (SFMR) (16–18) (Table 1). Details of the study populations are in Supplementary Table S1 and described in our earlier report (3); the present analysis includes additional cases and controls, primarily from the SFMR, which were not available at the time of our earlier analysis. Incident breast cancer cases were identified by self-report, linkage to clinic and/or statewide tumor registries, or death certificates with further confirmation by medical record review. Controls were selected from the underlying cohorts (MMHS, NHS, NHSII, SFMR) or from the source population (MCBCS, MCMAM) and typically matched to cases on age, menopausal status, and year of examination (MMHS, MCMAM, SFMR), blood draw (NHS, NHSII) or diagnosis (MCBCS) as described previously (3). From all studies, we excluded breast cancer cases diagnosed within 6 months of mammography and their matched controls, to minimize prevalent cancers at time of mammography. Covariate information was obtained from medical record review (MCMAM), self-administered questionnaires (NHS, NHSII), or both (MMHS, MCBCS) prior to (NHS, NHSII) or at the time of (MSBCS, MMHS, MCMAM, SFMR) mammography. In total, these analyses included 4095 breast cancer cases and 8558 controls.

This study was approved by the Institutional Review Boards at Mayo Clinic, Brigham and Women's Hospital, the University of California, San Francisco (UCSF), and the Connecticut Department of Public Health Human Investigations Committee. Informed consent was obtained or implied by return of questionnaires (NHS, NHSII).

Assessment of mammographic density

As described previously (3), dense area (DA) and non-dense area (NDA), were measured using two computer-assisted threshold techniques (Cumulus (19) and UCSF custom mammographic density software) (20) from digitized images of pre-diagnostic film screening mammograms of the craniocaudal view. Percent MD was calculated as the proportion of absolute DA over total breast area (DA + NDA). With the exception of NHS and NHSII, for which average DA and NDA of both breasts was used, DA and NDA were estimated from the contralateral breast for cases and corresponding side for matched controls.

We standardized PMD, DA and NDA measurements made within each study to remove variability in measurements due to reader (1, 21), time of density assessment, and age

distributions of different study populations for pooled analyses (Supplementary Figure S1). We have previously described and applied this method to percent MD using a logit transformation (3). For absolute dense and non-dense areas, an appropriate transformation was selected via the Box-Cox procedure. For DA, the square root transformation was selected while the 4th root was selected for non-dense area. Briefly the following procedure was implemented on each measure after appropriate transformation. First, we focused on women without breast cancer and estimated study-specific linear age trends in the medians of transformed MD (TMD) values using quantile regression. Study-specific age trends were removed by computing the difference between each individual's observed TMD and the age-predicted median TMD from the corresponding study set. Variability was standardized across studies by dividing the residuals within each study by the corresponding inter-quartile range (IQR), and then multiplying these re-scaled residual values by the IQR of the original residuals from all studies. This ensured that the variability in standardized TMD was consistent across studies, and roughly equivalent to the observed variability in TMD. Finally, we estimated an overall age by TMD trend from the original data, and added the age-predicted median TMD to the rescaled residuals from each individual. This reincorporated the known age trend in MD into the standardized TMD measurements (Supplementary Figure S2). These TMD values were back-transformed to the original scale for use in analyses. Of note, variability in the tails of the smoother and limited data under age 40 (n=68 controls), resulted in an apparent difference in the distribution for DA for the NHS2 study (Supplementary Figure 2).

Assessment of tumor characteristics among cases

Information on tumor type, histology, grade, nodal involvement, tumor size, and ER, PR, and HER2 status was obtained from state-wide Surveillance Epidemiology and End Results programs (SFMR), pathology reports (NHS, NHSII), state and clinic cancer registries (MMHS, MCMAM, MCBCS), and medical records (MMHS, MCMAM, MCBCS). For 313 cases in NHS, 52 cases in NHS II, and 194 cases in MCMAM with missing receptor data on pathology reports, receptor status was obtained from immunohistochemical staining performed on paraffin sections of the tumor tissue microarray (TMA) according to a standard protocol (22). A proportion of cases (18%; N=624 cases ranging from 8% to 34% across studies) were still missing HER2 status after incorporating the TMA data and were excluded from HER2 analyses. Another 2% were cases with borderline HER2 results (2+ without available FISH) and not used in analyses.

Statistical analyses

We categorized the standardized DA and NDA measurements into quartiles based on the control distribution across studies. We fit polytomous (multinomial) logistic regression models to estimate odds ratios (OR) and 95% confidence intervals (CI) for the associations of DA and NDA with risk of breast cancer overall as well as with breast cancer defined by tumor type (invasive or DCIS), histologic type (ductal or lobular), grade (well-differentiated, moderately differentiated, or poorly differentiated), tumor size (<1.1 cm, 1.1–2.0 cm, or 2.1+ cm), involvement of lymph nodes (positive or negative), and receptor status (ER+ or ER−; PR+ or PR−; HER2+ or HER2−). We also updated our prior analyses of percent MD

(3) with this larger sample size for comparison purposes; percent MD categories were 0–10%, 11–25% (reference), 26%–50%, and 51%+.

We pooled data across the six studies and adjusted for study site, age (continuous), and body mass index (BMI, continuous) in multivariable models. We further considered potential confounding by parity (nulliparous, parous, or unknown) and first-degree family history of breast cancer (yes, no, or unknown) by evaluating the magnitude of change in ORs observed after including each potential confounder individually in the model. Postmenopausal hormone therapy (current estrogen alone, current estrogen plus progesterone, never/former, or unknown) was also evaluated as a confounder among postmenopausal women in the subset of studies for which this information was available (MMHS, NHS, NHSII, and SFMR). Addition of these variables to the models did not substantially change risk estimates and were not included in final models. In secondary analyses, we considered models that mutually adjusted for continuous measures of square root DA and NDA.

Because our previous findings suggested differences of percent MD and tumor characteristics primarily for younger women, we stratified by ages <55 years vs. ≥55 years only. We evaluated whether the associations between DA or NDA and breast cancer differed by specific tumor characteristics, both overall and within age groups, using polytomous logistic regression models ($\mathbf{P}_{\text{heterogeneity}}$). For subtypes with a natural ordering, including tumor size and grade, tests of trend ($\mathbf{P}_{\text{trend}}$) across categories were used to assess significance. Formal tests of interaction ($\mathbf{P}_{\text{age-interaction}}$) assessed the significance of differential DA and NDA associations with each of the breast cancer characteristics and subtype by age groups.

Prior to pooling data across the six studies, study specific estimates were obtained by fitting separate models for each study and assessing individual associations between MD and each tumor subtype. We assessed the statistical significance of differences in associations by study site by testing for interactions between study group and DA or NDA category in the pooled analysis and, in general, found no evidence of differences across study (***P***-values >0.09) other than as noted in results below.

Analyses were performed using SAS software (version 9.3, SAS Institute, Cary, NC). All statistical tests were two-sided and ***P***-values <0.05 were considered statistically significant.

Results

Overall, mean age at mammogram was 57 years among both cases and controls. Median time to diagnosis at mammogram was 4.1 years (interquartile range: 2.3–6.0) for cases. DA and NDA were not strongly correlated in the combined study population (r=0.07 based on continuous measure) or across individual study populations (correlations ranged from 0.06 (NHS) to 0.29 (NHS2)). Among both cases and controls, median percent MD and DA was lower while NDA was higher in women ages ≥55 years than women <55 years. Further, within each age group, median percent MD and DA was higher among cases vs. controls. Median NDA was lower among cases vs. controls in women ages <55 years but similar in cases and controls ≥55 years (Table 1). DCIS was more common among women ages <55

years (15.8%) vs. women ≥55 years (11.7%), while, among invasive cancers, more aggressive tumor characteristics were evident in women <55 years at mammography compared to women ≥55 years (Table 2).

In general, results of our updated analyses for percent MD were consistent with our previous report which included a large subset of these data (3) and are presented in Tables 3 and 4. However, our earlier report stratified age into three categories, instead of two as shown here (Table 4). Consistent with our earlier analyses, we found significant positive associations between percent MD and breast cancer risk. Briefly, with the addition of new cases (mostly invasive) and controls, we found similar or stronger associations than what we previously reported. In the updated analyses, we continue to observe stronger associations with increasing tumor size, positive nodal status, and lobular (vs. ductal) cancer)(P_{het}<0.02) across age groups (Table 3). Among women <55 years, there were stronger associations with node positive vs. node negative tumors (Table 4). Of note, the associations of percent MD with ER-negative vs. ER-positive tumors are not statistically significantly different across the two age groups examined here, <55 vs. 55+ ($\mathbf{P}_{age\text{-}interaction}$ =0.12). However, when we analyzed by the original three age groups, the age-interaction remains ($\mathbf{P}_{age\text{-}interaction}$ =0.048) suggesting it is partially driven by differential associations across the older age groups (Data not shown). Below, we focus on results for DA and NDA.

Overall and invasive breast cancer and DCIS

Overall, DA was significantly positively associated with breast cancer risk while NDA was significantly inversely associated with breast cancer risk (Table 3) and across age groups (Table 4). Specifically, the ORs for overall breast cancer associated with DA were: Q1 vs. Q2, 0.65; Q3 vs. Q2, 1.22; Q4 vs. Q2, 1.55 (p-trend <0.001) and the ORs for overall breast cancer associated with NDA were: Q1 vs. Q2, 1.39; Q3 vs. Q2, 0.88; Q4 vs. Q2, 0.72 (p-trend <0.001). For DA, associations were similar by age; for NDA, however, the interaction with age was statistically significant ($\mathbf{P}_{age\text{-}interaction}$ <0.01) although the differences in associations by age were not clinically meaningful: <55 years (OR for Q1 vs. Q2, 1.44; 95% CI, 1.24–1.66) compared to those ≥55 years (corresponding OR, 1.33; 95% CI: 1.13–1.56) (Table 4).

DA was significantly positively associated with both invasive breast cancer and DCIS across all age groups (Tables 3 and 4; Figure 1). Among women ≥55 years, this association was stronger for invasive tumors than DCIS ($\mathbf{P}_{heterogeneity}$ = 0.03; Table 4; Figure 1); however, there was no evidence of a significant interaction between age and DA for associations with tumor type ($\mathbf{P}_{age\text{-}interaction}$ = 0.41). Again, even though a statistically significant association was seen by age ($\mathbf{P}_{age\text{-}interaction}$ =0.02), NDA was significantly inversely associated with risk of both invasive breast cancer and DCIS among both younger and older women (Tables 3 and 4; Figure 2).

Grade, invasive histology, size and nodal status

DA was significantly positively associated with all invasive tumor characteristics evaluated while NDA was significantly inversely associated with these characteristics (Tables 3 and 4). While there were no differences in the magnitude of associations of DA or NDA with

tumor histology, grade, or nodal involvement, we did observe heterogeneity of associations with tumor size. Specifically, DA was positively associated with invasive tumors of all sizes; however, stronger positive associations of DA and breast cancer were noted for larger tumors ≥2.1 cm compared to smaller tumors across all ages ($\mathbf{P}_{trend}$ <0.01) (Figure 1). For example, the overall ORs comparing women in Q4 of DA vs. Q2 were 1.42, 1.50, and 2.13 for tumors <1.1 cm, 1.1–2.0 cm, ≥2.1 cm, respectively (Table 3) and findings were similar among ages <55 and ≥55 years (Table 4; Figure 1; $\mathbf{P}_{age\text{-}interaction}$ =0.91). The opposite trend was observed for associations of NDA with tumor size, with a stronger inverse association noted for larger tumors compared to smaller tumors across age groups ($\mathbf{P}_{trend}$ <0.01), with the strongest associations most apparent for tumors 1.1–2.0 cm and 2.1+ cm in women ages <55 and ≥55 years (Table 4; Figure 2). This trend was also similar across age (**P**age-interaction =0.30).

ER, PR and HER2 receptor status

Among women of all ages, stronger associations of DA were noted for ER+ and PR+ tumors compared to hormone receptor negative tumors ($\mathbf{P}_{heterogeneity}$ <0.01). Although there was no significant evidence of differences by age ($\mathbf{P}_{age\text{-}interaction}$ >0.38), among women <55 years, stronger associations were observed for ER+ (OR for Q4 vs. Q2, 1.73; 95% CI, 1.45–2.07) vs. ER− (corresponding OR, 1.01; 95% CI, 0.74–1.39) ($\mathbf{P}_{heterogeneity}$ =0.02; Table 4; Figure 1) and PR+ (OR for Q4 vs. Q2, 1.79; 95% CI, 1.49–2.15) vs. PR− (corresponding OR, 1.13; 95% CI, 0.86, 1.49) ($\mathbf{P}_{heterogeneity}$ =0.01; Table 4; Figure 1). Similarly, although not significantly different by age group ($\mathbf{P}_{age\text{-}interaction}$ = 0.08), among women <55 years, NDA was more strongly inversely associated with ER− tumors (OR for Q4 vs. Q2, 0.48; 95% CI, 0.30, 0.77) than with ER+ tumors (corresponding OR, 0.8; 95% CI, 0.63–1.01) ($\mathbf{P}_{heterogeneity}$ =0.03; Table 4; Figure 2). In contrast, among women ages ≥55, DA and NDA were similarly associated with tumors defined by ER or PR status ($\mathbf{P}_{heterogeneity}$ >0.08; Table 4; Figure 2). Finally, DA and NDA were similarly associated with tumors defined by HER2 status (Tables 3 and 4).

Results were not materially changed in models that included mutual adjustment for DA and NDA (Data not shown). Finally, there was little evidence of differences across study (majority of ***P***-values >0.09). Between study heterogeneity was noted, however, for associations of DA with overall breast cancer (***P***=0.02) and tumor histology (***P***=0.04), suggesting caution when interpreting these results.

Discussion

In this large study, the positive associations between percent MD and breast cancer overall and by tumor characteristics were similar or stronger than in our first paper based on a subset of these data (23). In analyses of DA and NDA, we found that DA was significantly associated with increased breast cancer risk and NDA was significantly associated with decreased risk and that these were independent risk factors for breast cancer. Further, statistically significant associations of the absolute DA and NDA measures with breast cancer were apparent for all tumor characteristics evaluated. Our findings suggest greater magnitude of association for DA with ER+ vs. ER− disease and PR+ vs. PRv disease and

stronger associations of NDA with ER− vs. ER+ disease in women <55 years. We also observed significant positive and inverse trends for associations of DA and NDA, respectively, with tumor size across all ages.

Our findings of opposing associations of DA and NDA with breast cancer risk generally agree with most of the existing literature in this area, including a recent large meta-analysis that included several of the studies here (7). However, while the meta-analysis found that associations for NDA were attenuated in many studies upon adjustment for absolute DA (7), we did not observe attenuation in mutually adjusted models, possibly because correlations between DA and NDA were low (0.06–0.29) and similar across studies or because we adjusted for BMI, which is a surrogate for NDA. We conclude DA and absolute NDA are independent risk factors associated with breast cancer risk.

Few previous studies reported associations of absolute DA or NDA with breast cancer according to specific tumor characteristics. Consistent with our findings, in 601 cases and 667 controls from the Multiethnic Cohort, absolute DA was associated with both invasive breast cancer and DCIS (24); although in the present analysis, there was suggestion of a stronger association for invasive cancers vs. DCIS among women ≥55 years. Also in the Multiethnic Cohort, stronger associations of DA with ER+/PR+ vs. ER−/PR− tumors were observed (25). Like us, Eriksson et al. (26) reported stronger associations of absolute DA with ER+ vs. ER− tumors (p-value =0.065) and with PR+ vs. PR− (p-value = 0.099) in a case-only study of 110 breast cancer patients. Positive associations of absolute DA with ER + vs. ER− tumors and larger vs. smaller tumors were also observed in recent UK case-control study (27). Similar to our findings, a case-only study among postmenopausal women (n=286) reported a non-significant positive trend of DA with tumor size and a non-significant trend of NDA with tumor size as well as significant positive associations between DA and ER and PR positivity (28). Our study is among the first to comprehensively explore associations of absolute NDA with breast tumor characteristics and, to our knowledge, is the largest to date. Current hypotheses to explain associations between increased MD and breast cancer risk have been reviewed recently (29) and include the higher amount of fibroglandular tissue “at risk” of transformation into cancer (30) and the increased epithelial and fibroblast cellular activity and interaction between stroma and epithelium in dense tissue (31, 32) as well as hormonal mechanisms, including the influence of sex steroid hormones and growth factors on density and breast cancer risk (33). Evaluating associations by tumor characteristics can provide insight into these hypothesized mechanisms. If the mechanism of action were purely through hormonal influences, then we might expect to observe associations of DA with ER+ tumors only; however, we observed significant positive associations of DA with both ER+ and ER− tumors, although the magnitude of association was greater for ER+ tumors among women <55 years. Moreover, we observed strong inverse associations of NDA with ER− tumors in this age group, independent of DA. Our findings of independent associations of DA and NDA with breast cancer risk across tumor characteristics suggest that several causal pathways may play a role in associations with risk. Petterson and Tamimi (34) propose several mechanisms by which breast fat (nondense area) may lead to reduced risk of breast cancer, including the possible direct effect of adipose tissue on normal breast development, indirect effects of adipose tissue in regard to the endocrine environment of the breast, or via lobular involution, which is positively correlated

with NDA and inversely associated with breast cancer risk (35). On the other hand, some studies have suggested breast fat as a risk factor for breast cancer (6, 36).

As in our previously published analysis based on a subset of these data (23), we found that percent MD was more strongly associated with risk of ER-negative breast cancer than with ER-positive breast cancer among women < 55 years of age. Our current findings of the MD area phenotypes further suggest that the positive association observed between percent MD and ER-negative disease among women <55 years is driven by the inverse association of non-dense area with ER-negative disease in this group, rather than by a positive association with absolute dense breast area. Based on the results of our analyses and considering the current body of published literature on this topic, it appears that breast density (including percent and area measures) plays an important role in tumor aggressiveness, especially in younger women, giving differential associations observed with respect to tumor size, nodal status as well as ER-status. In light of the lack of significant age-interaction, however, we cannot discount an association of MD phenotypes with tumor aggressiveness among older women.

Limitations of the study have been described (3) and include variation in study design and populations, use of clinical pathology as opposed to central pathology review; changes in diagnostic criteria over time that may influence tumor characteristics and receptor status, in particular, and generalizability of results primarily to Caucasian women. Even with 4000 cases, power to detect age-interactions remained limited. Detection bias is also a potential limitation, given that extent of breast density may make earlier tumors more difficult to detect on screening mammogram (37). While we were not able to evaluate the influence of detection bias directly in this analysis due to the lack of high-quality data regarding interval vs. screen-detected cancers for most included studies, in the Breast Cancer Surveillance Consortium, Kerlikowske et al. reported that higher breast density in premenopausal women was more strongly related to aggressive tumors and that this finding persisted in analyses restricted to screen-detected cases only (38). We did find evidence of study heterogeneity for the analyses of DA with overall breast cancer and by invasive vs. *in situ* status, so these results should be cautiously interpreted. However, our associations of these absolute measures with overall breast cancer were consistent with the literature. Finally, this study relied on digitized film mammograms vs. more contemporary full field digital mammograms.

Strengths of this pooled analysis include the large sample size with mammograms available years prior to the cancer (for cases), standardized estimates of NDA and DA, detailed information on covariates and tumor characteristics from pathology reports, supplemented with information from TMAs, and screening mammograms assessed in a generally systematic fashion.

In summary, we found that percent MD and absolute dense breast area were associated with increased breast cancer risk while non-dense area was associated with decreased risk across all ages and invasive tumor characteristics. Among women <55 years, dense area was more strongly associated with an increased risk for ER+ vs. ER− tumors [p-heterogeneity (het) = 0.02] while non-dense area was more strongly associated with a decreased risk for ER− vs.

ER+ tumors [p-het = 0.03]. Dense area was similarly associated with increased risk (and non-dense area decreased risk) of both node-positive and node-negative tumors, while significant trends in the magnitude of these associations were observed with increasing tumor size.

Our results suggest DA is positively associated (and NDA, inversely associated) with breast cancer across tumor characteristics. Further, these results suggest differential associations for these phenotypes with ER+ vs. ER− tumors, particularly in younger women. As such, DA and NDA may be important to consider when developing age- and subtype-specific risk models for breast cancer. Further research is warranted to clarify the possible differential associations of DA and NDA on breast cancer risk according to tumor characteristics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

MD	Mammographic density
MMHS	Mayo Mammography Health Study
MCBCS	Mayo Clinic Breast Cancer Study
NHS and NHSII	Nurses' Health Study
MCMAM	Mayo Clinic Mammography Study

SFMR	San Francisco Bay Area Breast Cancer SPORE and San Francisco Mammography Registry
SEER	Surveillance Epidemiology and End Results
BMI	body mass index
OR	odds ratios
CI	confidence intervals

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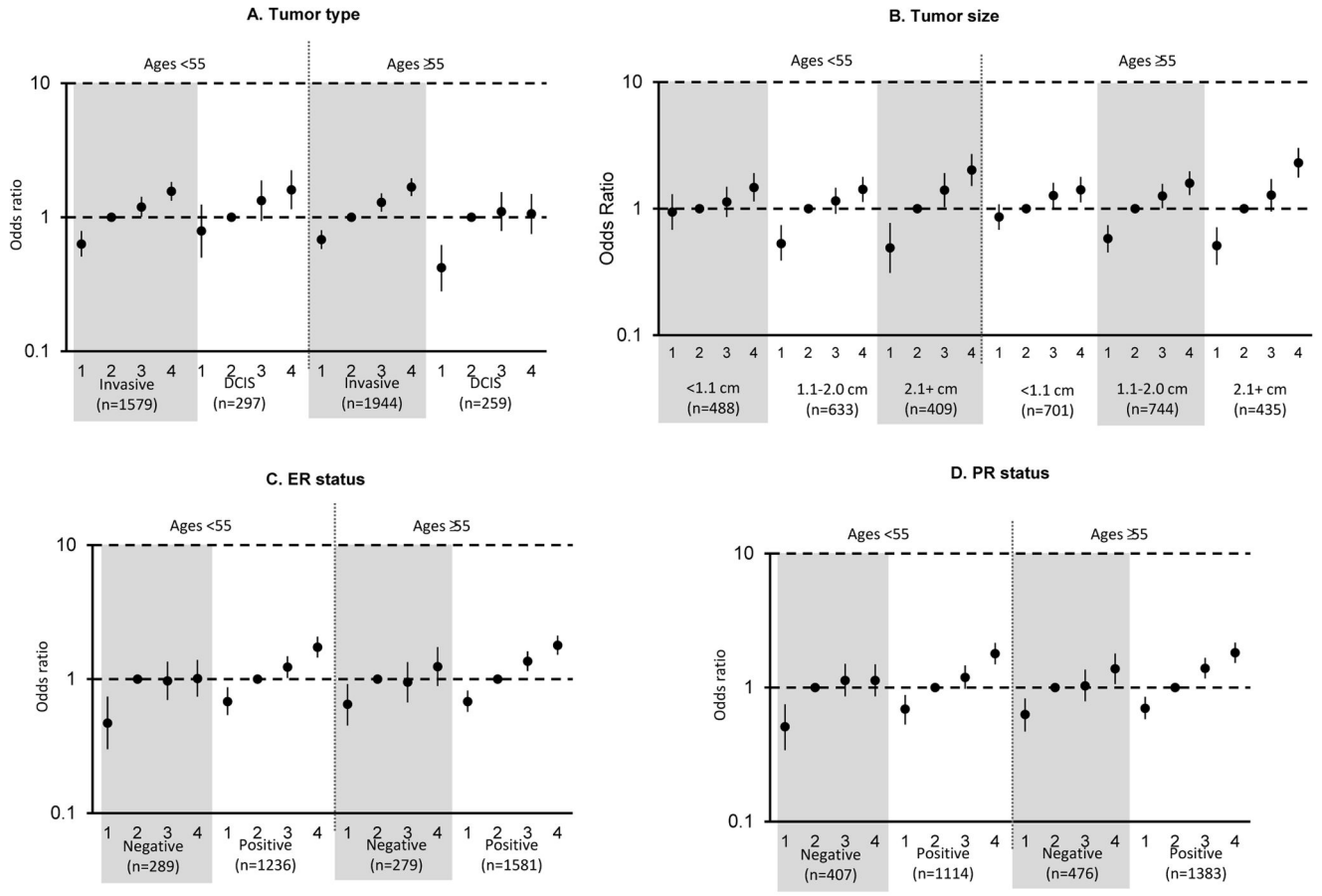

Figure 1. Associations of categorical dense area (DA) for breast cancer tumor type and selected tumor characteristics of invasive breast cancer, by age

dds ratios and 95% confidence intervals, adjusted for age, body mass index, and study, are shown for quartiles of DA. A) Tumor type, B) Tumor size, C) ER status, D) PR status.

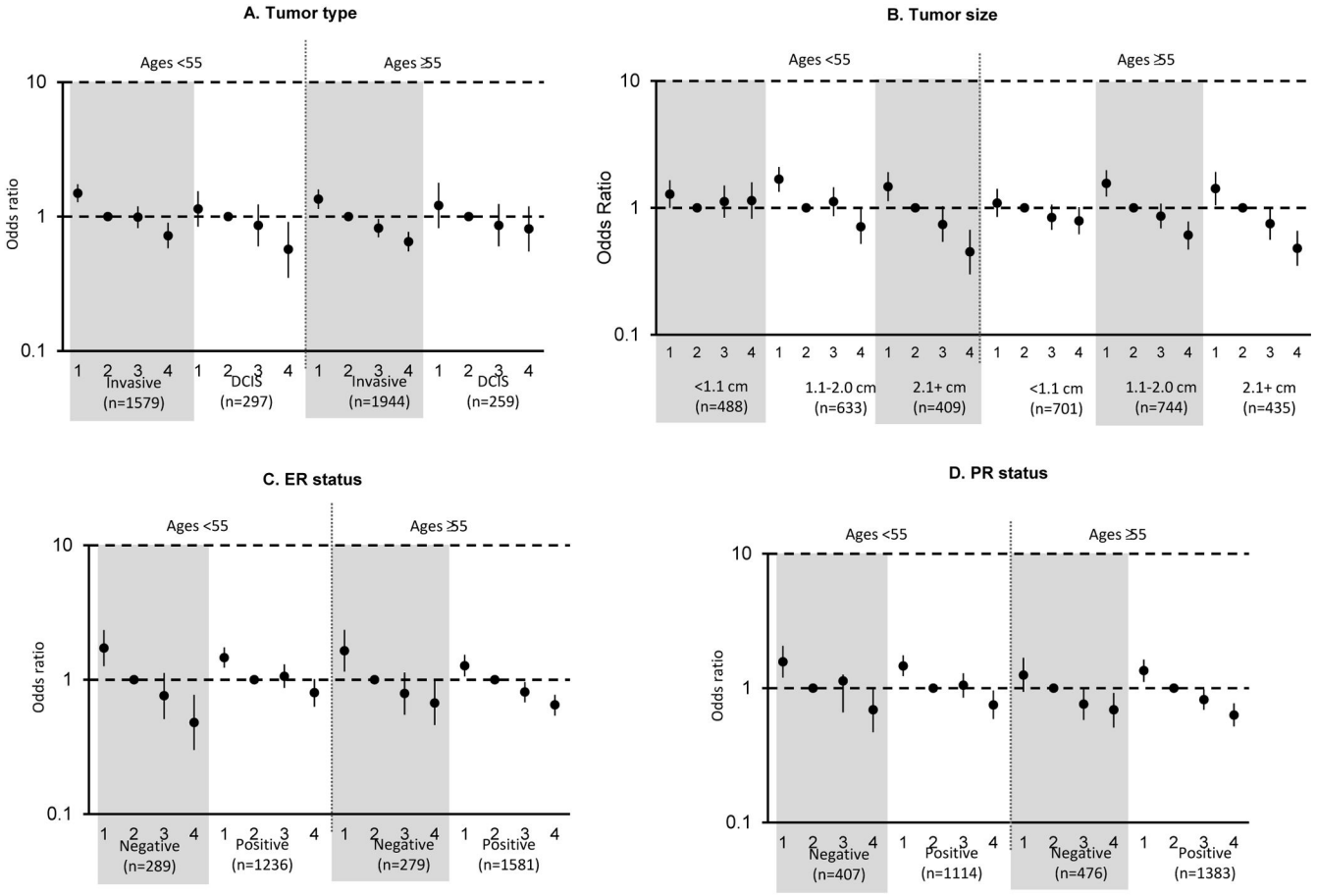

Figure 2. Associations of categorical non dense area (NDA) for breast cancer tumor type and selected tumor characteristics of invasive breast cancer, by age

Odds ratios and 95% confidence intervals, adjusted for age, body mass index, and study, are shown for quartiles of NDA. A) Tumor type, B) Tumor size, C) ER status, D) PR status.

Table 1

Baseline characteristics of study population by age.

	Age <55		Age ≥55	
	Cases	**Controls**	**Cases**	**Controls**
N	1884	4072	2211	4486
Standardized % mammographic density Median (IQR)	40.7 (30.2)	32 (30.8)	25 (26.1)	19 (23.2)
Standardized Dense Area cm^2 Median (IQR)	51.9 (44.4)	42.2 (41.8)	41.1 (43.0)	31.6 (37.3)
Standardized Nondense Area cm^2 Median (IQR)	79.6 (92.4)	98 (100.7)	130.7 (123.7)	138.6 (119.9)
Mean age at mammogram (SD)	47.2 (4.6)	47.3 (4.5)	64.9 (7.4)	65.1 (7.4)
Mean age at diagnosis (SD)	51.6 (5.5)	--	69 (7.6)	--
Mean BMI (SD)	24.2 (6.5)	25.2 (6)	25.6 (7.8)	25.9 (5.5)
Body mass index categories, kg/m^2				
<25	1072 (56.9%)	2352 (57.8%)	909 (41.1%)	2213 (49.3%)
25–29	507 (26.9%)	1007 (24.7%)	701 (31.7%)	1422 (31.7%)
30–34	157 (8.3%)	399 (9.8%)	319 (14.4%)	553 (12.3%)
35+	85 (4.5%)	275 (6.8%)	177 (8%)	275 (6.1%)
Unknown	63 (3.3%)	39 (1%)	105 (4.7%)	23 (0.5%)
Menopausal status				
Premenopausal	1159 (61.5%)	2629 (64.6%)	16 (0.7%)	44 (1%)
Postmenopausal	556 (29.5%)	1220 (30%)	2191 (99.1%)	4434 (98.8%)
Unknown	169 (9%)	223 (5.5%)	4 (0.2%)	8 (0.2%)
Parity				
Nulliparous	419 (22.2%)	901 (22.1%)	330 (14.9%)	624 (13.9%)
Parous	1315 (69.8%)	3046 (74.8%)	1675 (75.8%)	3526 (78.6%)
Unknown	150 (8%)	125 (3.1%)	206 (9.3%)	336 (7.5%)
Postmenopausal hormone therapy[a]				
Not current user	193 (41.1%)	498 (45.8%)	923 (51.6%)	2403 (61.9%)
Current, estrogen	90 (19.1%)	256 (23.5%)	272 (15.2%)	561 (14.5%)
Current, estrogen + progestin	155 (33%)	290 (26.7%)	373 (20.9%)	574 (14.8%)
Unknown	32 (6.8%)	44 (4%)	220 (12.3%)	343 (8.8%)
Family history				
No	1467 (77.9%)	3588 (88.1%)	1644 (74.4%)	3745 (83.5%)
Yes	315 (16.7%)	466 (11.4%)	463 (20.9%)	706 (15.7%)
Unknown	102 (5.4%)	18 (0.4%)	104 (4.7%)	35 (0.8%)

[a] Among postmenopausal women in MMHS, NHS, NHSII, and UCSF.

IQR: interquartile range

Table 2

Distribution (%) of breast cancer cases from six studies by age and tumor characteristics

	Age < 55		Age ≥55	
	N	%	N	%
Controls	4072	68.4	4486	67
Cases	1884	31.6	2211	33
Invasive	1579	83.8	1944	87.9
In situ	297	15.8	259	11.7
Unknown	8	0.4	8	0.4
Tumor characteristics				
Histology				
Ductal	1277	80.9	1437	73.9
Lobular	156	9.9	265	13.6
Mixed	88	5.6	133	6.8
Unknown/other	58	3.7	109	5.6
Histologic Grade				
Well differentiated	393	24.9	622	32
Moderately differentiated	605	38.3	739	38
Poorly differentiated	447	28.3	373	19.2
Unknown	134	8.5	210	10.8
Tumor size				
0.1–1.0 cm	488	30.9	701	36.1
1.1.–2.0 cm	633	40.1	744	38.3
2.1+ cm	409	25.9	435	22.4
Unknown	49	3.1	64	3.3
Involvement of lymph nodes				
Negative	1054	66.8	1323	68.1
Positive	445	28.2	422	21.7
Unknown	80	5.1	199	10.2
Estrogen Receptor status				
Negative	289	18.3	279	14.4
Positive	1236	78.3	1581	81.3
Borderline/Unknown	54	3.4	84	4.3
Progesterone Receptor status				
Negative	407	25.8	476	24.5
Positive	1114	70.6	1383	71.1
Borderline/Unknown	58	3.7	85	4.4
HER2 status				
Negative	1092	69.2	1268	65.2
Positive	231	14.6	223	11.5
Borderline/Unknown	256	16.2	453	23.3

Table 3

Associations of categories[a] of percent density, dense area, and non dense area with breast cancer overall and by morphological subtypes

	PERCENT DENSITY			DENSE AREA			NON DENSE AREA		
	No. cases	**No. controls**	**OR (95% CI)[b]**	**No. cases**	**No. controls**	**OR (95% CI)[b]**	**No. cases**	**No. controls**	**OR (95% CI)[b]**
Overall breast cancer									
Category 1	517	1784	0.63 (0.56, 0.72)	618	2139	0.65 (0.58, 0.74)	1280	2139	1.39 (1.25, 1.55)
Category 2 (REF)	1015	2597	1.00 (REF)	910	2140	1.00 (REF)	983	2140	1.00 (REF)
Category 3	1626	2890	1.62 (1.47, 1.79)	1134	2139	1.22 (1.10, 1.37)	943	2139	0.88 (0.78, 0.98)
Category 4	937	1287	2.34 (2.07, 2.65)	1433	2140	1.55 (1.40, 1.73)	889	2140	0.72 (0.63, 0.81)
Invasiveness									
In situ									
Category 1	51	1784	0.51 (0.37, 0.72)	73	2139	0.56 (0.42, 0.75)	184	2139	1.19 (0.94, 1.51)
Category 2 (REF)	140	2597	1.00 (REF)	135	2140	1.00 (REF)	143	2140	1.00 (REF)
Category 3	242	2890	1.58 (1.26, 1.98)	167	2139	1.18 (0.93, 1.50)	124	2139	0.85 (0.66, 1.10)
Category 4	123	1287	1.88 (1.42, 2.49)	181	2140	1.29 (1.02, 1.63)	105	2140	0.75 (0.56, 1.00)
Invasive									
Category 1	461	1784	0.64 (0.56, 0.73)	542	2139	0.67 (0.59, 0.76)	1089	2139	1.42 (1.27, 1.60)
Category 2 (REF)	875	2597	1.00 (REF)	770	2140	1.00 (REF)	836	2140	1.00 (REF)
Category 3	1377	2890	1.62 (1.45, 1.80)	961	2139	1.23 (1.10, 1.38)	818	2139	0.89 (0.79, 1.00)
Category 4	810	1287	2.40 (2.11, 2.74)	1250	2140	1.61 (1.44, 1.80)	780	2140	0.71 (0.62, 0.81)
p-het			0.18			0.25			0.40
Histology[c]									
Ductal									
Category 1	356	1784	0.67 (0.57, 0.77)	433	2139	0.72 (0.63, 0.83)	838	2139	1.38 (1.22, 1.56)
Category 2 (REF)	665	2597	1.00 (REF)	581	2140	1.00 (REF)	650	2140	1.00 (REF)
Category 3	1073	2890	1.62 (1.44, 1.82)	749	2139	1.27 (1.12, 1.44)	635	2139	0.90 (0.79, 1.03)
Category 4	620	1287	2.32 (2.01, 2.67)	951	2140	1.61 (1.42, 1.82)	591	2140	0.71 (0.61, 0.82)
Lobular									
Category 1	49	1784	0.51 (0.36, 0.72)	51	2139	0.49 (0.35, 0.70)	135	2139	1.59 (1.21, 2.10)
Category 2 (REF)	114	2597	1.00 (REF)	96	2140	1.00 (REF)	98	2140	1.00 (REF)
Category 3	148	2890	1.44 (1.11, 1.87)	107	2139	1.13 (0.85, 1.50)	95	2139	0.82 (0.61, 1.11)

	PERCENT DENSITY			DENSE AREA			NON DENSE AREA		
	No. cases	**No. controls**	**OR (95% CI)[b]**	**No. cases**	**No. controls**	**OR (95% CI)[b]**	**No. cases**	**No. controls**	**OR (95% CI)[b]**
Category 4	110	1287	3.00 (2.23, 4.04)	167	2140	1.83 (1.41, 2.37)	93	2140	0.65 (0.47, 0.89)
p-het			0.02			0.03			0.50
Histologic grade									
Well differentiated									
Category 1	139	1784	0.62 (0.50, 0.77)	157	2139	0.70 (0.56, 0.87)	284	2139	1.25 (1.03, 1.51)
Category 2 (REF)	274	2597	1.00 (REF)	215	2140	1.00 (REF)	247	2140	1.00 (REF)
Category 3	379	2890	1.44 (1.22, 1.71)	283	2139	1.35 (1.11, 1.63)	246	2139	0.91 (0.75, 1.10)
Category 4	223	1287	2.23 (1.81, 2.74)	360	2140	1.75 (1.45, 2.10)	238	2140	0.77 (0.62, 0.95)
Moderately differentiated									
Category 1	177	1784	0.65 (0.53, 0.79)	202	2139	0.69 (0.57, 0.84)	398	2139	1.37 (1.16, 1.62)
Category 2 (REF)	327	2597	1.00 (REF)	280	2140	1.00 (REF)	313	2140	1.00 (REF)
Category 3	523	2890	1.64 (1.40, 1.91)	353	2139	1.25 (1.05, 1.48)	329	2139	0.96 (0.81, 1.14)
Category 4	317	1287	2.53 (2.10, 3.04)	509	2140	1.81 (1.54, 2.13)	304	2140	0.74 (0.61, 0.90)
Poorly differentiated									
Category 1	99	1784	0.65 (0.50, 0.84)	120	2139	0.62 (0.48, 0.79)	279	2139	1.55 (1.27, 1.90)
Category 2 (REF)	184	2597	1.00 (REF)	188	2140	1.00 (REF)	195	2140	1.00 (REF)
Category 3	335	2890	1.79 (1.47, 2.17)	221	2139	1.12 (0.91, 1.38)	170	2139	0.80 (0.64, 0.99)
Category 4	202	1287	2.62 (2.08, 3.30)	291	2140	1.45 (1.19, 1.77)	176	2140	0.65 (0.51, 0.83)
p-het			0.68			0.77			0.76
Tumor size									
<1.1 cm									
Category 1	219	1784	0.90 (0.75, 1.09)	244	2139	0.90 (0.74, 1.08)	319	2139	1.19 (0.99, 1.42)
Category 2 (REF)	318	2597	1.00 (REF)	262	2140	1.00 (REF)	282	2140	1.00 (REF)
Category 3	429	2890	1.33 (1.13, 1.56)	314	2139	1.19 (1.00, 1.42)	280	2139	0.94 (0.78, 1.12)
Category 4	223	1287	1.70 (1.39, 2.07)	369	2140	1.42 (1.20, 1.69)	308	2140	0.93 (0.77, 1.14)
1.1 – 2.0 cm									
Category 1	149	1784	0.52 (0.43, 0.64)	188	2139	0.57 (0.47, 0.69)	463	2139	1.62 (1.37, 1.90)
Category 2 (REF)	349	2597	1.00 (REF)	320	2140	1.00 (REF)	311	2140	1.00 (REF)
Category 3	547	2890	1.60 (1.37, 1.86)	388	2139	1.20 (1.02, 1.41)	328	2139	0.96 (0.81, 1.14)
Category 4	332	1287	2.45 (2.05, 2.93)	481	2140	1.50 (1.29, 1.76)	275	2140	0.68 (0.56, 0.82)

	PERCENT DENSITY			DENSE AREA			NON DENSE AREA		
	No. cases	**No. controls**	**OR (95% CI)[b]**	**No. cases**	**No. controls**	**OR (95% CI)[b]**	**No. cases**	**No. controls**	**OR (95% CI)[b]**
2.1+ cm									
Category 1	74	1784	0.42 (0.32, 0.56)	91	2139	0.51 (0.39, 0.66)	273	2139	1.47 (1.21, 1.79)
Category 2 (REF)	189	2597	1.00 (REF)	165	2140	1.00 (REF)	214	2140	1.00 (REF)
Category 3	349	2890	2.02 (1.67, 2.45)	224	2139	1.32 (1.07, 1.64)	186	2139	0.74 (0.60, 0.92)
Category 4	232	1287	3.60 (2.88, 4.51)	364	2140	2.13 (1.75, 2.60)	171	2140	0.49 (0.39, 0.63)
p-het			<0.001			<0.001			<0.001
Involvement of lymph nodes									
Negative									
Category 1	314	1784	0.64 (0.55, 0.75)	370	2139	0.68 (0.59, 0.79)	722	2139	1.37 (1.20, 1.57)
Category 2 (REF)	609	2597	1.00 (REF)	520	2140	1.00 (REF)	565	2140	1.00 (REF)
Category 3	908	2890	1.50 (1.33, 1.69)	658	2139	1.24 (1.08, 1.41)	568	2139	0.93 (0.81, 1.07)
Category 4	546	1287	2.25 (1.95, 2.61)	829	2140	1.58 (1.39, 1.79)	522	2140	0.73 (0.63, 0.85)
Positive									
Category 1	89	1784	0.56 (0.43, 0.74)	117	2139	0.61 (0.48, 0.78)	300	2139	1.61 (1.32, 1.96)
Category 2 (REF)	189	2597	1.00 (REF)	186	2140	1.00 (REF)	202	2140	1.00 (REF)
Category 3	369	2890	1.96 (1.62, 2.37)	230	2139	1.18 (0.96, 1.45)	191	2139	0.86 (0.70, 1.07)
Category 4	220	1287	2.89 (2.31, 3.61)	334	2140	1.70 (1.40, 2.07)	174	2140	0.63 (0.49, 0.80)
p-het			0.01			0.39			0.11
ER status									
Negative									
Category 1	69	1784	0.7 (0.51, 0.95)	88	2139	0.57 (0.43, 0.75)	209	2139	1.66 (1.31, 2.10)
Category 2 (REF)	126	2597	1.00 (REF)	151	2140	1.00 (REF)	136	2140	1.00 (REF)
Category 3	236	2890	1.81 (1.43, 2.27)	153	2139	0.96 (0.76, 1.21)	113	2139	0.76 (0.59, 0.99)
Category 4	137	1287	2.49 (1.89, 3.26)	176	2140	1.11 (0.88, 1.40)	110	2140	0.61 (0.45, 0.81)
Positive									
Category 1	373	1784	0.63 (0.54, 0.72)	431	2139	0.69 (0.60, 0.79)	837	2139	1.38 (1.22, 1.56)
Category 2 (REF)	716	2597	1.00 (REF)	589	2140	1.00 (REF)	667	2140	1.00 (REF)
Category 3	1082	2890	1.57 (1.40, 1.76)	764	2139	1.28 (1.13, 1.45)	664	2139	0.90 (0.79, 1.03)
Category 4	646	1287	2.40 (2.09, 2.76)	1033	2140	1.74 (1.54, 1.97)	649	2140	0.73 (0.64, 0.85)
p-het			0.64			0.003			0.05

	PERCENT DENSITY			DENSE AREA			NON DENSE AREA		
	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]
PR status									
Negative									
Category 1	119	1784	0.67 (0.53, 0.86)	137	2139	0.59 (0.47, 0.73)	277	2139	1.41 (1.16, 1.72)
Category 2 (REF)	220	2597	1.00 (REF)	221	2140	1.00 (REF)	215	2140	1.00 (REF)
Category 3	349	2890	1.61 (1.34, 1.93)	245	2139	1.08 (0.89, 1.31)	191	2139	0.81 (0.66, 1.01)
Category 4	195	1287	2.23 (1.79, 2.78)	280	2140	1.24 (1.03, 1.50)	200	2140	0.72 (0.57, 0.90)
Positive									
Category 1	324	1784	0.63 (0.54, 0.73)	381	2139	0.70 (0.60, 0.82)	762	2139	1.42 (1.24, 1.61)
Category 2 (REF)	619	2597	1.00 (REF)	515	2140	1.00 (REF)	588	2140	1.00 (REF)
Category 3	971	2890	1.61 (1.43, 1.82)	670	2139	1.28 (1.12, 1.47)	590	2139	0.91 (0.79, 1.04)
Category 4	583	1287	2.47 (2.14, 2.86)	931	2140	1.79 (1.58, 2.04)	557	2140	0.71 (0.61, 0.83)
p-het			0.70			0.007			0.74
HER2 status									
Negative									
Category 1	325	1784	0.66 (0.57, 0.77)	355	2139	0.65 (0.56, 0.76)	686	2139	1.36 (1.19, 1.56)
Category 2 (REF)	591	2597	1.00 (REF)	517	2140	1.00 (REF)	543	2140	1.00 (REF)
Category 3	898	2890	1.56 (1.38, 1.76)	613	2139	1.17 (1.03, 1.34)	566	2139	0.96 (0.83, 1.10)
Category 4	546	1287	2.40 (2.07, 2.78)	875	2140	1.68 (1.48, 1.91)	565	2140	0.81 (0.70, 0.95)
Positive									
Category 1	52	1784	0.70 (0.49, 0.99)	63	2139	0.67 (0.48, 0.93)	154	2139	1.37 (1.06, 1.77)
Category 2 (REF)	92	2597	1.00 (REF)	92	2140	1.00 (REF)	121	2140	1.00 (REF)
Category 3	204	2890	2.16 (1.67, 2.80)	141	2139	1.46 (1.11, 1.92)	93	2139	0.72 (0.54, 0.95)
Category 4	106	1287	2.67 (1.96, 3.64)	158	2140	1.64 (1.25, 2.14)	86	2140	0.54 (0.39, 0.75)
p-het			0.07			0.21			0.04

[a] Categories are 1: 0–10%, 2: 11–25%, 3: 26–50%, and 4: 51%+ for PMD and quartiles for DA and NDA.

[b] adjusted for study site, age, BMI.

[c] mixed and other histology categories are excluded

p-het: test for heterogeneity in association by subtype

Table 4

Pooled associations of categories[a] of percent density, dense area, and non dense area for morphological subtypes of invasive breast cancer by age

	PERCENT DENSITY						DENSE AREA						NONDENSE AREA					
	Age < 55			Age ≥55			Age < 55			Age ≥55			Age < 55			Age ≥55		
	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]
Overall breast cancer																		
Category 1	109	530	0.60 (0.47, 0.77)	408	1254	0.61 (0.53, 0.71)	191	759	0.65 (0.53, 0.80)	427	1380	0.64 (0.55, 0.75)	822	1357	1.44 (1.24, 1.66)	458	782	1.33 (1.13, 1.56)
Category 2 (REF)	316	1016	1.00 (REF)	699	1581	1.00 (REF)	376	948	1.00 (REF)	534	1192	1.00 (REF)	456	1087	1.00 (REF)	527	1053	1.00 (REF)
Category 3	809	1604	1.68 (1.44, 1.97)	817	1286	1.60 (1.41, 1.83)	553	1135	1.22 (1.04, 1.43)	581	1004	1.26 (1.09, 1.46)	362	878	0.96 (0.81, 1.14)	581	1261	0.82 (0.71, 0.96)
Category 4	650	922	2.40 (2.02, 2.86)	287	365	2.16 (1.79, 2.61)	764	1230	1.56 (1.34, 1.81)	669	910	1.58 (1.37, 1.83)	244	750	0.70 (0.57, 0.86)	645	1390	0.67 (0.57, 0.79)
Invasiveness																		
In situ																		
Category 1	15	530	0.64 (0.35, 1.18)	36	1254	0.43 (0.29, 0.64)	33	759	0.79 (0.50, 1.24)	40	1380	0.42 (0.28, 0.62)	129	1357	1.14 (0.84, 1.54)	55	782	1.21 (0.82, 1.78)
Category 2 (REF)	44	1016	1.00 (REF)	96	1581	1.00 (REF)	56	948	1.00 (REF)	79	1192	1.00 (REF)	81	1087	1.00 (REF)	62	1053	1.00 (REF)
Category 3	138	1604	1.96 (1.37, 2.81)	104	1286	1.40 (1.04, 1.89)	91	1135	1.33 (0.94, 1.88)	76	1004	1.10 (0.79, 1.54)	58	878	0.86 (0.60, 1.23)	66	1261	0.86 (0.60, 1.24)
Category 4	100	922	2.38 (1.60, 3.54)	23	365	1.31 (0.80, 2.13)	117	1230	1.60 (1.15, 2.24)	64	910	1.06 (0.75, 1.49)	29	750	0.57 (0.35, 0.91)	76	1390	0.81 (0.55, 1.19)
Invasive																		
Category 1	92	530	0.58 (0.45, 0.76)	369	1254	0.63 (0.54, 0.74)	158	759	0.63 (0.51, 0.79)	384	1380	0.68 (0.58, 0.80)	688	1357	1.49 (1.28, 1.74)	401	782	1.35 (1.14, 1.59)
Category 2 (REF)	272	1016	1.00 (REF)	603	1581	1.00 (REF)	317	948	1.00 (REF)	453	1192	1.00 (REF)	374	1087	1.00 (REF)	462	1053	1.00 (REF)
Category 3	667	1604	1.62 (1.37, 1.92)	710	1286	1.63 (1.42, 1.87)	458	1135	1.19 (1.01, 1.42)	503	1004	1.29 (1.10, 1.51)	304	878	0.99 (0.82, 1.19)	514	1261	0.82 (0.70, 0.96)
Category 4	548	922	2.39 (1.99, 2.88)	262	365	2.27 (1.87, 2.76)	646	1230	1.56 (1.33, 1.83)	604	910	1.68 (1.44, 1.95)	213	750	0.72 (0.58, 0.90)	567	1390	0.65 (0.55, 0.77)
p-het			0.55			0.08			0.78			0.03			0.40			0.58
Histology[c]																		
Ductal																		
Category 1	82	530	0.65 (0.49, 0.86)	274	1254	0.65 (0.54, 0.77)	135	759	0.66 (0.52, 0.83)	298	1380	0.75 (0.63, 0.90)	546	1357	1.47 (1.24, 1.73)	292	782	1.29 (1.07, 1.55)
Category 2 (REF)	216	1016	1.00 (REF)	449	1581	1.00 (REF)	260	948	1.00 (REF)	321	1192	1.00 (REF)	302	1087	1.00 (REF)	348	1053	1.00 (REF)
Category 3	544	1604	1.67 (1.39, 2.00)	529	1286	1.61 (1.38, 1.88)	374	1135	1.19 (0.99, 1.42)	375	1004	1.35 (1.14, 1.61)	253	878	1.02 (0.84, 1.24)	382	1261	0.83 (0.69, 0.98)
Category 4	435	922	2.41 (1.97, 2.95)	185	365	2.12 (1.71, 2.63)	508	1230	1.50 (1.26, 1.78)	443	910	1.75 (1.47, 2.07)	176	750	0.74 (0.58, 0.93)	415	1390	0.65 (0.53, 0.78)
Lobular																		
Category 1	5	530	0.29 (0.11, 0.78)	44	1254	0.53 (0.36, 0.78)	12	759	0.59 (0.29, 1.18)	39	1380	0.45 (0.30, 0.68)	75	1357	1.55 (1.03, 2.33)	60	782	1.55 (1.06, 2.26)
Category 2 (REF)	27	1016	1.00 (REF)	87	1581	1.00 (REF)	26	948	1.00 (REF)	70	1192	1.00 (REF)	39	1087	1.00 (REF)	59	1053	1.00 (REF)
Category 3	57	1604	1.43 (0.89, 2.30)	91	1286	1.47 (1.08, 2.01)	42	1135	1.31 (0.80, 2.17)	65	1004	1.08 (0.76, 1.54)	22	878	0.65 (0.38, 1.12)	73	1261	0.90 (0.62, 1.29)
Category 4	67	922	3.14 (1.91, 5.17)	43	365	2.73 (1.83, 4.08)	76	1230	2.22 (1.41, 3.51)	91	910	1.68 (1.21, 2.32)	20	750	0.58 (0.32, 1.08)	73	1390	0.64 (0.43, 0.95)

	PERCENT DENSITY						DENSE AREA						NONDENSE AREA					
	Age < 55			Age ≥55			Age < 55			Age ≥55			Age < 55			Age ≥55		
	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]
p-het			0.07			0.27			0.18			0.08			0.31			0.79
Histologic grade																		
Well differentiated																		
Category 1	19	530	0.48 (0.29, 0.82)	120	1254	0.62 (0.49, 0.80)	39	759	0.72 (0.48, 1.07)	118	1380	0.67 (0.52, 0.87)	170	1357	1.31 (1.00, 1.71)	114	782	1.16 (0.89, 1.52)
Category 2 (REF)	72	1016	1.00 (REF)	202	1581	1.00 (REF)	72	948	1.00 (REF)	143	1192	1.00 (REF)	103	1087	1.00 (REF)	144	1053	1.00 (REF)
Category 3	159	1604	1.41 (1.05, 1.90)	220	1286	1.48 (1.20, 1.83)	111	1135	1.29 (0.95, 1.76)	172	1004	1.41 (1.11, 1.80)	75	878	0.91 (0.66, 1.25)	171	1261	0.90 (0.71, 1.15)
Category 4	143	922	2.31 (1.67, 3.18)	80	365	2.02 (1.51, 2.72)	171	1230	1.86 (1.39, 2.48)	189	910	1.70 (1.34, 2.16)	45	750	0.62 (0.41, 0.92)	193	1390	0.78 (0.60, 1.01)
Moderately differentiated																		
Category 1	44	530	0.77 (0.53, 1.13)	133	1254	0.59 (0.47, 0.75)	65	759	0.74 (0.54, 1.03)	137	1380	0.65 (0.51, 0.83)	254	1357	1.50 (1.19, 1.89)	144	782	1.26 (0.98, 1.61)
Category 2 (REF)	97	1016	1.00 (REF)	230	1581	1.00 (REF)	111	948	1.00 (REF)	169	1192	1.00 (REF)	137	1087	1.00 (REF)	176	1053	1.00 (REF)
Category 3	254	1604	1.74 (1.35, 2.25)	269	1286	1.61 (1.32, 1.97)	167	1135	1.25 (0.97, 1.62)	186	1004	1.27 (1.01, 1.60)	126	878	1.13 (0.87, 1.47)	203	1261	0.86 (0.68, 1.07)
Category 4	210	922	2.64 (2.00, 3.48)	107	365	2.43 (1.85, 3.18)	262	1230	1.81 (1.43, 2.30)	247	910	1.85 (1.49, 2.30)	88	750	0.82 (0.60, 1.12)	216	1390	0.65 (0.51, 0.83)
Poorly differentiated																		
Category 1	23	530	0.53 (0.32, 0.86)	76	1254	0.65 (0.48, 0.89)	39	759	0.52 (0.35, 0.77)	81	1380	0.67 (0.49, 0.91)	197	1357	1.47 (1.14, 1.90)	82	782	1.63 (1.18, 2.25)
Category 2 (REF)	71	1016	1.00 (REF)	113	1581	1.00 (REF)	95	948	1.00 (REF)	93	1192	1.00 (REF)	109	1087	1.00 (REF)	86	1053	1.00 (REF)
Category 3	202	1604	1.87 (1.40, 2.50)	133	1286	1.69 (1.29, 2.22)	142	1135	1.24 (0.94, 1.64)	79	1004	0.97 (0.71, 1.33)	76	878	0.85 (0.62, 1.16)	94	1261	0.77 (0.56, 1.05)
Category 4	151	922	2.53 (1.84, 3.49)	51	365	2.49 (1.73, 3.59)	171	1230	1.36 (1.04, 1.78)	120	910	1.59 (1.19, 2.12)	65	750	0.73 (0.51, 1.05)	111	1390	0.56 (0.40, 0.79)
p-het			0.48			0.91			0.36			0.40			0.70			0.15
Tumor size																		
<1.1 cm																		
Category 1	46	530	0.94 (0.65, 1.37)	173	1254	0.85 (0.68, 1.06)	70	759	0.94 (0.68, 1.30)	174	1380	0.86 (0.68, 1.08)	195	1357	1.28 (1.00, 1.65)	124	782	1.09 (0.85, 1.41)
Category 2 (REF)	96	1016	1.00 (REF)	222	1581	1.00 (REF)	98	948	1.00 (REF)	164	1192	1.00 (REF)	114	1087	1.00 (REF)	168	1053	1.00 (REF)
Category 3	196	1604	1.25 (0.96, 1.63)	233	1286	1.40 (1.14, 1.72)	134	1135	1.13 (0.86, 1.49)	180	1004	1.27 (1.01, 1.60)	97	878	1.12 (0.84, 1.50)	183	1261	0.84 (0.67, 1.06)
Category 4	150	922	1.63 (1.21, 2.17)	73	365	1.62 (1.20, 2.18)	186	1230	1.47 (1.14, 1.91)	183	910	1.41 (1.12, 1.78)	82	750	1.14 (0.82, 1.59)	226	1390	0.79 (0.62, 1.01)
1.1 – 2.0 cm																		
Category 1	32	530	0.50 (0.33, 0.76)	117	1254	0.51 (0.40, 0.65)	57	759	0.53 (0.39, 0.74)	131	1380	0.58 (0.45, 0.74)	288	1357	1.68 (1.34, 2.10)	175	782	1.56 (1.23, 1.98)
Category 2 (REF)	110	1016	1.00 (REF)	239	1581	1.00 (REF)	136	948	1.00 (REF)	184	1192	1.00 (REF)	139	1087	1.00 (REF)	172	1053	1.00 (REF)
Category 3	271	1604	1.63 (1.28, 2.07)	276	1286	1.59 (1.31, 1.93)	189	1135	1.15 (0.91, 1.46)	199	1004	1.26 (1.01, 1.57)	128	878	1.12 (0.86, 1.45)	200	1261	0.86 (0.69, 1.08)
Category 4	220	922	2.39 (1.83, 3.11)	112	365	2.43 (1.87, 3.17)	251	1230	1.42 (1.13, 1.78)	230	910	1.59 (1.28, 1.97)	78	750	0.71 (0.52, 0.99)	197	1390	0.61 (0.47, 0.78)
2.1+ cm																		
Category 1	12	530	0.28 (0.15, 0.54)	62	1254	0.44 (0.32, 0.61)	28	759	0.49 (0.31, 0.77)	63	1380	0.51 (0.36, 0.71)	183	1357	1.47 (1.13, 1.91)	90	782	1.42 (1.05, 1.92)
Category 2 (REF)	60	1016	1.00 (REF)	129	1581	1.00 (REF)	71	948	1.00 (REF)	94	1192	1.00 (REF)	107	1087	1.00 (REF)	107	1053	1.00 (REF)

	PERCENT DENSITY						DENSE AREA						NONDENSE AREA					
	Age < 55			Age ≥55			Age < 55			Age ≥55			Age < 55			Age ≥55		
	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]
Category 3	176	1604	2.10 (1.53, 2.88)	173	1286	2.00 (1.56, 2.56)	120	1135	1.40 (1.03, 1.91)	104	1004	1.28 (0.95, 1.71)	70	878	0.74 (0.54, 1.03)	116	1261	0.75 (0.56, 1.00)
Category 4	161	922	3.77 (2.69, 5.28)	71	365	3.24 (2.33, 4.51)	190	1230	2.02 (1.51, 2.70)	174	910	2.30 (1.76, 3.01)	49	750	0.45 (0.30, 0.67)	122	1390	0.48 (0.35, 0.66)
p-het			<0.001			<0.001			0.002			<0.001			0.001			0.006
Involvement of lymph nodes																		
Negative																		
Category 1	64	530	0.57 (0.42, 0.77)	250	1254	0.65 (0.54, 0.78)	110	759	0.66 (0.52, 0.86)	260	1380	0.68 (0.56, 0.82)	458	1357	1.53 (1.28, 1.83)	264	782	1.24 (1.02, 1.50)
Category 2 (REF)	198	1016	1.00 (REF)	411	1581	1.00 (REF)	211	948	1.00 (REF)	309	1192	1.00 (REF)	240	1087	1.00 (REF)	325	1053	1.00 (REF)
Category 3	427	1604	1.41 (1.17, 1.71)	481	1286	1.58 (1.35, 1.85)	309	1135	1.21 (0.99, 1.47)	349	1004	1.29 (1.08, 1.54)	210	878	1.08 (0.87, 1.33)	358	1261	0.84 (0.70, 1.00)
Category 4	365	922	2.16 (1.75, 2.66)	181	365	2.23 (1.79, 2.78)	424	1230	1.54 (1.28, 1.86)	405	910	1.64 (1.38, 1.95)	146	750	0.81 (0.63, 1.04)	376	1390	0.64 (0.53, 0.78)
Positive																		
Category 1	23	530	0.62 (0.37, 1.02)	66	1254	0.51 (0.38, 0.70)	38	759	0.53 (0.35, 0.78)	79	1380	0.66 (0.48, 0.91)	195	1357	1.47 (1.13, 1.90)	105	782	1.81 (1.34, 2.45)
Category 2 (REF)	59	1016	1.00 (REF)	130	1581	1.00 (REF)	91	948	1.00 (REF)	95	1192	1.00 (REF)	109	1087	1.00 (REF)	93	1053	1.00 (REF)
Category 3	205	1604	2.36 (1.73, 3.22)	164	1286	1.75 (1.36, 2.24)	123	1135	1.11 (0.83, 1.48)	107	1004	1.28 (0.96, 1.72)	84	878	0.91 (0.67, 1.24)	107	1261	0.85 (0.63, 1.14)
Category 4	158	922	3.40 (2.43, 4.76)	62	365	2.48 (1.77, 3.48)	193	1230	1.60 (1.22, 2.09)	141	910	1.83 (1.39, 2.42)	57	750	0.60 (0.41, 0.87)	117	1390	0.61 (0.44, 0.84)
p-het			0.02			0.28			0.56			0.78			0.54			0.06
ER status																		
Negative																		
Category 1	14	530	0.53 (0.29, 1.00)	55	1254	0.73 (0.51, 1.04)	28	759	0.47 (0.30, 0.74)	60	1380	0.65 (0.45, 0.92)	139	1357	1.72 (1.26, 2.34)	70	782	1.64 (1.15, 2.35)
Category 2 (REF)	42	1016	1.00 (REF)	84	1581	1.00 (REF)	74	948	1.00 (REF)	77	1192	1.00 (REF)	70	1087	1.00 (REF)	66	1053	1.00 (REF)
Category 3	130	1604	2.14 (1.48, 3.09)	106	1286	1.63 (1.21, 2.21)	88	1135	0.97 (0.70, 1.35)	65	1004	0.95 (0.67, 1.34)	47	878	0.76 (0.51, 1.12)	66	1261	0.79 (0.55, 1.13)
Category 4	103	922	3.16 (2.13, 4.70)	34	365	1.86 (1.21, 2.86)	99	1230	1.01 (0.74, 1.39)	77	910	1.24 (0.89, 1.73)	33	750	0.48 (0.30, 0.77)	77	1390	0.67 (0.46, 0.99)
Positive																		
Category 1	76	530	0.60 (0.45, 0.80)	297	1254	0.61 (0.51, 0.72)	125	759	0.68 (0.54, 0.87)	306	1380	0.68 (0.57, 0.82)	527	1357	1.46 (1.23, 1.74)	310	782	1.27 (1.06, 1.53)
Category 2 (REF)	221	1016	1.00 (REF)	495	1581	1.00 (REF)	234	948	1.00 (REF)	355	1192	1.00 (REF)	287	1087	1.00 (REF)	380	1053	1.00 (REF)
Category 3	509	1604	1.51 (1.26, 1.82)	573	1286	1.62 (1.40, 1.88)	348	1135	1.23 (1.02, 1.48)	416	1004	1.36 (1.15, 1.61)	247	878	1.06 (0.87, 1.30)	417	1261	0.81 (0.68, 0.96)
Category 4	430	922	2.30 (1.88, 2.81)	216	365	2.32 (1.89, 2.86)	529	1230	1.73 (1.45, 2.07)	504	910	1.79 (1.52, 2.11)	175	750	0.80 (0.63, 1.01)	474	1390	0.65 (0.54, 0.77)
p-het			0.22			0.47			0.02			0.09			0.02			0.48
PR status																		
Negative																		
Category 1	23	530	0.55 (0.33, 0.89)	96	1254	0.69 (0.53, 0.92)	39	759	0.51 (0.34, 0.75)	98	1380	0.63 (0.47, 0.83)	181	1357	1.57 (1.20, 2.06)	96	782	1.25 (0.94, 1.68)
Category 2 (REF)	72	1016	1.00 (REF)	148	1581	1.00 (REF)	96	948	1.00 (REF)	125	1192	1.00 (REF)	96	1087	1.00 (REF)	119	1053	1.00 (REF)
Category 3	180	1604	1.70 (1.27, 2.28)	169	1286	1.54 (1.21, 1.96)	131	1135	1.13 (0.86, 1.50)	114	1004	1.03 (0.79, 1.36)	74	878	0.91 (0.66, 1.26)	117	1261	0.76 (0.58, 1.00)

	PERCENT DENSITY						DENSE AREA						NONDENSE AREA					
	Age < 55			Age ≥55			Age < 55			Age ≥55			Age < 55			Age ≥55		
	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]	No. cases	No. controls	OR (95% CI)[b]
Category 4	132	922	2.29 (1.66, 3.17)	63	365	2.13 (1.53, 2.96)	141	1230	1.13 (0.86, 1.49)	139	910	1.38 (1.06, 1.79)	56	750	0.69 (0.47, 1.01)	144	1390	0.69 (0.51, 0.92)
Positive																		
Category 1	67	530	0.61 (0.45, 0.83)	257	1254	0.61 (0.51, 0.73)	112	759	0.69 (0.53, 0.88)	269	1380	0.70 (0.58, 0.85)	479	1357	1.46 (1.23, 1.75)	283	782	1.35 (1.11, 1.63)
Category 2 (REF)	188	1016	1.00 (REF)	431	1581	1.00 (REF)	209	948	1.00 (REF)	306	1192	1.00 (REF)	261	1087	1.00 (REF)	327	1053	1.00 (REF)
Category 3	462	1604	1.61 (1.33, 1.96)	509	1286	1.64 (1.41, 1.92)	303	1135	1.19 (0.98, 1.46)	367	1004	1.39 (1.17, 1.66)	222	878	1.05 (0.85, 1.29)	368	1261	0.82 (0.69, 0.98)
Category 4	397	922	2.49 (2.02, 3.08)	186	365	2.28 (1.83, 2.83)	490	1230	1.79 (1.49, 2.15)	441	910	1.82 (1.53, 2.16)	152	750	0.75 (0.59, 0.96)	405	1390	0.63 (0.52, 0.77)
p-het			0.73			0.64			0.007			0.15			0.68			0.73
HER2 status																		
Negative																		
Category 1	69	530	0.63 (0.46, 0.85)	256	1254	0.64 (0.53, 0.77)	106	759	0.61 (0.47, 0.79)	249	1380	0.66 (0.55, 0.80)	451	1357	1.39 (1.17, 1.67)	235	782	1.27 (1.03, 1.55)
Category 2 (REF)	186	1016	1.00 (REF)	405	1581	1.00 (REF)	221	948	1.00 (REF)	296	1192	1.00 (REF)	262	1087	1.00 (REF)	281	1053	1.00 (REF)
Category 3	455	1604	1.64 (1.35, 1.99)	443	1286	1.53 (1.30, 1.80)	294	1135	1.10 (0.91, 1.34)	319	1004	1.26 (1.05, 1.51)	219	878	1.03 (0.84, 1.26)	347	1261	0.91 (0.75, 1.09)
Category 4	382	922	2.52 (2.04, 3.13)	164	365	2.12 (1.69, 2.65)	471	1230	1.63 (1.35, 1.95)	404	910	1.75 (1.47, 2.09)	160	750	0.79 (0.62, 1.01)	405	1390	0.77 (0.63, 0.93)
Positive																		
Category 1	10	530	0.54 (0.26, 1.12)	42	1254	0.71 (0.47, 1.07)	20	759	0.68 (0.39, 1.19)	43	1380	0.63 (0.42, 0.96)	106	1357	1.48 (1.06, 2.08)	48	782	1.24 (0.83, 1.84)
Category 2 (REF)	31	1016	1.00 (REF)	61	1581	1.00 (REF)	38	948	1.00 (REF)	54	1192	1.00 (REF)	59	1087	1.00 (REF)	62	1053	1.00 (REF)
Category 3	115	1604	2.43 (1.60, 3.67)	89	1286	2.00 (1.42, 2.82)	82	1135	1.79 (1.21, 2.66)	59	1004	1.24 (0.84, 1.81)	40	878	0.83 (0.54, 1.26)	53	1261	0.64 (0.44, 0.94)
Category 4	75	922	2.82 (1.78, 4.45)	31	365	2.51 (1.58, 3.99)	91	1230	1.82 (1.23, 2.69)	67	910	1.55 (1.07, 2.24)	26	750	0.54 (0.32, 0.91)	60	1390	0.50 (0.33, 0.75)
p-het			0.11			0.54			0.07			0.92			0.38			0.16

[a] Categories are 1: 0–10%, 2: 11–25%, 3: 26–50%, and 4: 51%+ for PMD and quartiles for DA and NDA.

[b] adjusted for study site, age, BMI.

[c] mixed and other histology categories are excluded

p-het: test for heterogeneity in association by subtype