

Dense and Nondense Mammographic Area and Risk of Breast Cancer by Age and Tumor Characteristics

Kimberly A. Bertrand^{1,2}, Christopher G. Scott³, Rulla M. Tamimi^{1,2}, Matthew R. Jensen³, V. Shane Pankratz³, Aaron D. Norman⁴, Daniel W. Visscher⁵, Fergus J. Couch^{4,6}, John Shepherd⁷, Yunn-Yi Chen⁸, Bo Fan⁷, Fang-Fang Wu³, Lin Ma⁹, Andrew H. Beck¹⁰, Steven R. Cummings¹¹, Karla Kerlikowske¹², and Celine M. Vachon⁴

Abstract

Background: Mammographic density (MD) is a strong breast cancer risk factor. We previously reported associations of percent mammographic density (PMD) with larger and node-positive tumors across all ages, and estrogen receptor (ER)-negative status among women ages <55 years. To provide insight into these associations, we examined the components of PMD [dense area (DA) and nondense area (NDA)] with breast cancer subtypes.

Methods: Data were pooled from six studies including 4,095 breast cancers and 8,558 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 histopathologic characteristics and receptor status were calculated using polytomous logistic regression.

Results: DA was associated with increased breast cancer risk [OR for quartiles: 0.65, 1.00 (Ref), 1.22, 1.55; $P_{\text{trend}} < 0.001$]

and NDA was associated with decreased risk [ORs for quartiles: 1.39, 1.00 (Ref), 0.88, 0.72; $P_{\text{trend}} < 0.001$] 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 ($P_{\text{trend}} < 0.001$) but no differences by nodal status. Among women <55 years, DA was more strongly associated with increased risk of ER⁺ versus ER⁻ tumors ($P_{\text{het}} = 0.02$), while NDA was more strongly associated with decreased risk of ER⁻ versus ER⁺ tumors ($P_{\text{het}} = 0.03$).

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

Impact: DA and NDA are important to consider when developing age- and subtype-specific risk models. *Cancer Epidemiol Biomarkers Prev*; 24(5); 798–809. ©2015 AACR.

¹Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. ²Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. ³Department of Health Sciences Research, Division of Biomedical Statistics and Informatics, Mayo Clinic College of Medicine, Rochester, Minnesota. ⁴Department of Health Sciences Research, Division of Epidemiology, Mayo Clinic College of Medicine, Rochester, Minnesota. ⁵Department of Anatomic Pathology, Mayo Clinic College of Medicine, Rochester, Minnesota. ⁶Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, Minnesota. ⁷Department of Radiology, University of California, San Francisco, California. ⁸Department of Pathology, University of California, San Francisco, California. ⁹Department of Medicine, University of California, San Francisco, California. ¹⁰Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts. ¹¹San Francisco Coordinating Center, California Pacific Medical Center Research Institute, San Francisco, California. ¹²Departments of Epidemiology and Biostatistics and General Internal Medicine Section, Department of Veterans Affairs, University of California, San Francisco, California.

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Current address for V.S. Pankratz: Department of Internal Medicine, University of New Mexico Health Sciences Center, Albuquerque, New Mexico.

Corresponding Author: Celine M. Vachon, Mayo Clinic, 200 First Street SW, Charlton 6-239, Rochester, MN 55905. Phone: 507-284-9977; Fax: 507-284-1516; E-mail: vachon.celine@mayo.edu

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Introduction

Mammographic density (MD) represents the variability of breast tissue composition on the mammogram image. Radio-graphically, there are two main components of breast tissue: fat, which appears dark on a mammogram and is considered "nondense," 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 mammographic density (PMD; 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 with women in the lowest quartile, even after adjusting for other known breast cancer risk factors (2). The biologic mechanism by which MD increases breast cancer risk, however, remains largely unknown.

We reported PMD 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 nondense area may be independently associated with breast cancer risk (4–7). Few previous studies have evaluated the possible differential associations of dense and nondense breast area by breast cancer subtype or tumor characteristics. Therefore, we investigated the underlying associations of dense (fibroglandular) or nondense (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; refs. 8, 9), Mayo Clinic Breast Cancer Study (MCBCS; refs. 10, 11), Nurses' Health Study (NHS), and NHSII (12–14), Mayo Clinic Mammography Study (MCMAM; ref. 15), and the San Francisco Bay Area Breast Cancer SPORE and San Francisco Mammography Registry (SFMR; refs. 16–18; Table 1). Details of the study populations are in Supplementary Table S1 and described in our earlier report (3); the current 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) before (NHS, NHSII) or at the time of (MCBCS, MMHS, MCMAM, SFMR) mammography. In total, these analyses included 4,095 breast cancer cases and 8,558 controls.

This study was approved by the Institutional Review Boards at Mayo Clinic (Rochester, MN), Brigham and Women's Hospital (Boston, MA), the University of California, San Francisco (UCSF, San Francisco, CA), 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 nondense area (NDA), were measured using two computer-assisted threshold techniques [Cumulus (19) and UCSF custom mammographic density software (20)] from digitized images of prediagnostic film screening mammograms of the craniocaudal view. PMD 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 Fig. S1). We have previously described and applied this method to PMD using a logit transformation (3). For absolute dense and nondense areas, an appropriate transformation was selected via the Box–Cox procedure. For DA, the square root transformation

Table 1. Baseline characteristics of study population by age

	Age < 55		Age ≥ 55	
	Cases	Controls	Cases	Controls
N	1,884	4,072	2,211	4,486
Standardized % PMD, 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	1,072 (56.9%)	2,352 (57.8%)	909 (41.1%)	2,213 (49.3%)
25–29	507 (26.9%)	1,007 (24.7%)	701 (31.7%)	1,422 (31.7%)
30–34	157 (8.3%)	399 (9.8%)	319 (14.4%)	553 (12.3%)
35+	85 (4.5%)	275 (6.8%)	177 (8.0%)	275 (6.1%)
Unknown	63 (3.3%)	39 (1.0%)	105 (4.7%)	23 (0.5%)
Menopausal status				
Premenopausal	1,159 (61.5%)	2,629 (64.6%)	16 (0.7%)	44 (1.0%)
Postmenopausal	556 (29.5%)	1,220 (30.0%)	2,191 (99.1%)	4,434 (98.8%)
Unknown	169 (9.0%)	223 (5.5%)	4 (0.2%)	8 (0.2%)
Parity				
Nulliparous	419 (22.2%)	901 (22.1%)	330 (14.9%)	624 (13.9%)
Parous	1,315 (69.8%)	3,046 (74.8%)	1,675 (75.8%)	3,526 (78.6%)
Unknown	150 (8.0%)	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%)	2,403 (61.9%)
Current, estrogen	90 (19.1%)	256 (23.5%)	272 (15.2%)	561 (14.5%)
Current, estrogen + progestin	155 (33.0%)	290 (26.7%)	373 (20.9%)	574 (14.8%)
Unknown	32 (6.8%)	44 (4.0%)	220 (12.3%)	343 (8.8%)
Family history				
No	1,467 (77.9%)	3,588 (88.1%)	1,644 (74.4%)	3,745 (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%)

^aAmong postmenopausal women in MMHS, NHS, NHSII, and UCSF.

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was selected while the 4th root was selected for nondense 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 mammographic density (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 interquartile range (IQR), and then multiplying these rescaled 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 Fig. 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 Fig. S2).

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 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 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 PMD (3) with this larger sample size for comparison purposes; PMD 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 evalu-

ating 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 PMD and tumor characteristics primarily for younger women, we stratified by ages <55 years versus ≥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 (P_{het}). For subtypes with a natural ordering, including tumor size and grade, tests of trend (P_{trend}) across categories were used to assess significance. Formal tests of interaction ($P_{\text{age-interaction}}$) assessed the significance of differential DA and NDA associations with each of the breast cancer characteristics and subtype by age groups.

Before 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 ($P > 0.09$) other than as noted in results below.

Analyses were performed using SAS software (version 9.3, SAS Institute). 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 (IQR: 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 PMD and DA was lower while NDA was higher in women ages ≥55 years than women <55 years. Furthermore, within each age group, median PMD and DA was higher among cases versus controls. Median NDA was lower among cases versus controls in both age groups (Table 1). DCIS was more common among women ages <55 years (15.8%) versus women ≥55 years (11.7%), while, among invasive cancers, more aggressive tumor characteristics were evident in women <55 years at mammography compared with women ≥55 years (Table 2).

In general, results of our updated analyses for PMD 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 PMD 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

Table 2. Distribution (%) of breast cancer cases from six studies by age and tumor characteristics

	Age < 55 N (%)	Age ≥ 55 N (%)
Controls	4,072 (68.4)	4,486 (67.0)
Cases	1,884 (31.6)	2,211 (33.0)
Invasive	1,579 (83.8)	1,944 (87.9)
<i>In situ</i>	297 (15.8)	259 (11.7)
Unknown	8 (0.4)	8 (0.4)
Tumor characteristics		
Histology		
Ductal	1,277 (80.9)	1,437 (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 (32.0)
Moderately differentiated	605 (38.3)	739 (38.0)
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	1,054 (66.8)	1,323 (68.1)
Positive	445 (28.2)	422 (21.7)
Unknown	80 (5.1)	199 (10.2)
ER status		
Negative	289 (18.3)	279 (14.4)
Positive	1,236 (78.3)	1,581 (81.3)
Borderline/unknown	54 (3.4)	84 (4.3)
PR status		
Negative	407 (25.8)	476 (24.5)
Positive	1,114 (70.6)	1,383 (71.1)
Borderline/unknown	58 (3.7)	85 (4.4)
HER2 status		
Negative	1,092 (69.2)	1,268 (65.2)
Positive	231 (14.6)	223 (11.5)
Borderline/unknown	256 (16.2)	453 (23.3)

size, positive nodal status, and lobular (vs. ductal) cancer; $P_{\text{het}} < 0.02$) across age groups (Table 3). Among women <55 years, there were stronger associations with node-positive versus node-negative tumors (Table 4). Of note, the associations of PMD with ER-negative versus ER-positive tumors are not statistically significantly different across the two age groups examined here, <55 vs. 55+ ($P_{\text{age-interaction}} = 0.12$). However, when we analyzed by the original three age groups, the age-interaction remains ($P_{\text{age-interaction}} = 0.048$) 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 versus Q2, 0.65; Q3 versus Q2, 1.22; Q4 versus Q2, 1.55 ($P_{\text{trend}} < 0.001$) and the ORs for overall breast cancer associated with NDA were: Q1 versus Q2, 1.39; Q3 versus Q2, 0.88; Q4 versus Q2, 0.72 ($P_{\text{trend}} < 0.001$). For DA, associations were similar by age; for NDA, however, the interaction with age was statistically significant ($P_{\text{age-interaction}} < 0.01$) 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 with 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; Fig. 1). Among women ≥55 years, this association was stronger for invasive tumors than DCIS ($P_{\text{het}} = 0.03$; Table 4; Fig. 1); however, there was no evidence of a significant interaction between age and DA for associations with tumor type ($P_{\text{age-interaction}} = 0.41$). Again, even though a statistically significant association was seen by age ($P_{\text{age-interaction}} = 0.02$), NDA was significantly inversely associated with risk of both invasive breast cancer and DCIS among both younger and older women (Tables 3 and 4; Fig. 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 with smaller tumors across all ages ($P_{\text{trend}} < 0.01$; Fig. 1). For example, the overall ORs comparing women in Q4 of DA versus 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; Fig. 1; $P_{\text{age-interaction}} = 0.91$). The opposite trend was observed for associations of NDA with tumor size, with a stronger inverse association noted for larger tumors compared with smaller tumors across age groups ($P_{\text{trend}} < 0.01$), 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; Fig. 2). This trend was also similar across age ($P_{\text{age-interaction}} = 0.30$).

ER, PR, and HER2 receptor status

Among women of all ages, stronger associations of DA were noted for ER⁺ and PR⁺ tumors compared with hormone receptor negative tumors ($P_{\text{het}} < 0.01$). Although there was no significant evidence of differences by age ($P_{\text{age-interaction}} > 0.38$), among women <55 years, stronger associations were observed for ER⁺ (OR for Q4 versus Q2, 1.73; 95% CI, 1.45–2.07) vs. ER⁻ (corresponding OR, 1.01; 95% CI, 0.74–1.39; $P_{\text{het}} = 0.02$; Table 4; Fig. 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; $P_{\text{het}} = 0.01$; Table 4; Fig. 1). Similarly, although not significantly different by age group ($P_{\text{age-interaction}} = 0.08$), 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; $P_{\text{het}} = 0.03$; Table 4; Fig. 2). In contrast, among women ages ≥55, DA and NDA were similarly associated with tumors defined by ER or PR status ($P_{\text{het}} > 0.08$; Table 4; Fig. 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 $P > 0.09$). Between-study heterogeneity was noted, however, for associations of DA with overall breast cancer ($P = 0.02$) and

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Table 3. Associations of categories^a of percent density, DA, and NDA with breast cancer overall and by morphologic subtypes

	Percent density			DA			NDA		
	Cases, <i>n</i>	Controls, <i>n</i>	OR (95% CI) ^b	Cases, <i>n</i>	Controls, <i>n</i>	OR (95% CI) ^b	Cases, <i>n</i>	Controls, <i>n</i>	OR (95% CI) ^b
Overall breast cancer									
Category 1	517	1,784	0.63 (0.56–0.72)	618	2,139	0.65 (0.58–0.74)	1280	2,139	1.39 (1.25–1.55)
Category 2 (ref)	1,015	2,597	1.00 (ref)	910	2,140	1.00 (ref)	983	2,140	1.00 (ref)
Category 3	1,626	2,890	1.62 (1.47–1.79)	1134	2,139	1.22 (1.10–1.37)	943	2,139	0.88 (0.78–0.98)
Category 4	937	1,287	2.34 (2.07–2.65)	1433	2,140	1.55 (1.40–1.73)	889	2,140	0.72 (0.63–0.81)
Invasiveness									
<i>In situ</i>									
Category 1	51	1,784	0.51 (0.37–0.72)	73	2,139	0.56 (0.42–0.75)	184	2,139	1.19 (0.94–1.51)
Category 2 (ref)	140	2,597	1.00 (ref)	135	2,140	1.00 (ref)	143	2,140	1.00 (ref)
Category 3	242	2,890	1.58 (1.26–1.98)	167	2,139	1.18 (0.93–1.50)	124	2,139	0.85 (0.66–1.10)
Category 4	123	1,287	1.88 (1.42–2.49)	181	2,140	1.29 (1.02–1.63)	105	2,140	0.75 (0.56–1.00)
Invasive									
Category 1	461	1,784	0.64 (0.56–0.73)	542	2,139	0.67 (0.59–0.76)	1089	2,139	1.42 (1.27–1.60)
Category 2 (ref)	875	2,597	1.00 (ref)	770	2,140	1.00 (ref)	836	2,140	1.00 (ref)
Category 3	1,377	2,890	1.62 (1.45–1.80)	961	2,139	1.23 (1.10–1.38)	818	2,139	0.89 (0.79–1.00)
Category 4	810	1,287	2.40 (2.11–2.74)	1250	2,140	1.61 (1.44–1.80)	780	2,140	0.71 (0.62–0.81)
<i>P</i> _{het}			0.18			0.25			0.40
Histology ^c									
Ductal									
Category 1	356	1,784	0.67 (0.57–0.77)	433	2,139	0.72 (0.63–0.83)	838	2,139	1.38 (1.22–1.56)
Category 2 (ref)	665	2,597	1.00 (ref)	581	2,140	1.00 (ref)	650	2,140	1.00 (ref)
Category 3	1,073	2,890	1.62 (1.44–1.82)	749	2,139	1.27 (1.12–1.44)	635	2,139	0.90 (0.79–1.03)
Category 4	620	1,287	2.32 (2.01–2.67)	951	2,140	1.61 (1.42–1.82)	591	2,140	0.71 (0.61–0.82)
Lobular									
Category 1	49	1,784	0.51 (0.36–0.72)	51	2,139	0.49 (0.35–0.70)	135	2,139	1.59 (1.21–2.10)
Category 2 (ref)	114	2,597	1.00 (ref)	96	2,140	1.00 (ref)	98	2,140	1.00 (ref)
Category 3	148	2,890	1.44 (1.11–1.87)	107	2,139	1.13 (0.85–1.50)	95	2,139	0.82 (0.61–1.11)
Category 4	110	1,287	3.00 (2.23–4.04)	167	2,140	1.83 (1.41–2.37)	93	2,140	0.65 (0.47–0.89)
<i>P</i> _{het}			0.02			0.03			0.50
Histologic grade									
Well differentiated									
Category 1	139	1,784	0.62 (0.50–0.77)	157	2,139	0.70 (0.56–0.87)	284	2,139	1.25 (1.03–1.51)
Category 2 (ref)	274	2,597	1.00 (ref)	215	2,140	1.00 (ref)	247	2,140	1.00 (ref)
Category 3	379	2,890	1.44 (1.22–1.71)	283	2,139	1.35 (1.11–1.63)	246	2,139	0.91 (0.75–1.10)
Category 4	223	1,287	2.23 (1.81–2.74)	360	2,140	1.75 (1.45–2.10)	238	2,140	0.77 (0.62–0.95)
Moderately differentiated									
Category 1	177	1,784	0.65 (0.53–0.79)	202	2,139	0.69 (0.57–0.84)	398	2,139	1.37 (1.16–1.62)
Category 2 (ref)	327	2,597	1.00 (ref)	280	2,140	1.00 (ref)	313	2,140	1.00 (ref)
Category 3	523	2,890	1.64 (1.40–1.91)	353	2,139	1.25 (1.05–1.48)	329	2,139	0.96 (0.81–1.14)
Category 4	317	1,287	2.53 (2.10–3.04)	509	2,140	1.81 (1.54–2.13)	304	2,140	0.74 (0.61–0.90)
Poorly differentiated									
Category 1	99	1,784	0.65 (0.50–0.84)	120	2,139	0.62 (0.48–0.79)	279	2,139	1.55 (1.27–1.90)
Category 2 (ref)	184	2,597	1.00 (ref)	188	2,140	1.00 (ref)	195	2,140	1.00 (ref)
Category 3	335	2,890	1.79 (1.47–2.17)	221	2,139	1.12 (0.91–1.38)	170	2,139	0.80 (0.64–0.99)
Category 4	202	1,287	2.62 (2.08–3.30)	291	2,140	1.45 (1.19–1.77)	176	2,140	0.65 (0.51–0.83)
<i>P</i> _{het}			0.68			0.77			0.76
Tumor size									
<1.1 cm									
Category 1	219	1,784	0.90 (0.75–1.09)	244	2,139	0.90 (0.74–1.08)	319	2,139	1.19 (0.99–1.42)
Category 2 (ref)	318	2,597	1.00 (ref)	262	2,140	1.00 (ref)	282	2,140	1.00 (ref)
Category 3	429	2,890	1.33 (1.13–1.56)	314	2,139	1.19 (1.00–1.42)	280	2,139	0.94 (0.78–1.12)
Category 4	223	1,287	1.70 (1.39–2.07)	369	2,140	1.42 (1.20–1.69)	308	2,140	0.93 (0.77–1.14)
1.1–2.0 cm									
Category 1	149	1,784	0.52 (0.43–0.64)	188	2,139	0.57 (0.47–0.69)	463	2,139	1.62 (1.37–1.90)
Category 2 (ref)	349	2,597	1.00 (ref)	320	2,140	1.00 (ref)	311	2,140	1.00 (ref)
Category 3	547	2,890	1.60 (1.37–1.86)	388	2,139	1.20 (1.02–1.41)	328	2,139	0.96 (0.81–1.14)
Category 4	332	1,287	2.45 (2.05–2.93)	481	2,140	1.50 (1.29–1.76)	275	2,140	0.68 (0.56–0.82)
2.1+ cm									
Category 1	74	1,784	0.42 (0.32–0.56)	91	2,139	0.51 (0.39–0.66)	273	2,139	1.47 (1.21–1.79)
Category 2 (ref)	189	2,597	1.00 (ref)	165	2,140	1.00 (ref)	214	2,140	1.00 (ref)
Category 3	349	2,890	2.02 (1.67–2.45)	224	2,139	1.32 (1.07–1.64)	186	2,139	0.74 (0.60–0.92)
Category 4	232	1,287	3.60 (2.88–4.51)	364	2,140	2.13 (1.75–2.60)	171	2,140	0.49 (0.39–0.63)
<i>P</i> _{het}			<0.001			<0.001			<0.001

(Continued on the following page)

Table 3. Associations of categories^a of percent density, DA, and NDA with breast cancer overall and by morphologic subtypes (Cont'd)

	Percent density			DA			NDA		
	Cases, <i>n</i>	Controls, <i>n</i>	OR (95% CI) ^b	Cases, <i>n</i>	Controls, <i>n</i>	OR (95% CI) ^b	Cases, <i>n</i>	Controls, <i>n</i>	OR (95% CI) ^b
Involvement of lymph nodes									
Negative									
Category 1	314	1,784	0.64 (0.55-0.75)	370	2,139	0.68 (0.59-0.79)	722	2,139	1.37 (1.20-1.57)
Category 2 (ref)	609	2,597	1.00 (ref)	520	2,140	1.00 (ref)	565	2,140	1.00 (ref)
Category 3	908	2,890	1.50 (1.33-1.69)	658	2,139	1.24 (1.08-1.41)	568	2,139	0.93 (0.81-1.07)
Category 4	546	1,287	2.25 (1.95-2.61)	829	2,140	1.58 (1.39-1.79)	522	2,140	0.73 (0.63-0.85)
Positive									
Category 1	89	1,784	0.56 (0.43-0.74)	117	2,139	0.61 (0.48-0.78)	300	2,139	1.61 (1.32-1.96)
Category 2 (ref)	189	2,597	1.00 (ref)	186	2,140	1.00 (ref)	202	2,140	1.00 (ref)
Category 3	369	2,890	1.96 (1.62-2.37)	230	2,139	1.18 (0.96-1.45)	191	2,139	0.86 (0.70-1.07)
Category 4	220	1,287	2.89 (2.31-3.61)	334	2,140	1.70 (1.40-2.07)	174	2,140	0.63 (0.49-0.80)
<i>P</i> _{het}			0.01			0.39			0.11
ER status									
Negative									
Category 1	69	1,784	0.70 (0.51-0.95)	88	2,139	0.57 (0.43-0.75)	209	2,139	1.66 (1.31-2.10)
Category 2 (ref)	126	2,597	1.00 (ref)	151	2,140	1.00 (ref)	136	2,140	1.00 (ref)
Category 3	236	2,890	1.81 (1.43-2.27)	153	2,139	0.96 (0.76-1.21)	113	2,139	0.76 (0.59-0.99)
Category 4	137	1,287	2.49 (1.89-3.26)	176	2,140	1.11 (0.88-1.40)	110	2,140	0.61 (0.45-0.81)
Positive									
Category 1	373	1,784	0.63 (0.54-0.72)	431	2,139	0.69 (0.60-0.79)	837	2,139	1.38 (1.22-1.56)
Category 2 (ref)	716	2,597	1.00 (ref)	589	2,140	1.00 (ref)	667	2,140	1.00 (ref)
Category 3	1082	2,890	1.57 (1.40-1.76)	764	2,139	1.28 (1.13-1.45)	664	2,139	0.90 (0.79-1.03)
Category 4	646	1,287	2.40 (2.09-2.76)	1033	2,140	1.74 (1.54-1.97)	649	2,140	0.73 (0.64-0.85)
<i>P</i> _{het}			0.64			0.003			0.05
PR status									
Negative									
Category 1	119	1,784	0.67 (0.53-0.86)	137	2,139	0.59 (0.47-0.73)	277	2,139	1.41 (1.16-1.72)
Category 2 (ref)	220	2,597	1.00 (ref)	221	2,140	1.00 (ref)	215	2,140	1.00 (ref)
Category 3	349	2,890	1.61 (1.34-1.93)	245	2,139	1.08 (0.89-1.31)	191	2,139	0.81 (0.66-1.01)
Category 4	195	1,287	2.23 (1.79-2.78)	280	2,140	1.24 (1.03-1.50)	200	2,140	0.72 (0.57-0.90)
Positive									
Category 1	324	1,784	0.63 (0.54-0.73)	381	2,139	0.70 (0.60-0.82)	762	2,139	1.42 (1.24-1.61)
Category 2 (ref)	619	2,597	1.00 (ref)	515	2,140	1.00 (ref)	588	2,140	1.00 (ref)
Category 3	971	2,890	1.61 (1.43-1.82)	670	2,139	1.28 (1.12-1.47)	590	2,139	0.91 (0.79-1.04)
Category 4	583	1,287	2.47 (2.14-2.86)	931	2,140	1.79 (1.58-2.04)	557	2,140	0.71 (0.61-0.83)
<i>P</i> _{het}			0.70			0.007			0.74
HER2 status									
Negative									
Category 1	325	1,784	0.66 (0.57-0.77)	355	2,139	0.65 (0.56-0.76)	686	2,139	1.36 (1.19-1.56)
Category 2 (ref)	591	2,597	1.00 (ref)	517	2,140	1.00 (ref)	543	2,140	1.00 (ref)
Category 3	898	2,890	1.56 (1.38-1.76)	613	2,139	1.17 (1.03-1.34)	566	2,139	0.96 (0.83-1.10)
Category 4	546	1,287	2.40 (2.07-2.78)	875	2,140	1.68 (1.48-1.91)	565	2,140	0.81 (0.70-0.95)
Positive									
Category 1	52	1,784	0.70 (0.49-0.99)	63	2,139	0.67 (0.48-0.93)	154	2,139	1.37 (1.06-1.77)
Category 2 (ref)	92	2,597	1.00 (ref)	92	2,140	1.00 (ref)	121	2,140	1.00 (ref)
Category 3	204	2,890	2.16 (1.67-2.80)	141	2,139	1.46 (1.11-1.92)	93	2,139	0.72 (0.54-0.95)
Category 4	106	1,287	2.67 (1.96-3.64)	158	2,140	1.64 (1.25-2.14)	86	2,140	0.54 (0.39-0.75)
<i>P</i> _{het}			0.07			0.21			0.04

Abbreviation: *P*_{het}, test for heterogeneity in association by subtype.^aCategories are 1, 0%-10%; 2, 11%-25%; 3, 26%-50%; and 4, 51%+ for PMD and quartiles for DA and NDA.^bAdjusted for study site, age, and BMI.^cMixed and other histology categories are excluded.

tumor histology ($P = 0.04$), suggesting caution when interpreting these results.

Discussion

In this large study, the positive associations between PMD and breast cancer overall and by tumor characteristics were similar or stronger than in our first paper based on a subset of these data (3). 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 inde-

pendent risk factors for breast cancer. Furthermore, 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⁺ versus ER⁻ disease and PR⁺ versus PR⁻ disease and stronger associations of NDA with ER⁻ versus 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

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Table 4. Pooled associations of categories^a of percent density, DA, and NDA for morphologic subtypes of invasive breast cancer by age

Histology ^c	Percent density														
	Age < 55			Age ≥ 55			Age < 55			Age ≥ 55					
	Cases, n	Controls, n	OR (95% CI) ^b	Cases, n	Controls, n	OR (95% CI) ^b	Cases, n	Controls, n	OR (95% CI) ^b	Cases, n	Controls, n	OR (95% CI) ^b			
Overall breast cancer															
Category 1	530	1,254	0.60 (0.47-0.77)	408	1,254	0.61 (0.53-0.71)	191	759	0.65 (0.55-0.80)	427	1,380	0.64 (0.55-0.75)	822	1,357	1.44 (1.24-1.66)
Category 2 (ref)	316	1,581	1.00 (ref)	699	1,581	1.00 (ref)	376	948	1.00 (ref)	534	1,192	1.00 (ref)	456	1,087	1.00 (ref)
Category 3	809	1,604	1.68 (1.44-1.97)	817	1,286	1.60 (1.41-1.83)	553	1,135	1.22 (1.04-1.43)	581	1,004	1.26 (1.09-1.46)	362	878	0.96 (0.81-1.14)
Category 4	650	922	2.40 (2.02-2.86)	287	365	2.16 (1.79-2.61)	764	1,230	1.56 (1.34-1.81)	669	910	1.58 (1.37-1.83)	244	750	0.70 (0.57-0.86)
Invasiveness															
In situ															
Category 1	15	530	0.64 (0.35-1.18)	36	1,254	0.43 (0.29-0.64)	33	759	0.79 (0.50-1.24)	40	1,380	0.42 (0.28-0.62)	129	1,357	1.14 (0.84-1.54)
Category 2 (ref)	44	1,016	1.00 (ref)	96	1,581	1.00 (ref)	56	948	1.00 (ref)	79	1,192	1.00 (ref)	81	1,087	1.00 (ref)
Category 3	138	1,604	1.96 (1.37-2.81)	104	1,286	1.40 (1.04-1.89)	91	1,135	1.33 (0.94-1.88)	76	1,004	1.10 (0.79-1.54)	58	878	0.86 (0.60-1.23)
Category 4	100	922	2.38 (1.60-3.54)	23	365	1.31 (0.80-2.13)	117	1,230	1.60 (1.15-2.24)	64	910	1.06 (0.75-1.49)	29	750	0.57 (0.35-0.91)
Invasive															
Category 1	92	530	0.58 (0.45-0.76)	369	1,254	0.63 (0.54-0.74)	158	759	0.63 (0.51-0.79)	384	1,380	0.68 (0.58-0.80)	688	1,357	1.49 (1.28-1.74)
Category 2 (ref)	272	1,016	1.00 (ref)	603	1,581	1.00 (ref)	317	948	1.00 (ref)	453	1,192	1.00 (ref)	374	1,087	1.00 (ref)
Category 3	667	1,604	1.62 (1.37-1.92)	710	1,286	1.63 (1.42-1.87)	458	1,135	1.19 (1.01-1.42)	503	1,004	1.29 (1.10-1.51)	304	878	0.99 (0.82-1.19)
Category 4	548	922	2.39 (1.99-2.88)	262	365	2.27 (1.87-2.76)	646	1,230	1.56 (1.33-1.83)	604	910	1.68 (1.44-1.95)	213	750	0.72 (0.58-0.90)
<i>P</i> _{het}			0.55			0.08			0.78			0.03			0.40
Histology ^c															
Ductal															
Category 1	82	530	0.65 (0.49-0.86)	274	1,254	0.65 (0.54-0.77)	135	759	0.66 (0.52-0.83)	298	1,380	0.75 (0.63-0.90)	546	1,357	1.47 (1.24-1.73)
Category 2 (ref)	216	1,016	1.00 (ref)	449	1,581	1.00 (ref)	260	948	1.00 (ref)	321	1,192	1.00 (ref)	302	1,087	1.00 (ref)
Category 3	544	1,604	1.67 (1.39-2.00)	529	1,286	1.61 (1.38-1.88)	374	1,135	1.19 (0.99-1.42)	375	1,004	1.35 (1.14-1.61)	253	878	1.02 (0.84-1.24)
Category 4	435	922	2.41 (1.97-2.95)	185	365	2.12 (1.71-2.63)	508	1,230	1.50 (1.26-1.78)	443	910	1.75 (1.47-2.07)	176	750	0.74 (0.58-0.93)
Lobular															
Category 1	5	530	0.29 (0.11-0.78)	44	1,254	0.53 (0.36-0.78)	12	759	0.59 (0.29-1.18)	39	1,380	0.45 (0.30-0.68)	75	1,357	1.55 (1.03-2.33)
Category 2 (ref)	27	1,016	1.00 (ref)	87	1,581	1.00 (ref)	26	948	1.00 (ref)	70	1,192	1.00 (ref)	39	1,087	1.00 (ref)
Category 3	57	1,604	1.43 (0.89-2.30)	91	1,286	1.47 (1.08-2.01)	42	1,135	1.31 (0.80-2.17)	65	1,004	1.08 (0.76-1.54)	22	878	0.65 (0.38-1.12)
Category 4	67	922	3.14 (1.91-5.17)	43	365	2.73 (1.83-4.08)	76	1,230	2.22 (1.41-3.51)	91	910	1.68 (1.21-2.32)	20	750	0.58 (0.32-1.08)
<i>P</i> _{het}			0.07			0.27			0.18			0.08			0.31
Histologic grade															
Well differentiated															
Category 1	19	530	0.48 (0.29-0.82)	120	1,254	0.62 (0.49-0.80)	39	759	0.72 (0.48-1.07)	118	1,380	0.67 (0.52-0.87)	170	1,357	1.31 (1.00-1.71)
Category 2 (ref)	72	1,016	1.00 (ref)	202	1,581	1.00 (ref)	72	948	1.00 (ref)	143	1,192	1.00 (ref)	103	1,087	1.00 (ref)
Category 3	159	1,604	1.41 (1.05-1.90)	220	1,286	1.48 (1.20-1.83)	111	1,135	1.29 (0.95-1.76)	172	1,004	1.41 (1.11-1.80)	75	878	0.91 (0.66-1.25)
Category 4	143	922	2.31 (1.67-3.18)	80	365	2.02 (1.51-2.72)	171	1,230	1.86 (1.39-2.48)	189	910	1.70 (1.34-2.16)	45	750	0.62 (0.41-0.92)
Moderately differentiated															
Category 1	44	530	0.77 (0.53-1.13)	133	1,254	0.59 (0.47-0.75)	65	759	0.74 (0.54-1.03)	137	1,380	0.65 (0.51-0.83)	254	1,357	1.50 (1.19-1.89)
Category 2 (ref)	97	1,016	1.00 (ref)	230	1,581	1.00 (ref)	111	948	1.00 (ref)	169	1,192	1.00 (ref)	137	1,087	1.00 (ref)
Category 3	254	1,604	1.74 (1.35-2.25)	269	1,286	1.61 (1.32-1.97)	167	1,135	1.25 (0.97-1.62)	186	1,004	1.27 (1.01-1.60)	126	878	1.13 (0.87-1.47)
Category 4	210	922	2.64 (2.00-3.48)	107	365	2.43 (1.85-3.18)	262	1,230	1.81 (1.43-2.30)	247	910	1.85 (1.49-2.30)	88	750	0.82 (0.60-1.12)
Poorly differentiated															
Category 1	23	530	0.53 (0.32-0.86)	76	1,254	0.65 (0.48-0.89)	39	759	0.52 (0.35-0.77)	81	1,380	0.67 (0.49-0.91)	197	1,357	1.47 (1.14-1.90)
Category 2 (ref)	71	1,016	1.00 (ref)	113	1,581	1.00 (ref)	95	948	1.00 (ref)	93	1,192	1.00 (ref)	109	1,087	1.00 (ref)
Category 3	202	1,604	1.87 (1.40-2.50)	133	1,286	1.69 (1.29-2.22)	142	1,135	1.24 (0.94-1.64)	79	1,004	0.97 (0.71-1.33)	76	878	0.85 (0.62-1.16)
Category 4	151	922	2.53 (1.84-3.49)	51	365	2.49 (1.73-3.59)	171	1,230	1.36 (1.04-1.78)	120	910	1.59 (1.19-2.12)	65	750	0.73 (0.51-1.05)
<i>P</i> _{het}			0.48			0.91			0.36			0.40			0.70
Tumor size															
<1.1 cm															
Category 1	46	530	0.94 (0.65-1.37)	173	1,254	0.85 (0.68-1.06)	70	759	0.94 (0.68-1.30)	174	1,380	0.86 (0.68-1.08)	195	1,357	1.28 (1.00-1.65)
Category 2 (ref)	96	1,016	1.00 (ref)	222	1,581	1.00 (ref)	98	948	1.00 (ref)	164	1,192	1.00 (ref)	114	1,087	1.00 (ref)
Category 3	196	1,604	1.25 (0.96-1.63)	233	1,286	1.40 (1.14-1.72)	134	1,135	1.13 (0.86-1.49)	180	1,004	1.27 (1.01-1.60)	97	878	1.12 (0.84-1.50)
Category 4	150	922	1.63 (1.21-2.17)	73	365	1.62 (1.20-2.18)	186	1,230	1.47 (1.14-1.91)	183	910	1.41 (1.12-1.78)	82	750	0.79 (0.62-1.01)
1.1-2.0 cm															
Category 1	32	530	0.50 (0.33-0.76)	117	1,254	0.51 (0.40-0.65)	57	759	0.53 (0.39-0.74)	131	1,380	0.58 (0.45-0.74)	288	1,357	1.68 (1.34-2.10)
Category 2 (ref)	110	1,016	1.00 (ref)	239	1,581	1.00 (ref)	136	948	1.00 (ref)	184	1,192	1.00 (ref)	139	1,087	1.00 (ref)
Category 3	271	1,604	1.63 (1.28-2.07)	276	1,286	1.59 (1.31-1.93)	189	1,135	1.15 (0.91-1.46)	199	1,004	1.26 (1.01-1.57)	128	878	1.12 (0.86-1.45)
Category 4	220	922	2.39 (1.83-3.11)	112	365	2.43 (1.87-3.17)	251	1,230	1.42 (1.13-1.78)	230	910	1.59 (1.28-1.97)	78	750	0.71 (0.52-0.99)
<i>P</i> _{het}															

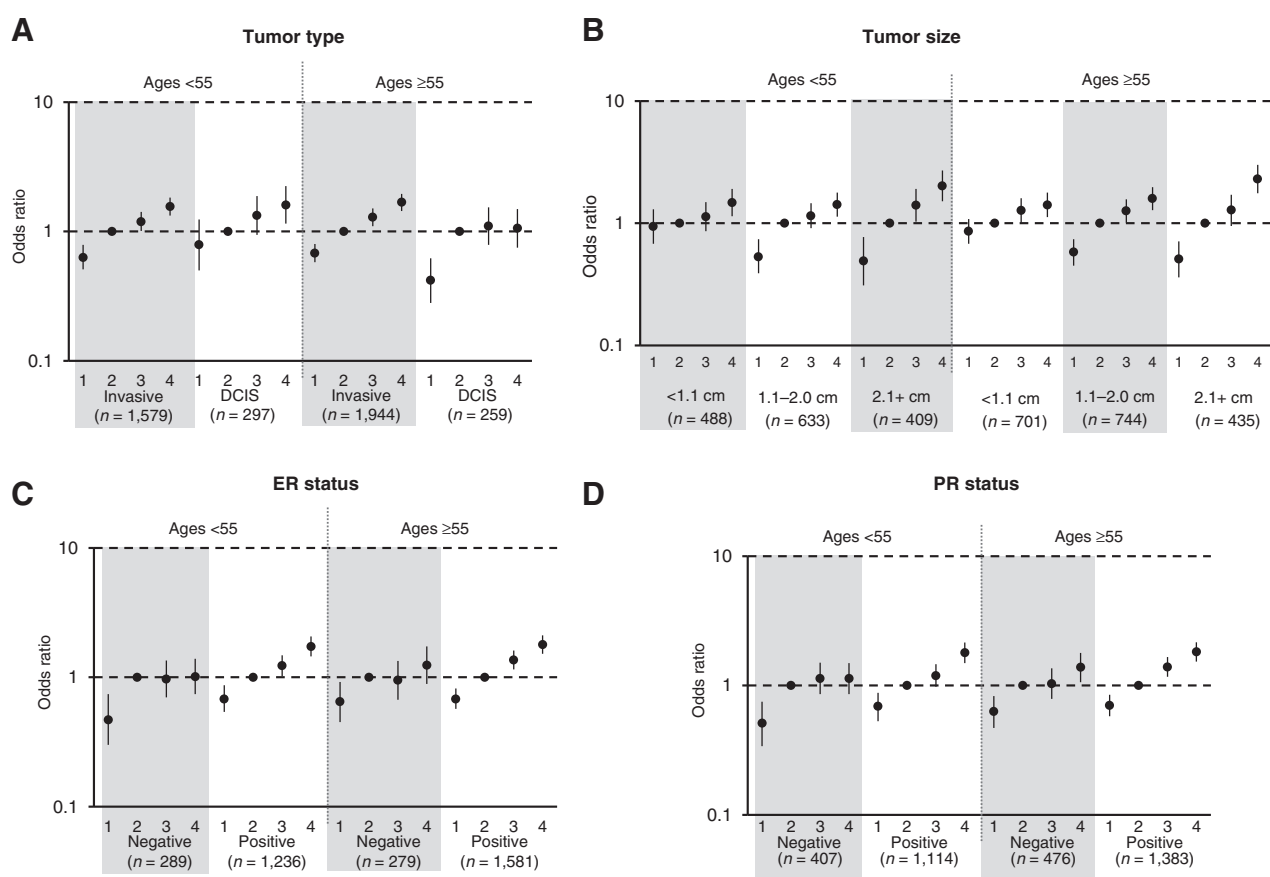
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Table 4. Pooled associations of categories^a of percent density, DA, and NDA for morphologic subtypes of invasive breast cancer by age (Cont'd)

	Percent density																	
	DA				NDA													
	Age < 55		Age ≥ 55		Age < 55		Age ≥ 55		Age < 55		Age ≥ 55							
Cases, n	Controls, n	OR (95% CI) ^b	Cases, n	Controls, n	OR (95% CI) ^b	Cases, n	Controls, n	OR (95% CI) ^b	Cases, n	Controls, n	OR (95% CI) ^b							
21+ cm																		
Category 1	12	530	0.28 (0.15–0.54)	62	1,254	0.44 (0.32–0.61)	28	759	0.49 (0.31–0.77)	63	1,380	0.51 (0.36–0.71)	183	1,357	1.47 (1.13–1.91)	90	782	1.42 (1.05–1.92)
Category 2 (ref)	60	1,016	1.00 (ref)	129	1,581	1.00 (ref)	71	948	1.00 (ref)	94	1,192	1.00 (ref)	107	1,087	1.00 (ref)	107	1,053	1.00 (ref)
Category 3	176	1,604	2.10 (1.53–2.88)	173	1,286	2.00 (1.56–2.56)	120	1,135	2.00 (1.53–2.70)	104	1,004	1.28 (0.95–1.71)	70	878	0.74 (0.54–1.03)	116	1,261	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	1,230	2.02 (1.51–2.70)	174	910	2.30 (1.76–3.01)	49	750	0.45 (0.30–0.67)	122	1,390	0.48 (0.35–0.66)
<i>P</i> _{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	1,254	0.65 (0.54–0.78)	110	759	0.66 (0.52–0.86)	260	1,380	0.68 (0.56–0.82)	458	1,357	1.53 (1.28–1.83)	264	782	1.24 (1.02–1.50)
Category 2 (ref)	198	1,016	1.00 (ref)	411	1,581	1.00 (ref)	211	948	1.00 (ref)	309	1,192	1.00 (ref)	240	1,087	1.00 (ref)	325	1,053	1.00 (ref)
Category 3	427	1,604	1.41 (1.17–1.71)	481	1,286	1.58 (1.35–1.85)	309	1,135	1.21 (0.99–1.47)	349	1,004	1.29 (1.08–1.54)	210	878	1.08 (0.87–1.33)	358	1,261	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	1,230	1.54 (1.28–1.86)	405	910	1.64 (1.38–1.95)	146	750	0.81 (0.65–1.04)	376	1,390	0.64 (0.53–0.78)
Positive																		
Category 1	23	530	0.62 (0.37–1.02)	66	1,254	0.51 (0.38–0.70)	38	759	0.53 (0.35–0.78)	79	1,380	0.66 (0.48–0.91)	195	1,357	1.47 (1.13–1.90)	105	782	1.81 (1.34–2.45)
Category 2 (ref)	59	1,016	1.00 (ref)	130	1,581	1.00 (ref)	91	948	1.00 (ref)	95	1,192	1.00 (ref)	109	1,087	1.00 (ref)	93	1,053	1.00 (ref)
Category 3	205	1,604	2.36 (1.73–3.22)	164	1,286	1.75 (1.36–2.24)	123	1,135	1.11 (0.83–1.48)	107	1,004	1.28 (0.96–1.72)	84	878	0.91 (0.67–1.24)	107	1,261	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	1,230	1.60 (1.22–2.09)	141	910	1.83 (1.39–2.42)	57	750	0.60 (0.41–0.87)	117	1,390	0.61 (0.44–0.84)
<i>P</i> _{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	1,254	0.73 (0.51–1.04)	28	759	0.47 (0.30–0.74)	60	1,380	0.65 (0.45–0.92)	139	1,357	1.72 (1.26–2.34)	70	782	1.64 (1.15–2.35)
Category 2 (ref)	42	1,016	1.00 (ref)	84	1,581	1.00 (ref)	74	948	1.00 (ref)	77	1,192	1.00 (ref)	70	1,087	1.00 (ref)	66	1,053	1.00 (ref)
Category 3	130	1,604	2.14 (1.48–3.09)	106	1,286	1.63 (1.21–2.21)	88	1,135	0.97 (0.70–1.35)	65	1,004	0.95 (0.67–1.34)	47	878	0.76 (0.51–1.12)	66	1,261	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	1,230	1.01 (0.74–1.39)	77	910	1.24 (0.89–1.73)	33	750	0.48 (0.30–0.77)	77	1,390	0.67 (0.46–0.99)
Positive																		
Category 1	76	530	0.60 (0.45–0.80)	297	1,254	0.61 (0.51–0.72)	125	759	0.68 (0.54–0.87)	306	1,380	0.68 (0.57–0.82)	527	1,357	1.46 (1.23–1.74)	310	782	1.27 (1.06–1.53)
Category 2 (ref)	221	1,016	1.00 (ref)	495	1,581	1.00 (ref)	234	948	1.00 (ref)	355	1,192	1.00 (ref)	287	1,087	1.00 (ref)	380	1,053	1.00 (ref)
Category 3	509	1,604	1.51 (1.26–1.82)	573	1,286	1.62 (1.40–1.88)	348	1,135	1.23 (1.02–1.48)	416	1,004	1.36 (1.15–1.61)	247	878	1.06 (0.87–1.30)	417	1,261	0.81 (0.68–0.96)
Category 4	430	922	2.30 (1.88–2.81)	216	365	2.32 (1.69–2.86)	529	1,230	1.73 (1.45–2.07)	504	910	1.79 (1.52–2.11)	175	750	0.80 (0.63–1.01)	474	1,390	0.65 (0.54–0.77)
<i>P</i> _{het}			0.22			0.47			0.02			0.09			0.03			0.48
PR status																		
Negative																		
Category 1	23	530	0.55 (0.33–0.89)	96	1,254	0.69 (0.53–0.92)	39	759	0.51 (0.34–0.75)	98	1,380	0.63 (0.47–0.83)	181	1,357	1.57 (1.20–2.06)	96	782	1.25 (0.94–1.68)
Category 2 (ref)	72	1,016	1.00 (ref)	148	1,581	1.00 (ref)	96	948	1.00 (ref)	125	1,192	1.00 (ref)	96	1,087	1.00 (ref)	119	1,053	1.00 (ref)
Category 3	180	1,604	1.70 (1.27–2.28)	169	1,286	1.54 (1.21–1.96)	131	1,135	1.13 (0.86–1.50)	114	1,004	1.03 (0.79–1.36)	74	878	0.91 (0.66–1.26)	117	1,261	0.76 (0.58–1.00)
Category 4	132	922	2.29 (1.66–3.17)	63	365	2.13 (1.53–2.96)	141	1,230	1.13 (0.86–1.49)	139	910	1.38 (1.06–1.79)	56	750	0.69 (0.47–1.01)	144	1,390	0.69 (0.51–0.92)
Positive																		
Category 1	67	530	0.61 (0.45–0.83)	257	1,254	0.61 (0.51–0.73)	112	759	0.69 (0.53–0.88)	269	1,380	0.70 (0.58–0.85)	479	1,357	1.46 (1.23–1.75)	283	782	1.35 (1.11–1.63)
Category 2 (ref)	188	1,016	1.00 (ref)	431	1,581	1.00 (ref)	209	948	1.00 (ref)	306	1,192	1.00 (ref)	261	1,087	1.00 (ref)	327	1,053	1.00 (ref)
Category 3	462	1,604	1.61 (1.33–1.96)	509	1,286	1.64 (1.41–1.92)	303	1,135	1.19 (0.98–1.46)	367	1,004	1.39 (1.17–1.66)	222	878	1.05 (0.85–1.29)	368	1,261	0.82 (0.69–0.98)
Category 4	397	922	2.49 (2.02–3.08)	186	365	2.28 (1.63–2.83)	490	1,230	1.79 (1.49–2.15)	441	910	1.82 (1.53–2.16)	152	750	0.75 (0.59–0.96)	405	1,390	0.63 (0.52–0.77)
<i>P</i> _{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	1,254	0.64 (0.53–0.77)	106	759	0.61 (0.47–0.79)	249	1,380	0.66 (0.55–0.80)	451	1,357	1.39 (1.17–1.67)	235	782	1.27 (1.03–1.55)
Category 2 (ref)	186	1,016	1.00 (ref)	405	1,581	1.00 (ref)	221	948	1.00 (ref)	296	1,192	1.00 (ref)	262	1,087	1.00 (ref)	281	1,053	1.00 (ref)
Category 3	455	1,604	1.64 (1.35–1.99)	443	1,286	1.53 (1.30–1.80)	294	1,135	1.10 (0.91–1.34)	319	1,004	1.26 (1.05–1.51)	219	878	1.03 (0.84–1.26)	347	1,261	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	1,230	1.63 (1.35–1.95)	404	910	1.75 (1.47–2.09)	160	750	0.79 (0.62–1.01)	405	1,390	0.77 (0.63–0.93)
Positive																		
Category 1	10	530	0.54 (0.26–1.12)	42	1,254	0.71 (0.47–1.07)	20	759	0.68 (0.39–1.19)	43	1,380	0.63 (0.42–0.96)	106	1,357	1.48 (1.06–2.08)	48	782	1.24 (0.83–1.84)
Category 2 (ref)	31	1,016	1.00 (ref)	61	1,581	1.00 (ref)	38	948	1.00 (ref)	54	1,192	1.00 (ref)	59	1,087	1.00 (ref)	62	1,053	1.00 (ref)
Category 3	115	1,604	2.43 (1.60–3.67)	89	1,286	2.00 (1.42–2.82)	82	1,135	1.79 (1.21–2.66)	59	1,004	1.24 (0.84–1.81)	40	878	0.83 (0.54–1.26)	53	1,261	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	1,230	1.82 (1.23–2.69)	67	910	1.55 (1.07–2.24)	26	750	0.54 (0.32–0.91)	60	1,390	0.50 (0.33–0.75)
<i>P</i> _{het}			0.11			0.54			0.07			0.92			0.38			0.16

Abbreviation: *P*_{het}, test for heterogeneity in association by subtype.^aCategories are 1, 0%–10%, 2, 11%–25%, 3, 26%–50%, and 4, 51%+ for PMD and quartiles for DA and NDA.^bAdjusted for study site, age, and BMI.^cMixed and other histology categories are excluded.

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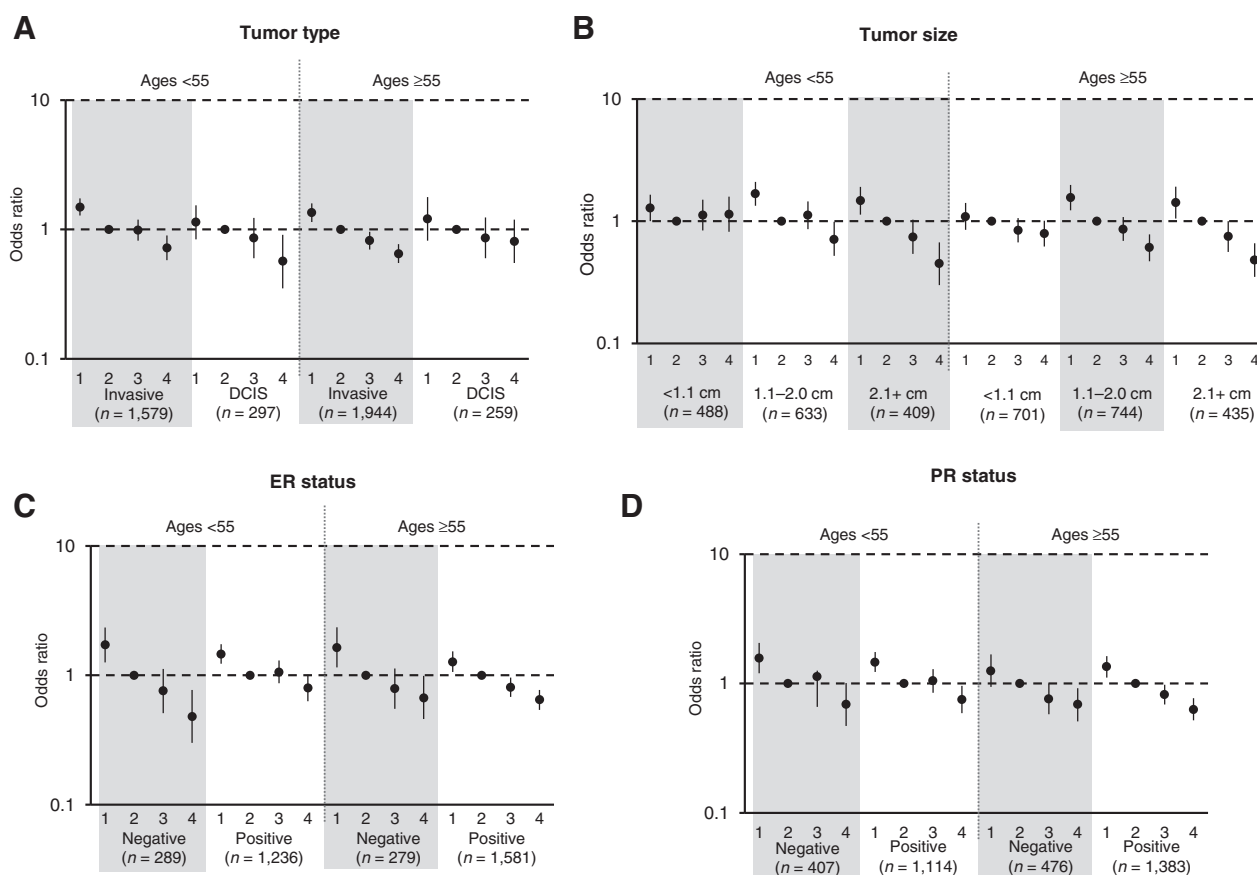
**Figure 1.**

Associations of categorical DA for breast cancer tumor type and selected tumor characteristics of invasive breast cancer, by age. ORs and 95% CIs, adjusted for age, body mass index, and study, are shown for quartiles of DA. Tumor type (A), tumor size (B), ER status (C), and PR status (D).

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 (23); although in the current analysis, there was suggestion of a stronger association for invasive cancers versus DCIS among women ≥ 55 years. Also in the Multiethnic Cohort, stronger associations of DA with ER⁺/PR⁺ versus ER⁻/PR⁻ tumors were observed (24). Like us, Eriksson and colleagues (25) reported stronger associations of absolute DA with ER⁺ versus ER⁻ tumors ($P = 0.065$) and with PR⁺ versus PR⁻ ($P = 0.099$) in a case-only study of 110 breast cancer patients. Positive associations of absolute DA with ER⁺ versus ER⁻ tumors and larger versus smaller tumors were also observed in recent UK case-control study (26). Similar to our findings, a case-only study

among postmenopausal women ($n = 286$) reported a nonsignificant positive trend of DA with tumor size and a nonsignificant trend of NDA with tumor size as well as significant positive associations between DA and ER and PR positivity (27). 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 (28) and include the higher amount of fibroglandular tissue "at risk" of transformation into cancer (29) and the increased epithelial and fibroblast cellular activity and interaction between stroma and epithelium in dense tissue (30, 31) as well as hormonal mechanisms, including the influence of sex steroid hormones and growth factors on density and breast cancer risk (32). 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

**Figure 2.**

Associations of categorical NDA for breast cancer tumor type and selected tumor characteristics of invasive breast cancer, by age. ORs and 95% CIs, adjusted for age, body mass index, and study, are shown for quartiles of NDA. Tumor type (A), tumor size (B), ER status (C), and PR status (D).

breast cancer risk across tumor characteristics suggest that several causal pathways may play a role in associations with risk. Petterson and Tamimi (33) propose several mechanisms by which breast fat (NDA) 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 (34). On the other hand, some studies have suggested breast fat as a risk factor for breast cancer (6, 35).

As in our previously published analysis based on a subset of these data (3), we found that PMD was more strongly associated with risk of ER⁻ breast cancer than with ER⁺ breast cancer among women <55 years of age. Our current findings of the MD area phenotypes further suggest that the positive association observed between PMD and ER⁻ disease among women <55 years is driven by the inverse association of NDA with ER⁻ disease in this group, rather than by a positive association with absolute dense breast area. On the basis of 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 > 4,000 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 (36). 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 versus screen-detected cancers for most included studies, in the Breast Cancer Surveillance Consortium, Kerlikowske and colleagues 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 (37). We did find evidence of study heterogeneity for the analyses of DA with overall breast cancer and by invasive versus *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

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film mammograms versus more contemporary full-field digital mammograms.

Strengths of this pooled analysis include the large sample size with mammograms available years before 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 PMD and absolute dense breast area were associated with increased breast cancer risk while NDA was associated with decreased risk across all ages and invasive tumor characteristics. Among women <55 years, DA was more strongly associated with an increased risk for ER⁺ versus ER⁻ tumors ($P_{\text{het}} = 0.02$) while NDA was more strongly associated with a decreased risk for ER⁻ versus ER⁺ tumors ($P_{\text{het}} = 0.03$). DA was similarly associated with increased risk (and NDA 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. Furthermore, these results suggest differential associations for these phenotypes with ER⁺ versus 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.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: K.A. Bertrand, C.G. Scott, R.M. Tamimi, F.J. Couch, S.R. Cummings, K. Kerlikowske, C.M. Vachon

Development of methodology: K.A. Bertrand, C.G. Scott, K. Kerlikowske

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K.A. Bertrand, C.G. Scott, R.M. Tamimi, D.W. Visscher,

F.J. Couch, J.A. Shepherd, Y.-Y. Chen, L. Ma, A.H. Beck, K. Kerlikowske, C.M. Vachon

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.A. Bertrand, C.G. Scott, M.R. Jensen, V.S. Pankratz, D.W. Visscher, J.A. Shepherd, Y.-Y. Chen, B. Fan, A.H. Beck, K. Kerlikowske, C.M. Vachon

Writing, review, and/or revision of the manuscript: K.A. Bertrand, C.G. Scott, R.M. Tamimi, V.S. Pankratz, A.D. Norman, D.W. Visscher, F.J. Couch, J.A. Shepherd, Y.-Y. Chen, B. Fan, A.H. Beck, S.R. Cummings, K. Kerlikowske, C.M. Vachon

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.D. Norman, F.J. Couch, C.M. Vachon

Study supervision: K.A. Bertrand, R.M. Tamimi, L. Ma, K. Kerlikowske, C.M. Vachon

Other (IT support): F.-F. Wu, K. Kerlikowske

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