Breast Cancer Res Treat (2017) 165:421–431
DOI 10.1007/s10549-017-4341-2

EPIDEMIOLOGY

Interaction of mammographic breast density with menopausal status and postmenopausal hormone use in relation to the risk of aggressive breast cancer subtypes

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Received: 9 January 2017 / Accepted: 13 June 2017 / Published online: 17 June 2017

Abstract

Purpose We examined the associations of mammographic breast density with breast cancer risk by tumor aggressiveness and by menopausal status and current postmenopausal hormone therapy.

Methods This study included 2596 invasive breast cancer cases and 4059 controls selected from participants of four nested case–control studies within four established cohorts: the Mayo Mammography Health Study, the Nurses' Health Study, Nurses' Health Study II, and San Francisco Mammography Registry. Percent breast density (PD), absolute dense (DA), and non-dense areas (NDA) were assessed from digitized film-screen mammograms using a computer-assisted threshold technique and standardized across studies. We used polytomous logistic regression to quantify the associations of breast density with breast cancer risk by tumor aggressiveness (defined as presence of at least two of the following tumor characteristics: size $\geq$2 cm, grade 2/3, ER-negative status, or positive nodes), stratified by menopausal status and current hormone therapy.

Electronic supplementary material The online version of this article (doi:10.1007/s10549-017-4341-2) contains supplementary material, which is available to authorized users.

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Results Overall, the positive association of PD and borderline inverse association of NDA with breast cancer risk was stronger in aggressive vs. non-aggressive tumors (≥51 vs. 11–25% OR 2.50, 95% CI 1.94–3.22 vs. OR 2.03, 95% CI 1.70–2.43, p-heterogeneity = 0.03; NDA 4th vs. 2nd quartile OR 0.54, 95% CI 0.41–0.70 vs. OR 0.71, 95% CI 0.59–0.85, p-heterogeneity = 0.07). However, there were no differences in the association of DA with breast cancer by aggressive status. In the stratified analysis, there was also evidence of a stronger association of PD and NDA with aggressive tumors among postmenopausal women and, in particular, current estrogen+progesterone users (≥51 vs. 11–25% OR 3.24, 95% CI 1.75–6.00 vs. OR 1.93, 95% CI 1.25–2.98, p-heterogeneity = 0.01; NDA 4th vs. 2nd quartile OR 0.43, 95% CI 0.21–0.85 vs. OR 0.56, 95% CI 0.35–0.89, p-heterogeneity = 0.01), even though the interaction was not significant.

Conclusion Our findings suggest that associations of mammographic density with breast cancer risk differ by tumor aggressiveness. While there was no strong evidence that these associations differed by menopausal status or hormone therapy, they did appear more prominent among current estrogen+progesterone users.

Keywords Breast density · Breast cancer subtypes · Tumor aggressiveness · Postmenopausal hormone therapy

Introduction

Mammographic breast density is a well-established and strong predictor of breast cancer risk [1–4]. Women with breasts of 75% or greater percent density (proportion of the total breast area that appears dense on the mammogram) are at 3- to 5-fold greater risk of breast cancer compared to women with mostly fatty breasts [3, 5, 6]. Absolute dense area of the breast that represents amount of fibroglandular tissue has also been shown to be positively associated with breast cancer risk [7–13], while non-dense area of the breast (representing adipose tissue) is inversely associated with breast cancer risk [7, 14].

A recent study found a stronger association of breast density defined with Breast Imaging Reporting and Data System classification (American College of Radiology) with breast cancer in premenopausal women and postmenopausal hormone users compared with postmenopausal women not on hormones [15]. We found similar results in an analysis from the Nurses' Health Study: the association between percent density and breast cancer risk appeared to be stronger in premenopausal women than in postmenopausal women without postmenopausal hormone use history and among postmenopausal women currently using hormones compared to postmenopausal women who never used hormones or with past hormone use [16]. Our previous studies have also demonstrated stronger associations between breast density and breast cancer subtypes with individual aggressive tumor characteristics including larger size, higher grade, estrogen receptor (ER) negative status, and positive nodal involvement [17, 18]. One study to date has shown increased risk of advanced stage breast cancer for postmenopausal hormone therapy users who had very high density (BI-RADS 4) compared to those with average density (BI-RADS 2) [15]. We extend this prior work by examining the associations of quantitative measures of breast density with tumor aggressiveness, defined using combination of aggressive tumor features such as higher grade, larger size, ER-negative status, and nodal involvement rather than individual tumor features. These features have been consistently linked to more aggressive tumor behavior and poorer survival [19–25]; tumor size and nodal involvement are used for breast cancer clinical staging [26]. We further examine these associations by menopausal status and postmenopausal hormone use. We used the data from four prospective cohorts to examine if associations of breast density phenotypes (percent breast density, absolute dense area, and non-dense area) with breast cancer risk differ by tumor aggressiveness, menopausal status, and current hormone use.

Methods

Study populations

Women included in this study were selected from participants of the Mayo Mammography Health Study (MMHS), the Nurses' Health Study (NHS), Nurses' Health Study II (NHSII), and San Francisco Mammography Registry (SFMR). These cohorts have been previously described in detail elsewhere [27–34]. From each cohort, a nested case–control study contributed participants to the current analysis.

MMHS is a prospective mammography cohort that recruited women from Minnesota, Wisconsin, and Iowa who were at age 35 years or older and had a screening mammogram at the Mayo Clinic during 2003–2006. Women without breast cancer (controls) were matched to incident breast cancer cases on age, menopausal status, year of exam, and state. This cohort contributed 372 cases and 638 controls to the current analysis.

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NHS and NHSII are prospective cohorts that followed registered nurses in the United States who were 30–55 years (NHS) or 25–42 years old (NHSII) at enrollment. Breast cancer cases were confirmed through medical record review by trained personnel. A nested case–control study within these cohorts was previously established to examine associations of various circulating biomarkers with breast cancer risk [17]. Women without cancer history (other than non-melanoma skin cancer) were matched 1:1 or 1:2 with breast cancer cases on age at the time of blood collection, menopausal status, and postmenopausal hormone use (current vs. not current) at blood draw, and day/time of blood draw; for NHS II, additional matching included race/ethnicity and day in the luteal phase [35]. This study contributed 912 cases and 1109 controls to the current analysis.

The SFMR is a population-based registry that collects demographic, clinical and risk factor information, mammographic findings, and cancer outcomes through linkage with state-wide California SEER program. A nested case–control study within this cohort contributed 1312 cases and 2312 controls to the current analysis. Cases were matched to controls on age, menopausal status, and year of mammogram.

In total, this analysis included 2596 invasive breast cancer cases and 4059 controls within these cohorts. This study was approved by the Institutional Review Boards at the Mayo Clinic, Brigham and Women's Hospital, and the University of California, San Francisco. Informed consent was obtained or implied by return of questionnaires (NHS, NHSII).

From all studies, we excluded breast cancer cases diagnosed within 6 months of mammography and their matched controls, to minimize prevalent cancers at the time of mammography.

Assessment of mammographic breast density

Mammographic breast density was estimated on digitized pre-diagnostic film-screen mammograms of the craniocaudal view using computer-assisted threshold techniques (Cumulus [36] and UCSF custom mammographic density software [37]). The two methods have previously shown very high agreement (intraclass correlation 0.94) [37]. Percent breast density was measured as percentage of the total area occupied by epithelial/stromal tissue (absolute dense area) divided by the total breast area. For NHS and NHSII mammograms, the average density of both breasts was used in the analysis. For MMHS and SFMR, breast density was estimated from the contralateral breast for cases and the corresponding side for matched controls. As reported previously, densities of the right and left breast for an individual woman are strongly correlated (Pearson correlation coefficient 0.86–0.96) [38] and the average density from both breasts is similar to density assessed on a randomly selected side [39].

Percent breast density, absolute dense area, and non-dense area measures were standardized across studies to account for inter-rater variability in the density assessment as previously described [18].

Assessment of breast tumor aggressiveness

Information on tumor type, histology, grade, nodal involvement, and tumor size was obtained from state-wide Surveillance Epidemiology and End Results programs (SFMR), pathology reports (NHS and NHSII), and state and clinic cancer registries and medical records (MMHS). Recent studies demonstrate that use of histomorphological characteristics of the tumor improves the prognostic accuracy of breast cancer staging [40]. In our analysis, tumors were defined as aggressive if they had at least two of the following criteria: size 2 cm and greater, differentiation grade 2 or 3, ER-negative status, and positive nodes. These histomorphological characteristics have been previously linked to poorer prognosis and patient survival [23–25, 41–44]. This approach takes into account both clinical characteristics (nodal involvement and tumor size) as well as selected histological and molecular features such as grade and ER status, respectively. Cases with unknown size, grade, nodal status, or ER status were excluded from the analysis ($n = 659$ or 20.2%). Characteristics of the cases included in the analysis were similar to characteristics of the cases excluded from this study due to the missing tumor characteristics (data not shown).

Covariates

Covariate information was obtained from self-administered questionnaires prior to mammography (NHS, NHSII, SFMR) or both self-administered questionnaires and medical record review at the time of mammography (MMHS). Cases with unknown menopausal status and postmenopausal women with unknown hormone therapy status were excluded from analysis ($n = 490$ or 15.7%). Control women who were previously matched to eligible cases were included in analyses unless they had unknown menopausal or hormone therapy status ($n = 470$ or 10.4% excluded). Characteristics of the women included in the analysis were similar to characteristics of those excluded from this study due to the missing data on menopausal status and hormone therapy, except for age, menopausal status, and hormone therapy as expected based on the exclusion criteria.

Statistical analysis

Standardized percent breast density was categorized as 0–10, 11–25% (reference), 26–50, and ≥51%, consistent with the previous analyses [18, 34, 45]. Absolute dense and non-dense areas were defined as quartiles based on the distribution in controls (absolute dense area: 1st: 0.0–20.0; 2nd: 20.1–36.6; 3rd: 36.7–60.5; 4th: >60.6 cm^2; non-dense area: 1st: 4.2–70.3; 2nd: 70.4–117.2; 3rd: 117.3–188.9; 4th: >189.0 cm^2). We used polytomous logistic regression to describe the associations of breast density measures with breast cancer risk by tumor aggressiveness, overall and stratified by woman's menopausal status and current hormone therapy (premenopausal, postmenopausal/estrogen therapy alone, postmenopausal/combined estrogen+progesterone therapy, and postmenopausal/no hormones). In this pooled analyses from four studies, the risk estimates were adjusted for study site, age (continuous), and body mass index (continuous). We further considered potential confounders including parity (nulliparous, parous, or unknown) and first-degree family history of breast cancer (yes, no, or unknown) by evaluating the magnitude of the change in odds ratios (OR) observed after including each potential confounder individually in the model. Addition of these variables to the models did not substantially change risk estimates and they were not included in the final models.

We first evaluated whether the associations of breast density measures with breast cancer risk differed for aggressive vs. non-aggressive tumor subtypes. Contrasts were used to construct a test of association of density by aggressiveness (p-heterogeneity) within the polytomous regression framework to investigate whether there was statistical evidence of differences in association of density with breast cancer risk by tumor aggressiveness. For these heterogeneity tests, density was modeled using an ordinal trend across quartiles in order to increase power. We next examined tests of two-way interactions to assess the significance of the differences in associations of breast density measures with tumor aggressiveness across the strata defined by woman's menopausal status and current hormone use using Wald Chi-square test. Finally, contrasts were also used to assess heterogeneity of the risk estimates by tumor aggressiveness within each of the strata.

We assessed the statistical significance of differences in associations by study through testing for interactions between study group and density in the pooled analysis, and found no evidence of differences across the studies (p-heterogeneity for percent density = 0.78, for absolute dense area = 0.26, and for non-dense area = 0.54).

In a secondary analysis, we excluded cases with mammogram date within 2 years of diagnosis (15% of the cases). Analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA). For all analyses, the level of statistical significance was assessed at 0.05 level. All tests were two-sided.

Results

Distribution of breast cancer risk factors by menopausal status and hormone use among cases and controls is presented in Table 1. Compared to controls, cases had a greater percent density and a larger absolute dense area in all strata. Cases also had a smaller area of non-dense breast tissue in all strata except postmenopausal women with no hormone use. There were no differences in BMI by case and control status among premenopausal women. Among postmenopausal women, mean BMI was greater among cases vs. controls across all strata but only reached statistical significance among those with no hormone use (27.3 vs. 26.1 kg/cm^2, $p < 0.001$). Further, there was a larger proportion of cases than controls with a positive family history of breast cancer, although only associations among the two largest groups, premenopausal and postmenopausal women not using hormones, were statistically significant ($p < 0.001$ for both).

Distribution of tumor grade, size, ER status, and nodal involvement by tumor aggressiveness are presented in Supplementary Table 1. Among cases defined as aggressive tumors, 52 (7%) met all four criteria, 219 (29%) met three criteria, and 473 (64%) cases met two of the four criteria. Among aggressive tumors, 46.6% were estrogen receptor-negative as compared to 4.2% among non-aggressive tumors.

In the overall analysis, percent breast density was more strongly associated with the risk of aggressive breast tumor subtypes vs. non-aggressive tumors (OR 2.50, 95% CI 1.94–3.22 vs. OR 2.03, 95% CI 1.70–2.43 for density ≥51 vs. 11–25%, respectively, p-heterogeneity = 0.03). The inverse association of non-dense area with breast cancer risk appeared to be stronger in aggressive breast tumor subtypes vs. non-aggressive tumors, though the difference did not reach statistical significance (OR 0.54, 95% CI 0.41–0.70 vs. OR 0.71, 95% CI 0.59–0.85 for 4th vs. 2nd quartile, respectively, p-heterogeneity = 0.07). The association of absolute dense area with the risk of breast cancer was similar for aggressive and non-aggressive tumors (OR 1.74, 95% CI 1.40–2.17 vs. OR 1.72, 95% CI 1.47–2.00 for 4th vs. 2nd quartile, respectively, p-heterogeneity = 0.45) (Table 2). We found no differences in the associations of breast density phenotypes with tumor aggressiveness by menopausal status/hormone therapy with any of the density measures (p-interaction = 0.80 for percent density, 0.91 for absolute dense area, and 0.36 for non-dense area) (Table 3). However, the largest significant difference in the

Table 1 Baseline characteristics of study population by menopausal status and current postmenopausal hormone use

	Premenopausal			Postmenopausal, estrogen only			Postmenopausal, estrogen+progesterone			Postmenopausal, no hormone use		
	Cases (n = 948)	Controls (n = 1488)	*p* value[a]	Cases (*n* = 281)	Controls (*n* = 438)	*p* value[a]	Cases (*n* = 463)	Controls (*n* = 542)	*p* value[a]	Cases (*n* = 904)	Controls (*n* = 1591)	*p* value[a]
Mean (SD)												
Percent breast density	42.6 (19.7)	36.6 (20.3)	<0.001	33.6 (18.4)	26.5 (18.3)	<0.001	35.8 (19.0)	29.7 (19.3)	<0.001	24.8 (17.5)	21.1 (16.9)	<0.001
Dense area, cm^2	63.0 (40.6)	53.6 (37.4)	<0.001	59.0 (42.7)	47.4 (44.1)	<0.001	60.3 (42.0)	46.9 (34.5)	<0.001	46.8 (38.9)	36.5 (31.4)	<0.001
Non-dense area, cm^2	105.6 (81.9)	119.4 (94.1)	<0.001	132.5 (95.6)	148.7 (98.8)	0.008	123.2 (85.1)	136.5 (95.8)	0.04	165.6 (112.9)	166.5 (115.2)	0.70
Age at mammogram, years	45.1 (4.5)	45.2 (4.4)	0.94	60.1 (8.0)	59.2 (8.5)	0.12	58.7 (7.1)	58.6 (7.8)	0.68	62.8 (8.6)	62.4 (8.5)	0.30
Age at diagnosis, years	49.6 (5.3)	NA		64.9 (8.4)	NA		62.8 (7.5)	NA		67.4 (8.6)	NA	
Body mass index, kg/m^2	24.9 (5.0)	25.0 (5.3)	0.55	26.1 (5.0)	25.9 (5.2)	0.63	24.9 (4.4)	24.6 (4.7)	0.09	27.3 (6.0)	26.1 (5.6)	<0.001
Frequency (%)												
Body mass index, kg/m^2			0.32			0.47			0.44			<0.001
<25	562 (59.3%)	927 (62.3%)		131 (46.6%)	225 (51.4%)		273 (59.0%)	341 (62.9%)		354 (39.2%)	794 (49.9%)	
25–29	233 (24.6%)	339 (22.8%)		90 (32.0%)	134 (30.6%)		119 (25.7%)	137 (25.3%)		290 (32.1%)	499 (31.4%)	
30–34	87 (9.2%)	116 (7.8%)		36 (12.8%)	51 (11.6%)		41 (8.9%)	42 (7.7%)		133 (14.7%)	180 (11.3%)	
35+	44 (4.6%)	88 (5.9%)		17 (6.0%)	28 (6.4%)		15 (3.2%)	21 (3.9%)		89 (9.8%)	116 (7.3%)	
Unknown	22 (2.3%)	18 (1.2%)		7 (2.5%)	0		15 (3.2%)	1 (0.2%)		38 (4.2%)	2 (0.1%)	
Parity			0.60			0.84			0.56			0.11
Nulliparous	254 (26.8%)	381 (25.6%)		46 (16.4%)	74 (16.9%)		132 (28.5%)	150 (27.7%)		190 (21.0%)	288 (18.1%)	
Parous	678 (71.5%)	1072 (72.0%)		230 (81.9%)	355 (81.1%)		307 (66.3%)	376 (69.4%)		690 (76.3%)	1242 (78.1%)	
Unknown	16 (1.7%)	35 (2.4%)		5 (1.8%)	9 (2.1%)		24 (5.2%)	16 (3%)		24 (2.7%)	61 (3.8%)	
Family history of breast cancer			<0.001			0.45			0.10			<0.001
No	770 (81.2%)	1314 (88.3%)		230 (81.9%)	372 (84.9%)		379 (81.9%)	472 (87.1%)		671 (74.2%)	1334 (83.8%)	
Yes	164 (17.3%)	172 (11.6%)		49 (17.4%)	66 (15.1%)		74 (16.0%)	69 (12.7%)		226 (25.0%)	257 (16.2%)	
Unknown	14 (1.5%)	2 (0.1%)		2 (0.7%)	0		10 (2.2%)	1 (0.2%)		7 (0.8%)	0	

NA not applicable

[a] *p* values are Kruskal–Wallis test for continuous, Wilcoxon test for BMI categories, and Chi-square test for discrete. Missing values not included in the tests

Table 2 Associations of breast density with breast cancer risk, by tumor aggressiveness (odds ratios and 95% confidence intervals)

Density category or quartile[a]	Percent density (categories)		Absolute dense area (quartiles)		Non-dense area (quartiles)	
	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)
Non-aggressive tumors	1852/4059		1852/4059		1852/4059	
1st	264/922	0.59 (0.49, 0.71)	292/1019	0.74 (0.62, 0.89)	547/1024	1.35 (1.15, 1.58)
2nd	479/1146	1.00 (reference)	377/1024	1.00 (reference)	440/1003	1.00 (reference
3rd	703/1367	1.43 (1.23, 1.65)	527/968	1.50 (1.28, 1.76)	466/1015	0.96 (0.82, 1.13)
4th	406/624	2.03 (1.70, 2.43)	656/1048	1.72 (1.47, 2.00)	399/1017	0.71 (0.59, 0.85)
Aggressive tumors[b]	744/4059		744/4059		744/4059	
1st	103/922	0.53 (0.40, 0.70)	105/1019	0.66 (0.50, 0.86)	225/1024	1.27 (1.02, 1.58)
2nd	205/1146	1.00 (reference)	153/1024	1.00 (reference)	197/1003	1.00 (reference)
3rd	366/1367	1.74 (1.41, 2.15)	206/968	1.41 (1.13, 1.78)	168/1015	0.75 (0.60, 0.95)
4th	219/624	2.50 (1.94, 3.22)	280/1048	1.74 (1.40, 2.17)	154/1017	0.54 (0.41, 0.70)
P-heterogeneity		0.03		0.45		0.07

Adjusted for age, body mass index, and study site

CI confidence interval, *OR* odds ratio

[a] Defined categories for percent density (0–10, 11–25, 26–50, and ≥51%) and quartiles for absolute dense and non-dense areas

[b] Defined as presence of at least two of the following tumor characteristics: size ≥2 cm, grade 2, positive nodes, ER−

risk estimates for aggressive vs. non-aggressive subtypes was noted for percent density and non-dense area among postmenopausal women, and in particular among those with combined estrogen+progesterone therapy (OR 3.24 vs. OR 1.93, respectively for density ≥51 vs. 11–25%; p-heterogeneity = 0.01; OR 0.43 vs. 0.56, respectively for 4th vs. 2nd quartile; p-heterogeneity = 0.01).

In a secondary analysis excluding cases with mammogram date within 2 years of diagnosis the results were similar (Supplementary Table 2).

Discussion

In this pooled analysis of four nested case–control studies, we investigated the association of breast density phenotypes with breast cancer risk according to tumor aggressiveness among 2596 women who developed breast cancer and 4059 matched controls. A stronger positive association of percent density and inverse association of non-dense area with aggressiveness of breast cancer were noted in the overall analysis. While there was no strong evidence that these associations differed by menopausal status or hormone therapy, they did appear more prominent among current estrogen and progesterone users.

We examine the associations of breast density phenotypes with the risk of breast cancer by tumor's aggressiveness defined using combination of histomorphological characteristics reflective of aggressive tumor behavior. Previous studies on the association of breast density with breast cancer subtypes, including our own [17, 18], examined these characteristics individually. The tumor represents a combination of histomorphological features and these features do not exist in isolation from one another. Recent studies demonstrate that use of histomorphological characteristics of the tumor improves the prognostic accuracy of breast cancer staging [40]. We could not, however, incorporate PR and HER2 receptor statuses in this classification as it resulted in significant decrease in sample size and loss in statistical power, especially since the primary aim of our analysis was to investigate differences in associations by menopausal status and hormone use.

Positive associations of breast density with tumor size, involvement of axillary nodes, and higher tumor grade have been reported in some [46–48], but not all studies [49]. We recently reported stronger associations of percent density with ER− tumors vs. ER+ tumors, as well as for larger tumors and tumors with higher grade in postmenopausal women from NHS [17]. In a pooled analysis which included the NHS, we found a stronger association of percent density with larger tumors and positive nodal involvement, but the stronger associations with ER− tumors were limited to women aged <55 years [18]. The results from our current analysis indicate a stronger association of percent density and suggestive stronger inverse association of non-dense area with more aggressive subtypes of breast cancer, and this association did not vary by menopausal status or hormone therapy. If breast density is associated with more aggressive breast cancer phenotypes

Table 3 Associations of breast density with breast cancer risk, by tumor aggressiveness and menopausal status/current postmenopausal hormone use (odds ratios and 95% confidence intervals)

Density category/quartile[a]	Percent density (categories)		Absolute dense area (quartiles)		Non-dense area (quartiles)	
	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)
Premenopausal	948/1488		948/1488		948/1488	
Non-aggressive tumors	647/1488		647/1488		647/1488	
1st	42/179	0.60 (0.40, 0.91)	55/227	0.70 (0.49, 1.00)	286/524	1.58 (1.24, 2.01)
2nd	108/309	1.00 (reference)	122/349	1.00 (reference)	149/410	1.00 (reference)
3rd	259/615	1.33 (1.01, 1.75)	190/421	1.30 (0.99, 1.70)	121/302	1.08 (0.81, 1.44)
4th	238/385	2.03 (1.51, 2.73)	280/491	1.64 (1.27, 2.11)	91/252	0.90 (0.63, 1.27)
Aggressive tumors	301/1488		301/1488		301/1488	
1st	15/179	0.49 (0.26, 0.92)	23/227	0.63 (0.37, 1.06)	117/524	1.12 (0.81, 1.53)
2nd	44/309	1.00 (reference)	57/349	1.00 (reference)	87/410	1.00 (reference)
3rd	137/615	1.85 (1.26, 2.72)	90/421	1.33 (0.93, 1.92)	59/302	0.85 (0.58, 1.23)
4th	105/385	2.42 (1.59, 3.68)	131/491	1.66 (1.18, 2.33)	38/252	0.55 (0.34, 0.89)
p-heterogeneity		0.36		0.76		0.95
All postmenopausal women	1674/2571		1674/2571		1674/2571	
Non-aggressive tumors	1205/2571		1205/2571		1205/2571	
1st	222/743	0.58 (0.47, 0.71)	237/792	0.75 (0.61, 0.92)	261/500	1.20 (0.97, 1.48)
2nd	371/837	1.00 (reference)	255/675	1.00 (reference)	291/593	1.00 (reference)
3rd	444/752	1.51 (1.26, 1.79)	337/547	1.62 (1.32, 1.98)	345/713	0.90 (0.74, 1.09)
4th	168/239	1.98 (1.55, 2.53)	376/557	1.76 (1.45, 2.15)	308/765	0.63 (0.50, 0.78)
Aggressive tumors	443/2571		443/2571		443/2571	
1st	75/743	0.52 (0.38, 0.71)	82/792	0.66 (0.48, 0.91)	108/500	1.40 (1.04, 1.89)
2nd	128/837	1.00 (reference)	96/675	1.00 (reference)	110/593	1.00 (reference)
3rd	168/752	1.70 (1.31, 2.20)	116/547	1.44 (1.07, 1.94)	109/713	0.71 (0.53, 0.95)
4th	72/239	2.60 (1.85, 3.64)	149/557	1.79 (1.35, 2.38)	116/765	0.51 (0.37, 0.71)
p-heterogeneity		0.05		0.52		0.03
Postmenopausal, E	281/438		281/438		281/438	
Non-aggressive tumors	206/438		206/438		206/438	
1st	24/104	0.54 (0.31, 0.95)	25/122	0.51 (0.28, 0.91)	52/86	1.19 (0.73, 1.95)
2nd	52/134	1.00 (reference)	37/89	1.00 (reference)	59/115	1.00 (reference)
3rd	92/153	1.51 (0.99, 2.31)	64/113	1.42 (0.86, 2.35)	53/123	0.78 (0.49, 1.24)
4th	38/47	2.06 (1.18, 3.62)	80/114	1.63 (1.00, 2.66)	42/114	0.67 (0.39, 1.14)
Aggressive tumors	75/438		75/438		75/438	
1st	12/104	0.78 (0.33, 1.82)	13/122	0.48 (0.22, 1.07)	17/86	1.22 (0.60, 2.48)
2nd	14/134	1.00 (reference)	17/89	1.00 (reference)	24/115	1.00 (reference)
3rd	38/153	2.56 (1.31, 5.03)	19/113	0.89 (0.43, 1.84)	19/123	0.55 (0.28, 1.09)
4th	11/47	2.88 (1.19, 7.00)	26/114	1.08 (0.54, 2.14)	15/114	0.32 (0.14, 0.71)
p-heterogeneity		0.56		0.25		0.10
Postmenopausal, E+P	463/542		463/542		463/542	
Non-aggressive tumors	344/542		344/542		344/542	
1st	38/103	0.60 (0.37, 0.96)	48/109	1.01 (0.64, 1.60)	97/146	1.11 (0.75, 1.64)
2nd	85/153	1.00 (reference)	63/153	1.00 (reference)	84/131	1.00 (reference)
3rd	149/200	1.50 (1.05, 2.13)	105/124	2.00 (1.34, 2.98)	104/141	1.05 (0.72, 1.55)
4th	72/86	1.93 (1.25, 2.98)	128/156	1.97 (1.35, 2.89)	59/124	0.56 (0.35, 0.89)
Aggressive tumors	119/542		119/542		119/542	
1st	5/103	0.24 (0.09, 0.65)	8/109	0.46 (0.20, 1.07)	48/146	1.65 (0.97, 2.80)
2nd	26/153	1.00 (reference)	23/153	1.00 (reference)	31/131	1.00 (reference)
3rd	54/200	1.90 (1.12, 3.24)	37/124	1.85 (1.04, 3.31)	20/141	0.51 (0.27, 0.96)

Table 3 continued

Density category/quartile[a]	Percent density (categories)		Absolute dense area (quartiles)		Non-dense area (quartiles)	
	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)
4th	34/86	3.24 (1.75, 6.00)	51/156	2.09 (1.21, 3.61)	20/124	0.43 (0.21, 0.85)
p-heterogeneity		0.01		0.10		0.01
Postmenopausal, no hormones	904/1591		904/1591		904/1591	
Non-aggressive tumors	655/1591		655/1591		655/1591	
1st	160/536	0.59 (0.46, 0.75)	164/561	0.75 (0.58, 0.97)	112/268	1.16 (0.86, 1.56)
2nd	234/550	1.00 (reference)	155/433	1.00 (reference)	148/347	1.00 (reference)
3rd	203/399	1.40 (1.11, 1.78)	168/310	1.48 (1.14, 1.94)	188/449	0.87 (0.66, 1.13)
4th	58/106	1.69 (1.17, 2.45)	168/287	1.61 (1.23, 2.10)	207/527	0.66 (0.49, 0.88)
Aggressive tumors	249/1591		249/1591		249/1591	
1st	58/536	0.53 (0.37, 0.77)	61/561	0.76 (0.51, 1.13)	43/268	1.23 (0.79, 1.91)
2nd	88/550	1.00 (reference)	56/433	1.00 (reference)	55/347	1.00 (reference)
3rd	76/399	1.40 (0.99, 1.97)	60/310	1.43 (0.96, 2.14)	70/449	0.86 (0.58, 1.27)
4th	27/106	2.10 (1.28, 3.46)	72/287	1.86 (1.27, 2.74)	81/527	0.64 (0.42, 0.98)
p-heterogeneity		0.39		0.56		0.76

p-interactions by menopausal status/hormone therapy: 0.80 for percent density, 0.91 for absolute dense area, and 0.36 for non-dense area

Adjusted for age, body mass index, and study site

CI confidence interval, *E−* estrogen only therapy, *E+P* combined estrogen+progesterone therapy, *OR* odds ratio

[a] Defined categories for percent density (0–10, 11–25, 26–50, and ≥51%) and quartiles for absolute dense and non-dense areas

it may suggest that the breast tissue environment underlying high breast density allows for more growth and increased proliferation, than in more fatty breasts. In addition, since mammographic sensitivity decreases with increasing density, aggressive cancers occurring in denser breasts may go undetected for a longer period of time permitting these already rapidly proliferating tumors to be larger at presentation [50–53]. A recent study by Kerlikowske et al. [15] found a stronger association of BI-RADS-defined breast density with the risk of more advanced stage of disease, mostly among postmenopausal women taking estrogen and progesterone hormone therapy, consistent with our suggestive findings in this study subgroup. In contrast to our study, this study used the TNM system based on the criteria of the American Joint Committee on Cancer to define advance disease stage (stage I or IIA: early-stage invasive cancer; IIB, III, or IV: late stage invasive cancer) [54]. This classification, however, does not take into account tumor grade and ER status, important characteristics reflective of tumor aggressiveness that has been consistently linked to less favorable tumor subtypes and worse patient outcomes [19–25]. Tumor grade has been incorporated in prognostic algorithms for treatment decision making [55] and has been shown to correlate with molecular signatures of the tumor (genetic, transcriptomic, and microarray-based genomic) [56–59]. Our current approach for classification of tumor subtypes accounts for various tumor features using their combination rather than individual characteristics and incorporates important information on tumor grade.

We found no evidence of interaction between menopausal status/current hormone use and breast density on tumor aggressiveness in the overall analysis. Kerlikowske and colleagues [15] found a stronger association of high breast density estimated by BI-RADS with breast cancer in premenopausal women and postmenopausal hormone users compared with postmenopausal women not on hormones. The study included invasive and in situ breast cancers identified among participants from seven mammography registries that participate in the Breast Cancer Surveillance Consortium [15]. The comparison of associations between breast density and tumor stage by menopausal status and postmenopausal hormone use included 10,514 invasive breast cancer cases with complete information on important study variables. The analysis in this study, however, was not stratified by the type of the current HT. The differences in our findings may be due to limited power in the current analysis. In our recent analysis from Nurses' Health Study, which is included in the sample here, the association between percent density and breast cancer risk appeared to be stronger in premenopausal women than in postmenopausal women without postmenopausal hormone use history and appeared to be stronger in postmenopausal women currently using hormones compared to

postmenopausal women who never used postmenopausal hormones or with past hormone use [16]. That study, however, did not examine different regimens of current therapy use and our current analysis did not include a separate category for past hormone users, limiting our comparison.

Strengths of this study include data from four established prospective cohorts with comprehensive follow-up, breast cancer risk factors, tumor characteristics, and standardized breast density estimates. Use of matching in the four nested case–control studies utilized in the current investigation allows us to minimize the potential confounding effect of selected factors. This study also has a few limitations. We pooled data from four different studies, which varied in study design, population characteristics, geography, and calendar year. Our study used clinical pathology information and not centralized pathology review. However, we found no evidence of between-study heterogeneity in our results and all analyses were adjusted for the study site. The study population was predominantly white which might reduce generalizability of the findings to non-Caucasian populations. We excluded women who did not have information on tumor characteristics, menopausal status, or hormone use but these were not materially different from those included in analyses. Finally, insufficient data on the tumor detection method (screening-detected vs. interval-detected cancer) did not allow us to clarify the extent to which our observations reflect delays in diagnosis rather than tumor biology.

In conclusion, we investigated the associations of mammographic breast density with breast cancer risk by combination of tumor's aggressiveness features and woman's menopausal status/current hormone therapy. Our results suggest that percent mammographic breast density is positively associated with the tumor aggressiveness while non-dense area is potentially inversely associated with the aggressiveness of tumors. These differences may be more prominent among postmenopausal women currently using estrogen and progesterone. Further studies are warranted to explain underlying biological processes and elucidate the possible pathways from high breast density to the aggressive subtypes of breast carcinomas. If our results are confirmed in subsequent investigations, the findings would suggest that early detection in this subgroup might be especially important to optimize breast cancer survival.

Acknowledgements This study was supported by the National Institutes of Health (Grant Numbers CA140286 to C. M.V. and K.K., CA087969 to R.M.T., UM1 CA176726 to W.W., UM1 CA186107 to M.S.), Mayo Clinic Specialized Program of Research Excellence (SPORE) in Breast Cancer (Grant Number P50 CA116201 to M.P.G. and J.N.I.), Mayo Clinic Cancer Center, and Breast Cancer Research Foundation. We would like to thank the participants and staff of the NHS and NHSII for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data.

Compliance with ethical standards

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

Conflict of interest The authors declare that they have no conflict of interest.

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