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ORIGINAL RESEARCH

# Mammographic density parameters and breast cancer tumor characteristics among postmenopausal women

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**Purpose:** Mammographic density is an important breast cancer risk factor, although it is not clear whether the association differs across breast cancer tumor subtypes. We examined the association between indicators of mammographic density and breast cancer risk by tumor subtype among postmenopausal women by investigating heterogeneity across tumor characteristics.

**Methods:** Mammographic density measures were determined for 477 breast cancer cases and 588 controls, all postmenopausal, in Vancouver, British Columbia, using digitized screening mammograms and Cumulus software. Mammographic dense (DA), non-dense (NDA), and percent dense (PDA) areas were treated as continuous covariates and categorized into quartiles according to the distribution in controls. For cases only, tests for heterogeneity between tumor subtypes were assessed by multinomial logistic regression. Associations between mammographic density and breast cancer risk were modeled for each subtype separately through unconditional logistic regression.

**Results:** Heterogeneity was apparent for the association of PDA with tumor size ($p$-heterogeneity=0.04). Risk did not differ across the other assessed tumor characteristics ($p$-heterogeneity values >0.05).

**Conclusion:** These findings do not provide strong evidence that mammographic density parameters differentially affect specific breast cancer tumor characteristics.

**Keywords:** mammographic density, breast cancer, tumor characteristics, heterogeneity, multinomial logistic regression

## Introduction

Mammographic density is an important breast cancer risk factor.[1–3] The association between breast cancer and many well-established risk factors has been shown to be different according to the characteristics of the tumor.[4–11] However, for mammographic density, this has not been established. Some studies report no heterogeneity in the association between mammographic density and breast cancer tumor characteristics;[12–22] while others indicate differences by hormone receptor status,[3,23–28] invasiveness,[22,29] phenotype,[30,31] tumor size,[22,26,28,32,33] and stage.[34] Most studies have limited the assessment of mammographic density qualitatively as defined by the BI-RADS classification, or quantitatively as percent dense area (PDA); the other mammographic density parameters, dense area (DA) and non-dense area (NDA) have seldom been taken into account.

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It is important to elucidate whether mammographic density parameters are associated differentially across different breast cancer tumor characteristics. Such knowledge could help us understand pathological pathways, as well as identify susceptible groups of women in the general population, providing evidence that would improve the formulation of screening protocols and risk-reducing interventions.[35]

# Materials and methods

## Study population

The examined data originate from the British Columbia (BC) study subpopulation belonging to the Canadian Breast Cancer Study (CBCS).[36] Incident female breast cancer cases aged 40 to 80 years diagnosed between 2005 and 2009 were recruited from the BC Cancer Registry; controls were enrolled from the Screening Mammography Program, from the same geographic area, and frequency-matched to cases in 5-year age groups. Participation was 54% among cases and 57% amid controls. This study was restricted to postmenopausal participants: 606 cases and 595 controls. The final sample, determined by the availability of screening film mammograms, was comprised of 477 cases and 588 controls. A questionnaire was used to collect information about personal characteristics and medical history.

## Mammographic density measurement

Briefly, as it has been previously described,[37] the most recent normal mammogram preceding recruitment into the study was selected for each participant. It was not possible to locate mammograms prior to study enrollment for 92 controls, so the mammogram after study enrollment, but closest to that date was chosen (average 2.3 years after enrollment, SD=0.7). The contralateral breast was selected for cases; for controls, the side was chosen at random. Mammograms were digitized using the same device (iCAD TotalLook Mammo Advantage); the craniocaudal view was used in all instances. Total breast area and DA were determined by using the interactive thresholding method,[38] via Cumulus software (Imaging Research Program, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada), by a blinded single reader (HAVG).

## Breast tumor characteristics assessment

The methodology has been outlined before;[35] in summary, among cases, information about tumor characteristics such as invasiveness, histology, size, breast cancer stage, estrogen receptor (ER), progesterone receptor (PR), and human epidermal factor receptor 2 (HER2) status was obtained from the BC Cancer Registry and BC Breast Cancer Outcomes Unit. ER status was defined from immunohistochemistry (IHC) results, classified into one of six categories: negative, weakly positive, moderately positive, strongly positive, receptors tested but not sufficient quantity for interpretation or borderline/equivocal and not tested. Tumors classified as weakly, moderately or strongly positive were identified as ER-positive. PR status was determined through IHC testing using the same methodology as the ER analysis. HER2 status was evaluated with IHC; scores 0 to 1+ were interpreted as negative, 2+ as borderline, and 3+ as positive. HER2 IHC borderline results were further discriminated through fluorescence in situ hybridization (FISH); a FISH result of more than 6.0 HER2 gene copies per nucleus was considered positive.

## Statistical analysis

Mammographic density parameters were analyzed as continuous covariates (DA and NDA expressed in terms of $cm^2$, the percentage for PDA) and categorized into quartiles according to the distribution in controls. Since data-driven methods for the selection of confounders are susceptible to generate biased estimation of the effect of the exposure of interest,[39] a direct acyclic diagram (DAG) was used to identify minimally sufficient adjustment sets of variables in the path between mammographic density parameters and breast cancer,[40,41] through DAGgity[42] (details can be found at Velásquez García et al).[37] Even though the resulting number of the adjustment variables is relatively large, which results in diminished statistical power, the implementation of a minimally sufficient adjustment set in the models provides the best trade between statistical power loss and estimation with reduced bias. The Akaike information criterion was used to find the best characterization of the adjustment set variables in the models, as follows: body mass index (BMI) (continuous), age (continuous), education (high school or less, college or trade certificate, undergraduate degree, graduate or professional degree), ethnicity (European, East Asian, Filipino, South Asian, mixed or other), age at menarche (continuous), age at first full-term pregnancy (never, younger than 20 years, 20–29 years, 30–39 years, older than 40 years), parity (yes, no), lifetime breastfeeding (continuous), use of oral contraceptives (never, <4.5 years, 4.5–10 years, >10 years), family history of breast cancer (positive, negative),

HRT (hormone replacement therapy: never, <5 years, 5–12 years, >12 years), lifetime smoking (continuous), and alcohol consumption (continuous). In addition, an age by BMI interaction term (continuous) was incorporated in all models, to allow the associations of breast cancer risk and BMI to be subject to age, as suggested by Baglietto et al.[2]

Tests for heterogeneity between subtypes for each of the tumor characteristic were assessed by multinomial logistic regression utilizing breast cancer cases only.[43,44] Adjusted odds ratios (aOR) and 95% CI were computed to estimate the associations between mammographic density parameters and breast cancer risk for each subtype separately using unconditional logistic regression, adjusted for the previously described variables. Trend tests were conducted by entering the relevant ordinal variable as a continuous variable into the model. Values were missing for some variables in 0.5–5.6% of the cases, and in 0.1–3.3% of controls;[37] missing values were imputed via multiple imputations by chained equations (five iterations), present in the *mice* R package.[45] Evaluations were also conducted after eliminating observations with missing values. Analyses were performed using Stata v.14.0 (Stata Corporation, College Station, TX, USA). All statistical tests were two-sided; the critical level of significance was set at 5%.

## Results

Table 1 shows the characteristics of the study participants according to case or control status. Table 2 indicates the distribution of tumor characteristics for cases: over 75% were invasive cancers, with most in the 1.1–2.0 cm size category (n=145, 39.2%), and stage I (n=189, 39.6%). As expected in a population-based study, over 80% of tumors were histologically ductal (n=310, 83.8%), ER positive (n=287, 77.6%), PR positive (n=212, 57.3%), and HER2 negative (n=265, 71.6%). Tumor characteristics evaluated in association with mammographic density were invasiveness and stage and, for invasive cases only, tumor size, histology, and receptor status were also considered.

Overall, when comparing the highest quartile with the lowest, DA (aOR=2.6, 95% CI 1.8–3.8, $p$-trend<0.001) and PDA (aOR=3.8, 95% CI 2.5–5.9, $p$-trend <0.001) were found directly associated to breast cancer in fully adjusted models; NDA (aOR=0.5, 95% CI 0.3–0.8, $p$-trend=0.025) was inversely related to breast cancer, controlling for the adjustment set variables. Similar results in terms of directions of the associations were obtained when using continuous values in the models (estimates for a 10-unit change in mammographic parameter value: DA, aOR=1.4, 95% CI 1.3–1.5, $p$-trend<0.001; PDA, aOR=1.4, 95% CI 1.3–1.6, $p$-trend<0.001; NDA, aOR=0.94, 95% CI 0.91–0.97, $p$-trend<0.001).

The results of the tests of heterogeneity among cases only, as well as the estimates of the associations between mammographic density parameters and breast cancer risk stratified by tumor characteristics, are shown in Table 3. Heterogeneity was found in the analyses by quartiles only for the association of PDA with tumor size ($p$-heterogeneity=0.04), and risk did not differ across the other assessed tumor characteristics ($p$-heterogeneity values >0.05). Sensitivity analyses eliminating observations with imputed values, as well as excluding the controls with breast density measured from mammograms taken after study enrollment, produced similar results (not shown). However, heterogeneity was found when assessing the association between PR status and PDA when observations with missing values eliminated ($p$-heterogeneity=0.01), as well as when using continuous values for mammographic density parameters ($p$-heterogeneity=0.016) in the main analyses with imputed values.

## Discussion

In this population-based case–control study, a consistent association between mammographic density and breast cancer risk was observed. The measured mammographic density parameters were found to be important risk factors for breast cancer in all tumor types. DA and PDA were confirmed as independent risk factors directly associated with breast cancer; NDA was also found to be an independent factor, inversely associated with breast cancer risk. Our observations indicate that these associations do not vary according to breast cancer tumor characteristics, which is in agreement with various previous reports.[12–20] However, the relatively small sample size of some subgroups (like ER negative or HER2 positive), as well as the inconsistent results regarding PR status heterogeneity in relation to PDA when performing sensitivity analyses, suggests that our study could be underpowered.

In this study, the purpose was not to evaluate absolute breast cancer subtype risk; instead, we estimated the relative risk (aOR) of cancer subtypes according to the value for breast density. In this way, OR can be calculated from a case–control study without knowledge of the exposure prevalence.

**Table 1** Characteristics of study population

| Variables[a] | | Cases (N=477) Mean (SD)/N (%) | Controls (N=588) Mean (SD)/N (%) |
|---|---|---|---|
| Age at study entry (years) | | 64.0 (7.7) | 62.9 (7.9) |
| Age at mammogram (years) | | 60.9 (7.7) | 63.0 (8.0) |
| Age at first mammogram (years) | | 47.7 (7.6) | 47.0 (6.8) |
| Ethnicity | European | 305 (63.9%) | 465 (79.1%) |
| | East Asian | 113 (23.7%) | 61 (10.3%) |
| | Filipino | 24 (5.1%) | 20 (3.4%) |
| | South Asian | 22 (4.6%) | 23 (3.9%) |
| | Mixed/Other | 13 (2.7%) | 19 (3.3%) |
| Education | High school or less | 197 (41.3%) | 180 (30.6%) |
| | College/trade certificate | 132 (27.7%) | 169 (28.7%) |
| | Undergraduate degree | 97 (20.3%) | 121 (20.6%) |
| | Graduate/professional degree | 51 (10.7%) | 118 (20.1%) |
| BMI (kg/m$^2$) 2 years before study entry | | 26.3 (5.1) | 25.1 (4.7) |
| Family history of breast cancer (%) | | 117 (24.5%) | 90 (15.3%) |
| Age at menarche (years) | | 13.0 (1.6) | 12.9 (1.5) |
| Ever been pregnant (yes) | | 370 (77.6%) | 443 (75.3%) |
| Age at first pregnancy (years)[b] | | 26.2 (5.5) | 25.8 (4.9) |
| Parity[b] | | 2.3 (1.1) | 2.4 (1.0) |
| Ever breastfed[b] (%) | | 367 (99.2%) | 439 (99.1%) |
| Lifetime breastfeeding[b] (months) | | 6.3 (5.1) | 7.1 (5.0) |
| Oral contraceptive use (years) | Never | 239 (50.1%) | 249 (42.4%) |
| | <4.5 years | 98 (20.5%) | 133 (22.6%) |
| | 4.5–10 years | 90 (18.9%) | 132 (22.4%) |
| | >10 years | 50 (10.5%) | 74 (12.6%) |
| HRT use (years) | Never | 286 (60.0%) | 343 (58.3%) |
| | <5 years | 62 (13.0%) | 85 (14.5%) |
| | 5–12 years | 84 (17.6%) | 101 (17.2%) |
| | >12 years | 45 (9.4%) | 59 (10.0%) |
| Nonsteroidal anti-inflammatory drugs use (years) | Never | 349 (73.2%) | 399 (67.9%) |
| | <2.34 years | 43 (9.0%) | 70 (11.9%) |
| | 2.34–8.5 years | 46 (9.6%) | 56 (9.5%) |
| | >8.5 years | 39 (8.2%) | 63 (10.7%) |
| Smoking (pack/years) | | 6.7 (13.7) | 6.4 (12.4) |
| Alcohol consumption (drinks/week) | | 2.8 (5.1) | 2.0 (5.0) |
| Dense area (cm$^2$) | | 20.68 (14.91) | 15.80 (11.81) |
| Non-dense area (cm$^2$) | | 113.34 (62.76) | 117.81 (62.28) |
| Percent dense area (%) | | 17.41 (10.94) | 14.40 (11.89) |

**Notes:** [a]Missing values were present in the following variables: BMI (0.5% of cases and 0.1% of controls), age at first full-term pregnancy (0.8% of cases and 3.3% of controls), lifetime breastfeeding (1.4% of cases and 1.1% of controls), use of oral contraceptives (2.1% of cases and 1.9% of controls), family history of breast cancer (5.6% of cases and 3.1% of controls), HRT (2.3% of cases and 2.5% of controls), lifetime smoking (0.7% of cases and controls), and alcohol consumption (0.7% of cases and 3.3% of controls). [b]Among parous women. Adapted by permission from Springer Nature: *Breast Cancer Res Treat*, Velásquez García HA, Sobolev BG, Gotay CC, et al, Mammographic non-dense area and breast cancer risk in postmenopausal women: a causal inference approach in a case–control study, 2018;170:159–168,[37] Copyright 2018.
**Abbreviation:** BMI, body mass index.

A strength of this study is that we opted for the DAG approach to select the covariates for adjustment, minimizing in this way the magnitude of the bias in our estimations.[46,47] Furthermore, the considerable amount of participants' information gathered in the CBCS made it possible to adjust for the identified minimally sufficient set. Another strength is the inclusion of in situ cases which enables the examination of previously reported differences in the association between mammographic density and invasiveness.[22,28] Other strengths are the

**Table 2** Distribution of tumor characteristics on cases

| Characteristic | | N (%) |
|---|---|---|
| Invasiveness | In situ | 107 (23.26) |
| | Invasive | 370 (76.74) |
| Breast cancer stage | 0 | 107 (22.43) |
| | I | 189 (39.62) |
| | II | 116 (24.32) |
| | III | 41 (8.60) |
| | IV | 7 (1.47) |
| | Unknown | 17 (3.56) |
| Histology[a] | Ductal | 310 (83.78) |
| | Lobular | 26 (7.03) |
| | Mixed | 11 (2.97) |
| | Other | 23 (6.22) |
| Tumor size[a] | <1.1 cm | 100 (27.03) |
| | 1.1–2.0 cm | |
| | >2.0 cm | |
| | 1.1–2.0 cm | 145 (39.19) |
| | >2.0 cm | |
| | >2.0 cm | 106 (28.65) |
| | >2.0 cm | |
| | Unknown | 19 (5.14) |
| ER status[a] | Positive | 287 (77.57) |
| | Negative | 66 (17.84) |
| | Unknown | 17 (4.59) |
| PR status[a] | Positive | 212 (57.30) |
| | Negative | 141 (38.11) |
| | Unknown | 17 (4.59) |
| HER2 status[a] | Positive | 88 (23.78) |
| | Negative | 265 (71.62) |
| | Unknown | 17 (4.59) |
| Phenotype group[a] (ER\|PR+ vs ER&PR-) | ER\|PR+ | 290 (78.38) |
| | ER&PR- | 63 (17.03) |
| | Unknown | 17 (4.59) |

**Note:** [a]Invasive cases only.
**Abbreviations:** ER, estrogen receptor; PR, progesterone receptor.

objective assessment of mammographic density via computer-assisted thresholding, and the use of craniocaudal views to limit the inclusion of subcutaneous fat in the mammographic density readings.[48]

Another limitation to be considered is the fact that, given the participation rates of the original study, potential response bias could be present in the information gathered through the questionnaire, used in the models' adjustment set. However, CBSC estimates for known breast cancer risk factors are similar to those published in other epidemiological studies,[36] indicating that important levels of biases are most likely not present. In addition, as mammographic density measurements are not usually revealed to screening participants in BC, it is implausible that breast density influenced enrolment in the study. Last, replication using larger independent datasets is necessary to confirm these results.

## Conclusion

In conclusion, our findings indicate that mammographic density parameters, although important risk factors for breast cancer, are not differentially associated with breast cancer tumor characteristics.

## Abbreviations

aOR, adjusted odds ratio; BC, British Columbia; BMI, body mass index; CBCS, Canadian Breast Cancer Study; DA, mammographic dense area; DAG, directed acyclic graph; ER, estrogen receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal factor receptor 2; HRT, hormone replacement therapy; IHC, immunohistochemistry; NDA, mammographic non-dense area; PDA, mammographic percent dense area; PR, progesterone receptor.

## Ethics approval and informed consent

Ethical approval for this study was provided by the University of British Columbia, British Columbia Cancer Agency Research Ethics Board (reference #H14-01614).

## Data availability

The analyzed datasets are available from the corresponding author on reasonable request.

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**Table 3** Associations of mammographic density parameters stratified by breast cancer tumor characteristics in postmenopausal women

| | Quartile | Controls | Dense area[a] | | | Non-dense area[b] | | | Percent dense area | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cases | aOR (95% CI) | *p*-trend | Cases | aOR (95% CI) | *p*-trend | Cases | aOR (95% CI) | *p*-trend |
| **Overall** | 1 | 147 | 86 | Reference | **<0.001** | 144 | Reference | **0.025** | 76 | Reference | **<0.001** |
| | 2 | 147 | 92 | 1.13 (0.75–1.71) | | 106 | 0.76 (0.51–1.12) | | 78 | 1.29 (0.84–1.99) | |
| | 3 | 147 | 107 | 1.34 (0.89–2.01) | | 112 | 0.75 (0.49–1.16) | | 154 | 3.09 (2.04–4.69) | |
| | 4 | 147 | 192 | 2.55 (1.74–3.73) | | 115 | 0.52 (0.31–0.85) | | 169 | 3.84 (2.48–5.95) | |
| | Continuous | 588 | **477** | 1.39 (1.25–1.54)◊ | **<0.001** | | 0.94 (0.91–0.97)◊ | **<0.001** | | 1.44 (1.26–1.64)◊ | **<0.001** |
| **Invasiveness** | | | | | | | | | | | |
| **In situ** | 1 | 147 | 23 | Reference | 0.075 | 46 | Reference | **0.022** | 15 | Reference | **0.001** |
| | 2 | 147 | 21 | 1.02 (0.50–2.07) | | 26 | 0.75 (0.40–1.39) | | 15 | 1.16 (0.51–2.62) | |
| | 3 | 147 | 26 | 1.12 (0.56–2.25) | | 16 | 0.39 (0.18–0.84) | | 34 | 2.81 (1.33–5.97) | |
| | 4 | 147 | 37 | 1.75 (0.92–3.36) | | 19 | 0.41 (0.17–0.98) | | 43 | 3.31 (1.51–7.29) | |
| | Continuous | 588 | 107 | 1.26 (1.06–1.49)◊ | **0.010** | | 0.91 (0.86–0.97)◊ | **0.003** | | 1.31 (1.07–1.61)◊ | **0.010** |
| **Invasive** | 1 | 147 | 63 | Reference | **<0.001** | 98 | Reference | 0.148 | 61 | Reference | **<0.001** |
| | 2 | 147 | 71 | 1.21 (0.77–1.89) | | 80 | 0.78 (0.51–1.20) | | 63 | 1.38 (0.85–2.19) | |
| | 3 | 147 | 81 | 1.48 (0.94–2.31) | | 96 | 0.91 (0.57–1.46) | | 120 | 3.22 (2.05–5.06) | |
| | 4 | 147 | 155 | 2.84 (1.88–4.29) | | 96 | 0.59 (0.34–1.00) | | 126 | 4.08 (2.54–6.56) | |
| | Continuous | 588 | 370 | 1.43 (1.28–1.60)◊ | **<0.001** | | 0.95 (0.91–0.98)◊ | **0.002** | | 1.46 (1.27–1.68)◊ | **<0.001** |
| **Invasiveness *p*-heterogeneity*** | | | 0.157 \| 0.337 | | | 0.218 \| 0.275 | | | 0.689 \| 0.566 | | |
| **Histology** (restricted to ductal and lobular invasive subtypes) | | | | | | | | | | | |
| **Ductal** | 1 | 147 | 56 | Reference | **<0.001** | 85 | Reference | 0.146 | 54 | Reference | **<0.001** |
| | 2 | 147 | 63 | 1.18 (0.74–1.90) | | 67 | 0.76 (0.48–1.20) | | 53 | 1.39 (0.85–2.28) | |
| | 3 | 147 | 61 | 1.27 (0.78–2.05) | | 78 | 0.84 (0.51–1.38) | | 97 | 2.99 (1.86–4.83) | |
| | 4 | 147 | 130 | 2.72 (1.76–4.19) | | 80 | 0.58 (0.32–1.02) | | 106 | 3.87 (2.34–6.38) | |
| | Continuous | 588 | 310 | 1.41 (1.25–1.58) | **<0.001** | | 0.94 (0.91–0.98) | **0.002** | | 1.45 (1.25–1.68) | **<0.001** |
| **Lobular** | 1 | 147 | 3 | Reference | **0.008** | 7 | Reference | 0.921 | 4 | Reference | **0.006** |
| | 2 | 147 | 4 | 1.41 (0.28–7.16) | | 5 | 0.89 (0.24–3.27) | | 2 | 0.61 (0.10–3.85) | |
| | 3 | 147 | 5 | 2.04 (0.43–9.67) | | 8 | 1.20 (0.32–4.44) | | 9 | 3.67 (0.89–15.20) | |
| | 4 | 147 | 14 | 4.91 (1.24–19.56) | | 6 | 0.99 (0.21–4.76) | | 11 | 5.08 (1.13–22.80) | |
| | Continuous | 588 | 26 | 1.49 (1.12–1.98)◊ | **0.006** | | 0.98 (0.88–1.09)◊ | 0.657 | | 1.43 (1.01–2.04)◊ | **0.044** |
| **Histology *p*-heterogeneity*** | | | 0.279 \| 0.362 | | | 0.590 \| 0.984 | | | 0.403 \| 0.493 | | |

(*Continued*)

**Table 3** (Continued).

| | Quartile | Controls | Dense area[a] | | | Non-dense area[b] | | | Percent dense area | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cases | aOR (95% CI) | *p*-trend | Cases | aOR (95% CI) | *p*-trend | Cases | aOR (95% CI) | *p*-trend |
| **Tumor size** (missing for 19 invasive cases) | | | | | | | | | | | |
| **<1.1 cm** | 1 | 147 | 23 | Reference | 0.094 | 22 | Reference | 0.336 | 25 | Reference | 0.179 |
| | 2 | 147 | 20 | 0.91 (0.45–1.83) | | 20 | 1.05 (0.50–2.21) | | 18 | 0.73 (0.36–1.52) | |
| | 3 | 147 | 20 | 0.93 (0.46–1.89) | | 29 | 1.49 (0.68–3.29) | | 31 | 1.58 (0.81–3.11) | |
| | 4 | 147 | 37 | 1.65 (0.87–3.12) | | 29 | 1.38 (0.57–3.37) | | 26 | 1.38 (0.66–2.92) | |
| | Continuous | 588 | 100 | 1.27 (1.05–1.52)◊ | **0.011** | | 1.00 (0.95–1.06)◊ | 0.870 | | 1.16 (0.92–1.45)◊ | 0.213 |
| **1.1–2.0 cm** | 1 | 147 | 22 | Reference | **<0.001** | 41 | Reference | 0.139 | 20 | Reference | **<0.001** |
| | 2 | 147 | 26 | 1.39 (0.71–2.69) | | 27 | 0.60 (0.33–1.10) | | 22 | 1.77 (0.86–3.63) | |
| | 3 | 147 | 33 | 1.95 (1.02–3.72) | | 42 | 0.93 (0.50–1.72) | | 47 | 4.30 (2.20–8.40) | |
| | 4 | 147 | 64 | 3.46 (1.92–6.22) | | 35 | 0.46 (0.22–0.97) | | 56 | 6.95 (3.40–14.21) | |
| | Continuous | 588 | 145 | 1.50 (1.29–1.73)◊ | **<0.001** | | 0.92 (0.88–0.97)◊ | **0.002** | | 1.56 (1.29–1.87)◊ | **<0.001** |
| **>2.0 cm** | 1 | 147 | 17 | Reference | **<0.001** | 26 | Reference | 0.247 | 16 | Reference | **<0.001** |
| | 2 | 147 | 20 | 1.61 (0.76–3.44) | | 26 | 0.90 (0.47–1.76) | | 20 | 2.36 (1.06–5.27) | |
| | 3 | 147 | 21 | 1.85 (0.86–3.97) | | 22 | 0.72 (0.34–1.55) | | 32 | 5.28 (2.38–11.71) | |
| | 4 | 147 | 48 | 4.22 (2.11–8.41) | | 32 | 0.61 (0.26–1.43) | | 38 | 7.58 (3.30–17.42) | |
| | Continuous | 588 | 106 | 1.51 (1.29–1.77)◊ | **<0.001** | | 0.95 (0.90–1.00)◊ | 0.071 | | 1.53 (1.25–1.88)◊ | **<0.001** |
| **Tumor size *p*-heterogeneity*** | | | 0.638 \| 0.353 | | | 0.379 \| 0. 306 | | | **0.044** \| 0.163 | | |
| **Breast cancer stage** (missing for 17 cases) | | | | | | | | | | | |
| **Stage 0** | 1 | 147 | 23 | Reference | 0.075 | 46 | Reference | **0.022** | 15 | Reference | **0.001** |
| | 2 | 147 | 21 | 1.02 (0.50–2.07) | | 26 | 0.75 (0.40–1.39) | | 15 | 1.16 (0.51–2.62) | |
| | 3 | 147 | 26 | 1.12 (0.56–2.25) | | 16 | 0.39 (0.18–0.84) | | 34 | 2.81 (1.33–5.97) | |
| | 4 | 147 | 37 | 1.75 (0.92–3.36) | | 19 | 0.41 (0.17–0.98) | | 43 | 3.31 (1.51–7.29) | |
| | Continuous | 588 | 107 | 1.26 (1.05–1.49)◊ | **0.010** | | 0.91 (0.85–0.97)◊ | **0.003** | | 1.31 (1.07–1.61)◊ | **0.010** |
| **Stage I** | 1 | 147 | 38 | Reference | **0.001** | 47 | Reference | 0.737 | 37 | Reference | **<0.001** |
| | 2 | 147 | 35 | 0.96 (0.55–1.68) | | 36 | 0.74 (0.42–1.29) | | 30 | 0.97 (0.54–1.76) | |
| | 3 | 147 | 40 | 1.23 (0.71–2.14) | | 54 | 1.02 (0.57–1.83) | | 64 | 2.67 (1.55–4.59) | |
| | 4 | 147 | 76 | 2.15 (1.30–3.54) | | 52 | 0.76 (0.39–1.49) | | 58 | 2.74 (1.52–4.94) | |
| | Continuous | 588 | 189 | 1.34 (1.17–1.53)◊ | **<0.001** | | 0.96 (0.92–1.00)◊ | 0.081 | | 1.33 (1.12–1.58)◊ | **0.001** |

(*Continued*)

**Table 3** (Continued).

| | Quartile | Controls | Dense area[a] | | | Non-dense area[b] | | | Percent dense area | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cases | aOR (95% CI) | *p*-trend | Cases | aOR (95% CI) | *p*-trend | Cases | aOR (95% CI) | *p*-trend |
| **Stage II** | 1 | 147 | 19 | Reference | **<0.001** | 29 | Reference | 0.285 | 19 | Reference | **<0.001** |
| | 2 | 147 | 23 | 1.55 (0.76–3.16) | | 31 | 1.09 (0.57–2.05) | | 24 | 2.01 (0.97–4.17) | |
| | 3 | 147 | 22 | 1.55 (0.74–3.21) | | 22 | 0.78 (0.37–1.68) | | 29 | 3.25 (1.54–6.86) | |
| | 4 | 147 | 52 | 3.80 (1.98–7.29) | | 34 | 0.66 (0.28–1.51) | | 44 | 5.99 (2.79–12.83) | |
| | Continuous | 588 | 116 | 1.52 (1.30–1.78)◊ | **<0.001** | | 0.95 (0.90–1.00)◊ | 0.075 | | 1.54 (1.26–1.88)◊ | **<0.001** |
| **Stage III and IV** | 1 | 147 | 5 | Reference | **<0.001** | 14 | Reference | 0.298 | 5 | Reference | **<0.001** |
| | 2 | 147 | 9 | 2.17 (0.64–7.30) | | 7 | 0.42 (0.15–1.23) | | 7 | 2.96 (0.79–11.03) | |
| | 3 | 147 | 12 | 3.74 (1.14–12.19) | | 17 | 1.01 (0.39–2.65) | | 17 | 8.69 (2.53–29.76) | |
| | 4 | 147 | 22 | 5.14 (1.72–15.33) | | 10 | 0.36 (0.10–1.27) | | 19 | 12.64 (3.42–46.64) | |
| | Continuous | 588 | 48 | 1.55 (1.25–1.92)◊ | **<0.001** | | 0.93 (0.85–1.01)◊ | 0.082 | | 1.56 (1.17–2.07)◊ | **0.002** |
| **Breast cancer stage *p*-heterogeneity*** | | | 0.349 \| 0.488 | | | 0.338 \| 0.451 | | | 0.516 \| 0.390 | | |
| **ER status** (missing for 17 invasive cases) | | | | | | | | | | | |
| **Negative** | 1 | 147 | 11 | Reference | **0.004** | 15 | Reference | 0.634 | 13 | Reference | **0.005** |
| | 2 | 147 | 15 | 1.60 (0.67–3.82) | | 12 | 0.97 (0.29–2.38) | | 9 | 0.97 (0.37–2.54) | |
| | 3 | 147 | 11 | 1.32 (0.52–3.35) | | 20 | 1.45 (0.59–3.59) | | 23 | 2.99 (1.27–7.03) | |
| | 4 | 147 | 29 | 3.15 (1.41–7.02) | | 19 | 1.11 (0.38–3.22) | | 21 | 2.92 (1.15–7.40) | |
| | Continuous | 588 | 66 | 1.44 (1.19–1.73)◊ | **<0.001** | | 0.97 (0.90–1.04)◊ | 0.354 | | 1.40 (1.10–1.80)◊ | **0.007** |
| **Positive** | 1 | 147 | 51 | Reference | **<0.001** | 75 | Reference | 0.184 | 48 | Reference | **<0.001** |
| | 2 | 147 | 52 | 1.13 (0.69–1.84) | | 62 | 0.77 (0.49–1.23) | | 52 | 1.43 (0.86–2.38) | |
| | 3 | 147 | 63 | 1.50 (0.93–2.43) | | 73 | 0.92 (0.55–1.51) | | 87 | 3.10 (1.89–5.08) | |
| | 4 | 147 | 121 | 2.74 (1.76–4.28) | | 77 | 0.60 (0.34–1.07) | | 100 | 4.23 (2.52–7.10) | |
| | Continuous | 588 | 287 | 1.43 (1.27–1.61)◊ | **<0.001** | | 0.95 (0.92–0.99)◊ | **0.009** | | 1.44 (1.24–1.68)◊ | **<0.001** |
| **ER status *p*-heterogeneity*** | | | 0.639 \| 0.835 | | | 0.224 \| 0.707 | | | 0.281 \| 0.631 | | |
| **PR status** (missing for 17 invasive cases) | | | | | | | | | | | |
| **Negative** | 1 | 147 | 20 | Reference | **<0.001** | 46 | Reference | 0.098 | 18 | Reference | **<0.001** |
| | 2 | 147 | 23 | 1.14 (0.57–2.28) | | 28 | 0.62 (0.34–1.12) | | 20 | 1.74 (0.82–3.70) | |
| | 3 | 147 | 34 | 1.89 (0.98–3.65) | | 35 | 0.75 (0.40–1.42) | | 46 | 4.75 (2.35–9.60) | |
| | 4 | 147 | 64 | 3.34 (1.82–6.11) | | 32 | 0.45 (0.20–0.99) | | 57 | 6.58 (3.15–13.77) | |
| | Continuous | 588 | 141 | 1.51 (1.31–1.75)◊ | **<0.001** | | 0.92 (0.87–0.97)◊ | **0.002** | | 1.59 (1.32–1.91)◊ | **<0.001** |

(*Continued*)

**Table 3** (Continued).

| | Quartile | Controls | Dense area[a] | | | Non-dense area[b] | | | Percent dense area | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cases | aOR (95% CI) | *p*-trend | Cases | aOR (95% CI) | *p*-trend | Cases | aOR (95% CI) | *p*-trend |
| **Positive** | 1 | 147 | 42 | Reference | **<0.001** | 44 | Reference | 0.938 | 43 | Reference | **<0.001** |
| | 2 | 147 | 44 | 1.29 (0.76–2.19) | | 46 | 0.99 (0.58–1.70) | | 41 | 1.31 (0.76–2.25) | |
| | 3 | 147 | 40 | 1.32 (0.76–2.27) | | 58 | 1.23 (0.69–2.17) | | 64 | 2.59 (1.52–4.41) | |
| | 4 | 147 | 86 | 2.64 (1.61–4.30) | | 64 | 0.89 (0.47–1.69) | | 64 | 3.26 (1.86–5.73) | |
| | Continuous | 588 | 212 | 1.39 (1.21–1.58)◊ | **<0.001** | | 0.97 (0.94–1.01)◊ | 0.175 | | 1.33 (1.13–1.58)◊ | **0.001** |
| **PR status *p*-heterogeneity*** | | | 0.215 \| 0.051 | | | 0.190 \| 0.113 | | | 0.071 \| **0.016** | | |
| **HER2 status** (missing for 17 invasive cases) | | | | | | | | | | | |
| **Negative** | 1 | 147 | 43 | Reference | **<0.001** | 67 | Reference | 0.135 | 43 | Reference | **<0.001** |
| | 2 | 147 | 49 | 1.29 (0.78–2.17) | | 61 | 0.82 (0.51–1.32) | | 43 | 1.46 (0.85–2.50) | |
| | 3 | 147 | 59 | 1.71 (1.03–2.85) | | 61 | 0.78 (0.46–1.33) | | 90 | 3.83 (2.29–6.39) | |
| | 4 | 147 | 114 | 3.21 (2.01–5.14) | | 76 | 0.61 (0.33–1.10) | | 89 | 4.88 (2.82–8.44) | |
| | Continuous | 588 | 265 | 1.47 (1.30–1.66)◊ | **<0.001** | | 0.95 (0.92–0.99)◊ | **0.013** | | 1.49 (1.28–1.74)◊ | **0.001** |
| **Positive** | 1 | 147 | 19 | Reference | **0.018** | 23 | Reference | 0.645 | 18 | Reference | **0.009** |
| | 2 | 147 | 18 | 0.99 (0.47–2.07) | | 13 | 0.66 (0.30–1.44) | | 18 | 1.21 (0.58–2.56) | |
| | 3 | 147 | 15 | 0.91 (0.42–1.98) | | 32 | 1.60 (0.76–3.35) | | 20 | 1.63 (0.75–3.50) | |
| | 4 | 147 | 36 | 2.02 (1.05–3.90) | | 20 | 0.83 (0.33–2.12) | | 32 | 2.63 (1.22–5.65) | |
| | Continuous | 588 | 88 | 1.31 (1.10–1.57)◊ | **0.002** | | 0.96 (0.90–1.02)◊ | 0.174 | | 1.30 (1.05–1.62)◊ | **0.015** |
| **HER2 status *p*-heterogeneity*** | | | 0.175 \| 0.242 | | | 0.332 \| 0.891 | | | 0.112 \| 0.443 | | |
| **Phenotype group (ER\|PR+vs ER&PR-)** (missing for 17 invasive cases) | | | | | | | | | | | |
| **ER&PR -** | 1 | 147 | 11 | Reference | **0.004** | 15 | Reference | 0.881 | 13 | Reference | **0.002** |
| | 2 | 147 | 13 | 1.37 (0.55–3.56) | | 12 | 0.92 (0.37–2.25) | | 7 | 0.73 (0.26–2.05) | |
| | 3 | 147 | 11 | 1.31 (0.51–3.55) | | 17 | 1.12 (0.44–2.85) | | 22 | 2.95 (1.24–7.02) | |
| | 4 | 147 | 28 | 3.07 (1.36–7.60) | | 19 | 0.99 (0.34–2.89) | | 21 | 3.09 (1.21–7.91) | |
| | Continuous | 588 | 63 | 1.45 (1.20–1.76)◊ | **<0.001** | | 0.96 (0.89–1.03)◊ | 0.247 | | 1.46 (1.13–1.88)◊ | **0.003** |
| **ER\|PR +** | 1 | 147 | 51 | Reference | **<0.001** | 75 | Reference | 0.221 | 48 | Reference | **<0.001** |
| | 2 | 147 | 54 | 1.18 (0.72–1.92) | | 62 | 0.78 (0.49–1.23) | | 54 | 1.51 (0.91–2.49) | |
| | 3 | 147 | 63 | 1.51 (0.93–2.45) | | 76 | 0.96 (0.58–1.59) | | 88 | 3.11 (1.90–5.09) | |
| | 4 | 147 | 122 | 2.77 (1.77–4.32) | | 77 | 0.61 (0.34–1.09) | | 100 | 4.20 (2.50–7.03) | |
| | Continuous | 588 | 290 | 1.42 (1.26–1.61)◊ | **<0.001** | | 0.95 (0.92–0.99)◊ | **0.011** | | 1.43 (1.23–1.67)◊ | **<0.001** |
| **Phenotype group *p*-heterogeneity*** | | | 0.680 \| 0.999 | | | 0.371 \| 0.959 | | | 0.420 \| 0.932 | | |

**Notes:** ‡All models adjusted for BMI, age, BMI by age interaction, education, ethnicity, age at menarche, parity, age at first full-term pregnancy, lifetime breastfeeding, lifetime use of oral contraceptives, family history of breast cancer, lifetime use of hormone replacement therapy, lifetime smoking, and alcohol consumption. [a]Adjusted for ‡ +dense area. [b]Adjusted for ‡ +non-dense area.

*Categorical | Continuous. ◊ Estimate per 10-unit change in mammographic density parameter (continuous). Bold values in this table correspond to statistically significant *p*-values (<0.05).

**Abbreviations:** aOR, adjusted odds ratio; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal factor receptor 2.

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The authors report no conflicts of interest in this work.

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