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The influence of mammographic density on breast tumor characteristics

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Abstract Mammographic density (MD) is a well-established risk factor for breast cancer. Whether MD influences the tumor phenotype remains to be clarified. Previous studies are highly inconsistent and most lack important covariate information. This is a case-only study within a population-based case–control study. Cases were all postmenopausal women, aged 50–74 years, with incident breast cancer, diagnosed 1993–1995, and with no history of previous cancer ($n = 2{,}720$). 1,747 women with mammograms and information on tumor characteristics were included in analyses. MD was assessed using a computer-assisted thresholding technique. We used linear, logistic, and multinomial logistic regression, adjusting for possible confounders, to study density and tumor characteristics. PD was only statistically significantly associated with tumor size in our study (regression coefficient 0.031, $p = 0.017$). The effect of PD on tumor size was greater when mode of detection was excluded from the model (regression coefficient 0.043, $p = 0.001$). No other associations between PD and the tumor characteristics studied (lymph node metastasis, ER-status, PR-status, grade, and histopathological classification) were observed. In summary, PD was positively associated with tumor size in postmenopausal women. However, the relationship was at least partially confounded by mode of detection. Although there may be a true biological relationship between MD and more highly proliferative tumors, it also seems that part of this relationship is due to masking delaying diagnosis. In conclusion, PD does not seem to be differentially associated with tumor phenotype, except for tumor size, after taking mode of detection into consideration.

Keywords Mammographic density · Breast cancer · Tumor characteristics · Tumor size

Abbreviation

BMI	Body mass index
CI	Confidence interval
ER	Estrogen receptor
HRT	Hormone replacement therapy
MD	Mammographic density
OR	Odds ratio
PD	Percentage density
PR	Progesterone receptor

Introduction

Mammographic density (MD) is one of the strongest risk factors for breast cancer. Women with highest density (>75 %) have a 4–6 fold increased risk compared to women with completely fatty breasts [1]. Whether density only is related to risk of breast cancer or it also influences tumor subtype remains to be clarified. Previous published studies on the relationship between MD and tumor characteristics are highly inconsistent [2–15].

MD consists of epithelium and stroma which is radiodense, as are tumors. Consequently, density can hide

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tumors, a phenomenon referred to as masking [16]. In accordance, density decreases mammographic sensitivity [17, 18]. Hence, it would be expected that tumors emanating from dense breasts are diagnosed at a later stage, i.e., are of greater size and more often present with lymph node metastasis, than tumors emanating from non-dense breasts.

Further, if MD is a hormonally responsive trait, as has been suggested [19], tumors diagnosed in dense breasts may be more likely to be estrogen receptor (ER) positive than tumors diagnosed in non-dense breasts [20]. In contrast, a recent study on postmenopausal women was the first to report a positive association between PD and ER-negative tumors [10]. Masking was not taken into account which could have confounded this association. However, for masking, or rather a delay in diagnosis, to confound the relationship between PD and tumor characteristics, histopathological features, such as receptor status and grade, must be able to change over time, which is debated [21, 22].

The inconsistencies between previous studies pertaining to MD and tumor characteristics may be due to differences in study design and study population composition (e.g., menopausal status and ethnicity), small sample sizes, lack of important covariate information (e.g. BMI, hormone replacement therapy [HRT], menopausal status, and mode of detection), and differences in assessment of density (visual estimation using a categorical assessment, e.g., BI-RADS, versus quantitative, computer-assisted techniques, e.g. Cumulus).

Our population-based study of postmenopausal women exploring the relationship between density and tumor characteristics includes one of the largest populations of breast cancer cases, with the most detailed covariate information of all studies (to date) including mode of detection. Measurements have also been carried out using a quantitative, computer-assisted technique to minimize exposure misclassification [23].

Materials and methods

Study population

This study is an extension of a large case–control study, CAHRES, among all Swedish residents born in Sweden and aged 50–74 years at time of enrollment, 1st October, 1993 to 31st March, 1995. Details on data collection and subjects have been described previously [24–26]. All women with incident of primary invasive breast cancer were identified via the six Swedish Regional Cancer Registries. The study identified 3,979 women, of whom 84 % ($n = 3{,}345$) participated in the original study. However, of the included cases, 19 were diagnosed outside of the study period, one case had a diagnosis other than breast cancer, and 58 cases had non-invasive breast cancer, rendering them ineligible.

For this study, the inclusion criteria was further refined to only include postmenopausal women who had no prior diagnosis of cancer other than non-melanoma skin cancer. Menopause was defined as the age at the last menstrual period or the age at bilateral oophorectomy if at least 1 year prior to date of study entrance. 198 premenopausal women and 202 women with unknown menopausal status who were younger than 55 for non-smokers or 54 for smokers (the 90th percentile of age at natural menopause of study subjects) were thus excluded from the study as were 147 women with previous cancer. The study base thus consisted of 2,720 breast cancer cases.

Using the Swedish national registration numbers, we obtained addresses for participants from 1975 to 1995 through the civil registry. During 2007 and 2008, we visited all mammography screening units and radiology departments conducting screening mammography throughout Sweden. For the eligible participants in this study, we managed to collect mammograms for 2,046 women (75 %). We used the mammogram closest to diagnosis, excluding post-diagnostic mammograms. 107 women who only had post-diagnostic mammograms available were thus excluded. The median difference from date of mammography to study entrance was 50 days.

Since studies have shown that MD may differ histologically in pre- and postmenopausal women [27] and also may be affected differentially by hormones [28, 29], we excluded women who lacked postmenopausal mammograms ($n = 79$).

Tumors appear white on a mammogram and can thereby distort density measurements. Hence, we used the mammogram of the breast contralateral to the tumor, excluding women with missing information on tumor side ($n = 3$) or lacking contralateral mammograms ($n = 62$, of which 19 had bilateral breast cancer). Images of poor quality, including breasts with silicone implants, were also omitted, excluding 21 women.

Following a decision of the Ethical Review Board of the University of Lund, written informed consent was sought to retrieve information from medical records. 24 women were excluded due to lack of written consent. Medical records for 3 women were not identified. The final data set thus included 1,747 women.

Descriptive characteristics (all variables in Table 1) did not differ between included and excluded women (data not shown) except for a slight difference in age (62.9 for included women compared to 63.6 for excluded women, $p = 0.015$).

Table 1 Comparison of patient characteristics across PD groups

	All cases (n = 1,747)		
	PD < 25 % (n = 1,310) n (%) or mean	PD ≥ 25 % (n = 437) n (%) or mean	p Value
Age at mammography	63.1	59.0	<0.001
BMI	26.3	23.9	<0.001
Age at menarche	13.5	13.5	0.749
Oral contraceptive use			<0.001
Yes	408 (31)	180 (41)	
No	896 (69)	258 (59)	
Parity and age at first birth			0.007
Nulliparous	172 (13)	79 (18)	
Parity ≤2 and age at first birth ≤25	380 (29)	134 (31)	
Parity ≤2 and age at first birth >25	400 (31)	140 (32)	
Parity >2 and age at first birth ≤25	263 (20)	62 (14)	
Parity >2 and age at first birth >25	94 (7)	23 (5)	
Breast feeding			0.177
Yes	923 (80)	312 (77)	
No	228 (20)	93 (23)	
Age at menopause	50.4	50.5	0.577
HRT use			<0.001
Never	958 (74)	239 (55)	
Past	68 (5)	69 (16)	
Current	266 (21)	123 (29)	
Previous benign breast disease			<0.001
Yes	157 (12)	86 (20)	
No	1,147 (88)	350 (80)	
Breast cancer heredity*			0.504
Yes	199 (16)	62 (14)	
No	1,072 (84)	371 (86)	

* Family history of breast cancer in a first-degree relative

Data collection and classification

Questionnaire data

Data on sociodemographic, anthropometric, hormonal, and lifestyle factors were collected by means of a postal questionnaire. Since date of mammography was prior to study entrance, the variables age, menopausal status, and HRT-use were reassessed according to date of mammography. We were not able to do this with BMI as we only had information on BMI at study entrance and 1 year prior to study entrance. However, it has previously been shown that inter-individual variations in BMI are small [30] and the difference in BMI at study entrance and 1 year prior to this was 0.05 units (SD 1.2) for our study participants.

We used the national registration number to retrieve patient records and register information. Between 2000 and 2002, we collected information on primary surgery, adjuvant treatment (endocrine therapy, chemotherapy, and radiotherapy), tumor characteristics, and reason for diagnostic mammography from surgical and oncological patient records throughout Sweden.

Mammographic density data

Film mammograms of the medio-lateral oblique view were digitized using an Array 2905HD Laser Film Digitizer (Array Corporation, Tokyo, Japan), which covers a range of 0–4.7 optical density. The medio-lateral oblique view was used since this was the routine view used at mammography screening in Sweden. The density resolution was set at 12-bit spatial resolution. We used Cumulus, a computer-assisted thresholding technique, to assess density [31] of the mammogram contralateral to the tumor. For each image, a trained observer (LE) set the appropriate gray-scale threshold levels defining the edge of the breast

and distinguishing dense from non-dense tissue. The software calculated the total number of pixels within the entire region of interest and within the region identified as dense. The percentage density (PD) was then calculated from these values (dense area/total breast area). The images were measured together with approximately the same amount of images for healthy women and the reader was blinded to case–control status and also, naturally, to tumor characteristics. A random 10 % of the images were included as replicates to assess the intra-observer reliability, which was high with an R^2 of 0.92.

Classifications

HRT was classified according to recency (current, former, and never use). Since the influence of HRT on MD diminishes within 3 weeks of cessation [32], former users were those who discontinued HRT-use more than 1 month prior to the date of mammography. There were no individuals classified as never users who started using HRT after date of mammography. All compounds, modes of administration, and potencies were included in the HRT variable except for low potency, estrogen-only pharmaceuticals, since the latter have not been shown to increase breast cancer risk [33].

Since there were few observations in the categories of asymptomatic women referred for mammographic examination, these were combined with the group of women with symptomatic cancers. Mode of detection was thus treated as a binary variable—screening- versus non-screening-detected cancer.

Grade was classified according to the Nottingham histologic grade or the Bloom–Richardson scale into three groups [34]. Tumors were considered ER-positive or progesterone receptor (PR)-positive if they contained $\geq$0.05 fmol receptor/μg DNA or $\geq$10 fmol receptor/mg protein.

Statistical analysis

Density was used as a binary variable throughout because we felt that this was more clinically relevant than a continuous measure and more easily interpreted. The cut-off was set at 25 % defining the highest quartile in our cohort. We could not categorize PD according to the commonly used categories introduced by Boyd et al. [35, 36] since the categories did not fit our postmenopausal study population whose density measurements are lower and more homogeneous than a combined pre- and postmenopausal population.

Descriptive statistics for background variables were compared across high and lower density groups using χ^2 tests of association and Student t tests. We performed regression analyses treating tumor characteristics as outcomes and density as a covariate; we used linear regression for studying tumor size (tumor size was transformed by power of 0.2 to obtain an approximately normal distribution), multinomial logistic regression for grade and histological classification, and logistic regression for all other outcomes. Tests of heterogeneity in effect sizes across subgroups were carried out for grade and histological classification. We included age (continuous), BMI (continuous), HRT-use (categorical), age at menarche (continuous), previous oral contraceptive use (binary), parity and age at first birth combined into one categorical variable (nulliparous, parity $\leq$ 2 and age at first birth $\leq$25, parity $\leq$2 and age at first birth >25, parity >2 and age at first birth $\leq$25, and lastly, parity >2 and age at first birth >25), breast feeding ever (binary), age at menopause (continuous), previous benign breast disease (binary), family history of breast cancer in a first-degree relative (binary), and mode of detection (to try to account for masking) as potential confounders. We did not adjust for tumor size, presence of lymph node metastasis, or grade since this would risk depleting a true, biological effect of density on tumor characteristics or over-adjustment, since mode of detection also is associated with these factors.

The decision to use covariates as continuous or categorical variables was based on the goodness of fit of the model which was ascertained using AIC [37]. All analyses were carried out using the statistical software, STATA 11.2.

Results

Age at mammography ($p < 0.001$), BMI ($p < 0.001$), previous oral contraceptive use ($p < 0.001$), parity and age at first birth ($p = 0.007$), HRT-use ($p < 0.001$), and previous benign breast disease ($p < 0.001$) were associated with PD (Table 1). There were statistically significant differences between women with high PD compared to women with lower PD for mode of detection ($p = 0.011$) and tumor size ($p = 0.007$) (Table 2).

There was a varying degree of missing data for the different tumor characteristics. Less than 5 % of our study population had missing information on tumor size, presence of lymph node metastasis, tumor histology, and mode of detection, respectively. However, for grade, ER-, and PR-status we had missing information on ~30 % of the study population for each respective variable.

Table 3 shows the results from the analyses of PD and tumor characteristics. PD was positively associated with tumor size (regression coefficient 0.031 for tumor size, $p = 0.017$). When we excluded mode of detection from the model, the regression coefficient increased slightly and

Table 2 Description of mode of detection and tumor characteristics based on PD

	All cases ($n = 1,747$) n (%) or mean	PD < 25 % ($n = 1,310$) n (%) or mean	PD ≥ 25 % ($n = 437$) n (%) or mean	p Value
Mode of detection				0.011
Screening-detected	1,115 (64)	867 (67)	248 (57)	
Referral for check-up (no symptoms)	25 (1)	18 (1)	7 (2)	
Referral due to HRT-use (no symptoms)	21 (1)	15 (1)	6 (1)	
Symptomatic	551 (32)	384 (30)	167 (39)	
Referral, other reason	18 (1)	13 (1)	5 (1)	
Tumor size (mm)	16.8	16.4	18.0	0.007
Lymph node metastasis				0.581
Positive	480 (28)	362 (29)	118 (27)	
Negative	1,221 (72)	905 (71)	316 (73)	
ER-status				0.733
ER-positive	971 (79)	727 (79)	244 (78)	
ER-negative	256 (21)	189 (21)	67 (22)	
PR-status				0.779
PR-positive	808 (67	602 (67)	206 (68)	
PR-negative	396 (33)	298 (33)	98 (32)	
ERPR-status				0.752
ERPR-positive	764 (78)	574 (78)	190 (79)	
ERPR-negative	210 (22)	160 (22)	50 (21)	
Histologic classification				0.230
Ductal	1,268 (73)	957 (73)	311 (72)	
Lobular	199 (11)	140 (11)	59 (14)	
Other	268 (15)	206 (16)	62 (14)	
Grade				0.382
1	197 (17)	151 (17)	46 (15)	
2	510 (43)	382 (44)	128 (42)	
3	475 (40)	342 (39)	133 (43)	

became highly significant (regression coefficient 0.043, $p = 0.001$) (results not shown in Table 3). There was a borderline statistically significant association between PD and grade 3 tumors (OR 1.56 for grade 3, $p = 0.069$). A test of heterogeneity revealed that there was no difference in risk associated with PD between different categories of grade ($p = 0.192$).

Discussion

MD is one of the strongest risk factors for breast cancer and we investigated whether MD also is associated with tumor phenotype. Among the tumor characteristics studied, we only found an association between PD and tumor size. Interestingly, neither presence of lymph node metastasis nor hormone receptor status was associated with PD.

Although we saw a statistically significant, positive association between PD and tumor size, the effect size was relatively small. The association became more pronounced when mode of detection was excluded from the model, lending support to the hypothesis that it is due to masking. However, dense breasts may also give rise to more highly proliferative tumors which may be the reason why there still is an association between PD and tumor size even after adjustment for mode of detection. To try to disentangle the cause of this relationship in an epidemiological study is difficult, but an investigation of the association between PD and proliferation rate could give a clue to the etiology. Unfortunately, we were not able to study this due to too many missing values for proliferation rate (~70 % missing values).

Since MD decreases screening sensitivity [17, 18], our a priori hypothesis was that density would be correlated with both tumor size and lymph node metastasis. However, we found no evidence of an association between PD and the latter. Previous studies have been inconsistent [2, 6, 7, 10, 13]. The ability for breast tumors to metastasize is not only dependent on time but also on the acquired ability to

Table 3 Association between PD (≥25 % vs. <25 %) and tumor characteristics

Outcome variable	Effect size[a]	95 % CI	*p* Value
Regression coefficient			
Tumor size			
mm^0.2	0.031	0.005–0.056	0.017
Odds ratio (OR)			
ER-status			
ER-negative	1.00 (Ref.)		
ER-positive	1.07	0.72–1.60	0.725
PR-status			
PR-negative	1.00 (Ref.)		
PR-positive	1.17	0.83–1.66	0.369
ERPR-status			
ERPR-negative	1.00 (Ref.)		
ERPR-positive	1.31	0.83–2.06	0.247
Lymph node metastasis			
Negative	1.00 (Ref.)		
Positive	0.88	0.65–1.19	0.394
Grade (WHO)			
1	1.00 (Ref.)		
2	1.36	0.85–2.19	0.205[b]
3	1.56	0.97–2.52	0.069[b]
Histologic classification			
Ductal	1.00 (Ref.)		
Lobular	1.22	0.82–1.82	0.335
Other	1.08	0.74–1.57	0.689

Adjusted for age, BMI, HRT, age at menarche, oral contraceptive use, parity and age at first birth combined, breast feeding, age at menopause, previous benign breast disease, breast cancer heredity (first-degree relative), and mode of detection

[a] Odds ratios in all cases except for tumor size for which a (linear) regression coefficient is presented. PD coded as 0 = <25 %, 1 = ≥25 %

[b] $p = 0.192$ for heterogeneity across subgroups

invade vessels, survive migration, extravasate, and colonize distant sites [38]. Hence, although density may cause a delay in diagnosis, it does not per se imply a direct association with lymph node metastasis.

Although MD is a hormonally responsive trait [19], we saw no association between density and hormone receptor status. This is in line with most previous studies [15, 36] but is in contrast with another study of postmenopausal women in which higher density was associated with increased risk of ER-negative cancers [10]. However, mode of detection was not accounted for and the proportions of ever-users of HRT (76 % of the study population) and women with previous benign breast disease (59 % of the study population) were very high, both of which contribute to increased PD [23, 39] and increased risk of interval cancers [40, 41]. In our study, 50 % of the participants were ever-users of HRT (including all compounds and modes of administration) and 14 % had previous benign breast disease. The proportions were the same as for women lacking density measurements as was the proportion of ER-negative cancers. Thus, we believe that our results are representative.

Heusinger et al. [14] recently published a large study on PD and tumor characteristics, including both pre-and postmenopausal women, in which they found that PD was associated with lower ER-expression. However, although there was a difference between categories of ER-expression that was highly statistically significant ($p = <0.0001$), and although the tumors with highest ER-expression (>80 %) were associated with lowest PD (35 %, 95 % CI 33–36), differences in PD were very small, with overlapping confidence intervals, and there was no dose–response relationship. Tumors with an ER-expression of 10–65 %, and thus ER-positive tumors, were associated with highest PD (39 %, 95 % CI 38–41), and were not significantly different from tumors with an ER-expression of 0–9 % (PD 38 %, 95 % CI 36–40) ($p = 0.21$) which were referred to as ER-negative, by the authors. Thus, their results are not directly applicable to ER-status.

All other previous studies showing an association between density and ER-status have lacked adjustment for important hormonal confounders such as BMI, menopausal status, and HRT-use [3–6, 9]. Furthermore, some were case–control or cohort studies in which no assessments of differences in effect size across subgroups were carried out [4, 5, 9]. In the latter cases, density was associated with all tumor characteristics studied and all values of the tumor characteristics studied, e.g., lymph node positive and negative tumors. Since density is one of the strongest risk factors for breast cancer, it would be expected that density would increase all subtypes of breast cancer in relation to controls. However, if there is no difference in effect size across subgroups, density does not affect one specific subtype more than another.

We treated PD as a binary variable, since we believed that this was more clinically relevant than a continuous measure of PD. However, re-analyses using PD as a continuous variable gave similar results as those presented, i.e., PD is only associated with tumor size (data not shown).

Our study has several strengths; the population-based study design, study size, detailed covariate information, including mode of detection, and quantitative, semi-automated density measurements.

A limitation of our study population is that it was solely composed of postmenopausal women; hence, our results may not be applicable to pre-menopausal populations. MD may differ histologically in pre- and postmenopausal

women [27], and has been shown to be influenced by different hormonal factors depending on menopausal status [28, 29]. Furthermore, both age and menopausal status influence tumor characteristics [42]. Thus, well-conducted studies are needed to investigate the relationship between MD and tumor characteristics in pre-menopausal women.

Conclusions

PD was positively associated with tumor size in postmenopausal women. However, the relationship was at least partially confounded by mode of detection. Thus, although there may be a true biological relationship between MD and more highly proliferative tumors, it also seems that part of this relationship is due to masking delaying diagnosis. In conclusion, PD does not seem to be differentially associated with tumor phenotype, except for tumor size, after taking mode of detection into consideration.

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Ethical approval Approval of the study was given by the ethical review board at the Karolinska Institutet (Stockholm, Sweden) and six other ethical review boards in the respective regions from which the subjects were based.

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

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