Research Article

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Volumetric Breast Density from Full-Field Digital Mammograms and Its Association with Breast Cancer Risk Factors: A Comparison with a Threshold Method

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Abstract

Introduction: Breast density, a strong breast cancer risk factor, is usually measured on the projected breast area from film screen mammograms. This is far from ideal, as breast thickness and technical characteristics are not taken into account. We investigated whether volumetric density measurements on full-field digital mammography (FFDM) are more strongly related to breast cancer risk factors than measurements with a computer-assisted threshold method.

Methods: Breast density was measured on FFDMs from 370 breast cancer screening participants, using a computer-assisted threshold method and a volumetric method. The distribution of breast cancer risk factors among quintiles of density was compared between both methods. We adjusted for age and body mass index (BMI) with linear regression analysis.

Results: High percent density was strongly related to younger age, lower BMI, nulliparity, late age at first delivery and pre/perimenopausal status, to the same extent with both methods (all $P < 0.05$). Similarly strong relationships were seen for the absolute dense area but to a lesser extent for absolute dense volume. A larger dense volume was only significantly associated with late age at menopause, use of menopausal hormone therapy, and, in contrast to the other methods, high BMI.

Conclusion: Both methods related equally well to known breast cancer risk factors.

Impact: Despite its alleged higher precision, the volumetric method was not more strongly related to breast cancer risk factors. This is in agreement with other studies. The definitive relationship with breast cancer risk still needs to be investigated. *Cancer Epidemiol Biomarkers Prev; 19(12); 3096–105. ©2010 AACR.*

Introduction

Breast density, which represents the relative amounts of fibroglandular and fat tissue in the breast, is one of the strongest independent risk factors for breast cancer (1, 2). Fibroglandular tissue is radiographically dense and appears white on a mammogram, whereas fat tissue is radiographically lucent and appears dark on a mammogram. The radiographic appearance of the female breast varies among individuals due to differences in the relative amount of these tissues. Numerous studies have reported that high breast density (high amount of fibroglandular tissue) increases the risk of breast cancer 2- to 6-fold compared with women with low breast density (1, 2).

Nowadays, one of the most frequently used techniques for the quantification of breast density on a mammogram is a computer-assisted threshold method (3). This quantitative method measures the projected area of dense fibroglandular tissue on a film screen mammogram that has been digitized for this purpose. It has the limitation that it does not take into account the thickness of the dense tissue. Moreover, technical characteristics such as radiation dose and projection angle are seldomly registered, but can influence the density measurement. Another disadvantage is the subjectivity introduced by the reader who has to set the threshold manually, which could cause observer bias. To increase the accuracy and reproducibility of mammographic breast density measurement, several research groups developed fully or semiautomated methods to quantify volumetric breast density on a mammogram (4–6). These volumetric methods are expected to

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Note: Impact Statement: Despite its alleged higher precision, the volumetric method was not more strongly related to breast cancer risk factors. This is in agreement with other studies. The definitive relationship with breast cancer risk still needs to be investigated.

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give a more precise estimate of the amount of fibroglandular tissue in the breast and therefore even stronger breast cancer risk estimates in relation to breast density than observed with the computer-assisted threshold method.

A volumetric breast density measurement method that can be used on digitized film screen mammograms is the so called Standard Mammogram Form (SMF; ref. 6). To use it on existing mammograms, imaging acquisition parameters such as tube voltage, spectrum, and exposure time should ideally have been registered. However, in the first clinical studies, density measured with the volumetric SMF method showed weaker associations with breast cancer risk than density measured with the threshold method (7, 8). Another volumetric method for breast density assessment on digitized film screen mammograms, based on a calibration step-wedge, also shows a slightly weaker relationship with breast cancer risk than was shown for the threshold method (9).

Volumetric methods for full-field digital mammography (FFDM) have also been developed (5). These methods have the advantage that it can take into account different energy spectra for different anode target/filter materials; information that is automatically stored in the header of raw (unprocessed) full-field digital mammograms. The calibration data, to be used for the volumetric estimations, are much more reliable than those that can be obtained from film screen mammograms. In addition, FFDM has the advantage that the pixel value is known to be linearly related to exposure. With film screen mammography this relationship is not linear and has to be estimated from film curves first. As a result, volumetric breast density estimates are expected to be much more accurate and reproducible for FFDM than for film screen mammography. The volume of fibroglandular tissue assessed with a volumetric method for FFDM shows very high correlation with the volume assessed with MRI (5), but its association with breast cancer risk factors or breast cancer risk has not yet been investigated.

Evaluation of the relationship between volumetric measurements from FFDM and breast cancer risk will give the ultimate proof but will take a long follow-up since FFDM has only recently been introduced in practice as a routine screening method. To date no studies have compared the volumetric method on FFDM with the computer-assisted threshold method for quantification of breast density. The purpose of this study is to investigate to what extent the new volumetric method correlates with the computer-assisted threshold method and whether the volumetric method is more strongly related to known breast cancer risk factors than the widely used threshold method.

Materials and Methods

Study population

For this study, we included 370 women who participated in the nationwide breast cancer screening program in the Netherlands. We selected women from the city of Utrecht where FFDM has been used for breast cancer screening since 2004.

The study population comprised 2 subpopulations. The first group consisted of screening participants who were also participants of one of the Dutch cohorts of the European Prospective Investigation into Cancer and Nutrition (Prospect-EPIC; ref. 10). More than 17,000 participants had been enrolled into this cohort between 1993 and 1997 and filled out lifestyle and food questionnaires at that time and also donated a blood sample. Participants were then aged 48 to 50 years. During follow-up participants again filled out questionnaires on past and current morbidity, and on (changes in) reproductive and lifestyle factors: one 3–5 years and one approximately 8 years after enrollment. For our study, we selected participants from this cohort who were still in follow-up and participating in the breast cancer screening program in the city of Utrecht in 2004–2007 and had at least one FFDM examination in that period. One hundred ninety women were randomly selected. They were 57 to 59 years old at the time of the FFDM examination.

To increase the variation in breast density in our study population, we included a second group of 180 breast cancer screening participants in the city of Utrecht who were 49 to 50 years old when they received their first FDDM examination between June 2007 and September 2007. To obtain information on breast cancer risk factors, these women were administered a questionnaire on lifestyle and reproductive characteristics with questions similar to those in the Prospect-EPIC questionnaires mentioned above. All participants signed informed consent for the use of questionnaire information and the retrieval and analysis of their mammograms. The study has been approved by the Institutional Review Board of the University Medical Center Utrecht.

Digital mammograms

The mammograms used in this study were raw (unprocessed) digital mammograms and all required parameters were obtained from their DICOM headers (Digital Imaging and Communications in Medicine). The images were acquired with a Hologic Selenia FFDM system. To examine the mammograms with the computer-assisted threshold method, the mammograms were processed to make them look similar to the digitized film images for which threshold method was designed originally (11). For the volumetric method, the mammograms did not need further processing.

Threshold method

The Cumulus software (University of Toronto, Canada) was used for measuring the density of the breast with a computer-assisted threshold method (3). Breast density was assessed on mediolateral oblique (MLO) mammograms, which is the routine view for breast cancer screening in the Netherlands. It has been observed that the proportions of breast density on craniocaudal (CC) views and MLO views and on left and right views

show very strong correlation and that representative information on breast density is provided in a single view (12). For each study subject, breast density was assessed on the left view. Mammograms were randomly ordered in 14 batches of 26 mammograms and read by a single trained observer (M.L.). For each image, the pectoralis muscle was masked out and the breast area was selected. The edge of the breast and the dense area were set by the reader, after which the cumulus software calculated the percent density as the total dense area divided by the total breast area (3). A test batch with 26 randomly selected MLO views was read 3 times, at different time points between sets unknown to the reader, and the intracorrelation coefficients were 0.96, 0.96, and 1.00 for the percent density, dense area, and total breast area, respectively.

Volumetric method

The method used for volumetric breast density analysis has been described earlier by van Engeland et al. (5) In short, the thickness of dense tissue mapping to a pixel is determined by using a physical model of image acquisition. Depending on the parameters tube voltage, anode and filter materials, breast thickness, effective attenuation coefficients for fatty and dense tissue are computed. Next, these coefficients are used in a monochromatic computation of total and dense tissue volume. The composition of the tissue at a given pixel is computed using a reference value for fatty tissue determined by the maximum pixel value in the breast tissue projection. This internal calibration with the reference value forms an essential difference with the SMF method. For the determination of the breast density, all views available for each woman were used and the mean of all measurements was taken. Large-scale epidemiological studies using the threshold method often rely on one view, because the method is very labor-intensive. With the volumetric method, however, the number of views does not pose any logistical problems, as it is fully automatic. For 302 women 4 views were available and for 68 women only MLO mammograms were available. As the volumetric method is fully automatic and therefore 100% reproducible, the repeatability of a density measurement made on the same film is not appraised.

Statistical methods

For all analyses, we used a natural logarithmic transformation of the percent and absolute density measurements, because neither threshold measurements nor volumetric measurements were normally distributed. We calculated the correlation between the threshold method and the volumetric method with Pearson's correlation coefficient and accompanying 95% confidence intervals using these transformed measures. To describe the relationship between measurements from both methods with breast cancer risk factors, we calculated for each quintile of percent density the mean (or median when the variable was not normally distributed) age at mammogram, body mass index (BMI), age at menarche, age at first delivery, number of children, and age at menopause. Proportions were calculated for the categorical variables menopausal status (pre or perimenopausal/postmenopausal), nulliparous (yes/no), HT use (ever/never), pill use (ever/ never), and family history (yes/no).

To examine the presence of a linear trend in the distribution of the risk factors over the density quintiles, we used a test for linearity for normally distributed continuous data, a Jonckheere Terpstra test for skewed continuous data and a chi-square linear trend test for proportions. The same analyses were done for absolute density, were the absolute dense area was calculated by the number of pixels times the size of 1 pixel in squared centimeters (cm^2) for the threshold method and cubic centimeters (cm^3) for the volumetric method. Linear regression models were used to adjust relationships between density measurements and breast cancer risk factors for age and BMI, known from the literature as the most important determinants of breast density (13). To be able to compare regression coefficients between the different methods with their different scales, we used a change of one standard deviation (SD) in the density measure as the outcome. VasserStats was used to calculate the 95% confidence intervals for the correlation coefficients. All other analyses were conducted using SPSS 15.0.

Results

The median age of the total study participants was 57 years and their mean BMI was 25.6 kg/m^2. Half of the participants in the study ($N = 18.2$, 49.2%) were pre- or perimenopausal and 50.8% was postmenopausal. The mean age at menopause of the postmenopausal women was 48.4 years. This distribution is inherent to the inclusion of 1 older (median: 57 years, 57–59) and 1 younger study population (median 50 years, 49–51). Twenty-one percent of the women were nulliparous and the median number of children was 2 (Table 1).

One thousand three hundred forty-four mammograms of 370 women were included in the study. Of 302 women, 4 views [mediolateral oblique (MLO) and craniocaudal (CC), left and right] were available; 68 women only had an MLO image of both breasts. Using the threshold method, percent breast density varied between 0.29% and 87.04% (median 15.7%). The percent dense volume measured with the volumetric method varied, between 2.8% and 31.6% (median 7.0; Fig. 1A).

The Pearson correlation between the threshold and volumetric method for the natural log transformed percent density is 0.76 (95% CI, 0.71–0.80). The correlation between the absolute dense area and absolute dense volume is lowest, namely 0.21 (95% CI, 0.11–0.31) and the correlation between log transformed values of the total breast area and total breast volume is highest, namely 0.96 (95% CI, 0.96–0.97; Fig. 1).

In Table 2, the results are shown for the relation between the breast cancer risk factors and quintiles of

Table 1. Patient characteristics

	Study participants ($N = 370$)	
	Mean	**SD**
Age at examination, y	53.9	4.2
BMI, kg/m^2	25.6	4.8
Age at menarche, y	13.1	1.5
Age at menopause, y	48.4	5.5
Age at first delivery, y	25.9	4.9
	Median	**Interquartile range**
Age at examination, y	57	50–58
Number of live born children, *N*	2	1–2
	Proportion	***N***
Postmenopausal, % (*N*)	50.8	188
Nulliparous, % (*N*)	21.4	79
Family history of breast cancer, % (*N*)	16.5	61
Ever use of HT, % (*N*)	30.8	114
Ever use of pill, % (*N*)	88.4	327
	Median	**Interquartile range**
Percent density (threshold method), %	15.7	6.4–30.8
Dense area, cm^2	25.0	11.5–41.9
Nondense area, cm^2	130.4	84.5–175.8
Total breast area, cm^2	160.0	123.8–198.5
Percent density (volumetric method), %	7.0	5.5–10.0
Dense volume, cm^3	66.1	46.0–89.8
Non dense volume, cm^3	820.0	540.5–1,178.4
Total breast volume, cm^3	886.1	587.2–1,276.9

percent breast density, measured with the computer-assisted threshold method and the volumetric method. Both the threshold method and the volumetric method show a significant trend over quintiles for density for age at mammogram, BMI, age at first delivery, and the proportions of nulliparous and postmenopausal women. Breast tissue tends to be denser when a woman is younger, pre- or perimenopausal, has a lower BMI, has no or few children, or gave birth to their first child at a later age. Women who were older at menarche had a somewhat higher percent density with both methods. Nor the threshold method, neither the volumetric method shows significant trends for ever use of hormone therapy (HT) or ever use of pill, and breast density. No significant trend was observed for age at menopause or first-degree family history of breast cancer and breast density either.

Table 3 shows the results for the relation between breast cancer risk factors and absolute density. The absolute dense area measured with the computer-assisted threshold method shows a significant P value for trend for age at mammogram, BMI, age at menarche, age at first delivery, and the proportions of nulliparous and postmenopausal women. The absolute dense volume was significantly associated BMI and age at menopause only. The relationship between BMI and absolute dense volume has the opposite direction compared to that observed with the threshold method.

The standardized regression coefficients for percent density and absolute dense area adjusted for age and BMI are listed in Table 4. The adjusted regression coefficients were largely consistent with the trends observed in Tables 2 and 3. After adjustment for age and BMI, HT use became significantly associated with dense volume (volumetric method). Furthermore, after adjustment, menopausal status was not longer statistically significantly related to percent density measured with the volumetric method.

Discussion

In this study, we compared for the first time a fully automatic volumetric method to measure density on FFDM with a commonly used computer-assisted

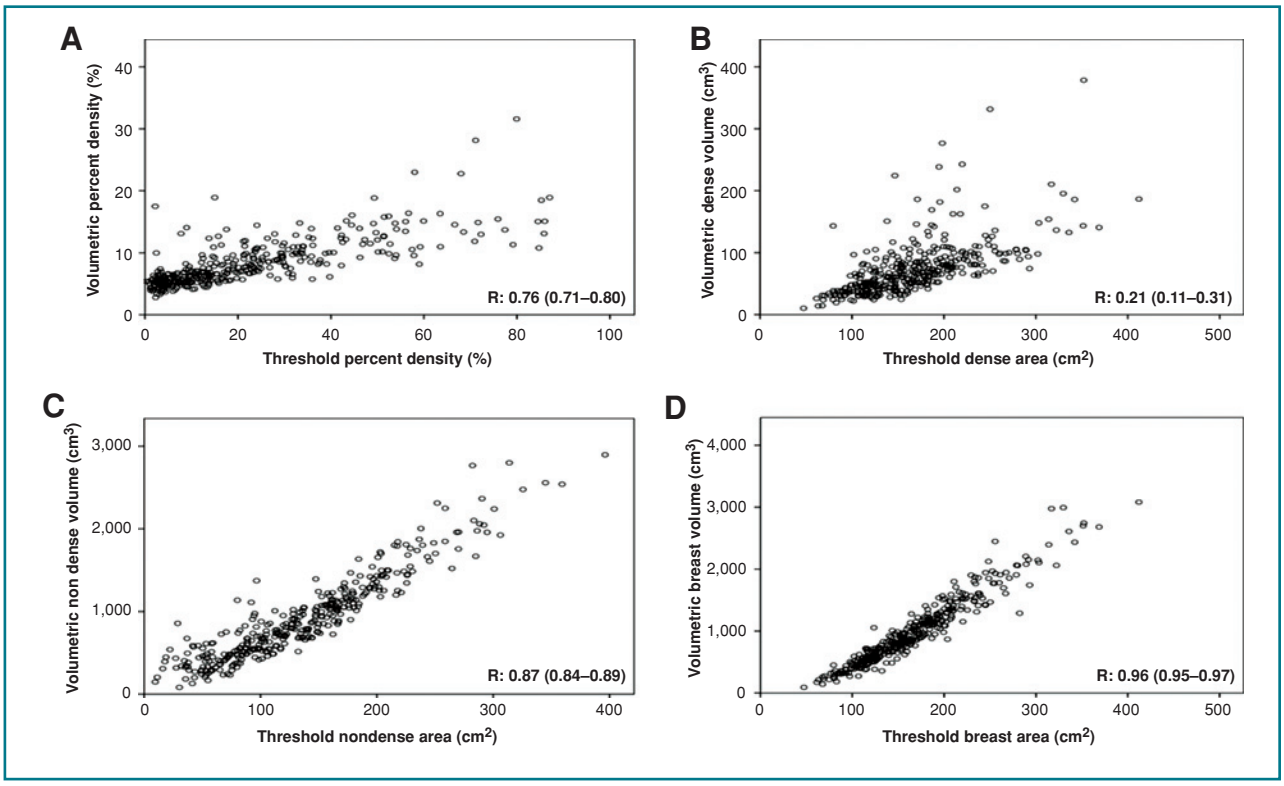

Figure 1. A, correlation between volumetric percent density and threshold percent density. B, correlation between volumetric dense volume and threshold dense area. C, correlation between volumetric non-dense volume and threshold non-dense area. D, correlation between volumetric breast area and threshold breast area.

threshold method. The methods show strong correlation with respect to total breast volume/area and also for percent density. The correlation between dense volume and dense area was moderate. A perfect correlation is not expected, however, as the volumetric method measures and takes into account other aspects of the image than the threshold method. Similar findings have been reported for the SMF method and other volumetric methods for film screen mammograms (8, 9, 14).

When measuring percent density, both methods were equally strongly related with the breast cancer risk factors. The absolute density showed stronger relationships with breast cancer risk factors when using the threshold method than when using the volumetric method.

With both methods, we could clearly confirm the established determinants of high percent density, that is young age, low BMI, nulliparity, late age at first delivery, premenopausal status, and HT use (15–18). With respect to absolute density, the dense area was more strongly related with the known breast cancer risk factors than the dense volume, as mentioned above. The largest discrepancy occurred for BMI. High BMI was significantly related to low absolute dense area but at the same time significantly related to high dense volume.

Many studies have shown that women with higher BMI have a lower percent breast density (13, 17). In most studies, this was explained by a strong correlation between BMI and the nondense (fat) tissue in the breast, and not by a lower amount of dense tissue (17, 19). In some studies, however, higher BMI seemed to be related to both a lower amount of nondense tissue and dense tissue (13). We too observed here that the absolute amount of dense tissue as measured with the threshold method was significantly lower in women with a high BMI.

This relationship seems in contradiction with the finding that high BMI increases breast cancer risk, especially in postmenopausal women (20). Our finding of the dense volume, as measured with the volumetric method, being much larger in women with high BMI would be in agreement with the effect of BMI on breast cancer risk. High BMI was also related to larger dense volume in earlier studies on volumetric methods, based on digitized film screen mammograms (8, 14, 21). In this way, the volumetric method could provide new insight into the relationship BMI, density, and breast cancer risk.

Most previous studies on volumetric methods were based on the SMF method, where volumetric density is measured from digitized film screen mammograms through the estimation of the breast thickness. Three studies have examined the performance of this method and none showed that the volumetric method was superior to the threshold method in indicating a stronger relationship with breast cancer risk factors and/

Table 2. Percent density: Distribution of breast cancer risk factors by quintiles of threshold and volumetric methods

	Threshold method, percent density						Volumetric method, percent density					
	1 ($N = 74$)	2 ($N = 74$)	3 ($N = 74$)	4 ($N = 74$)	5 ($N = 74$)	P_{trend}	1 ($N = 74$)	2 ($N = 74$)	3 ($N = 74$)	4 ($N = 74$)	5 ($N = 74$)	P_{trend}
Age at examination (mean), y	55.2	54.3	54.3	54.3	52.0	<**0.001**	54.0	54.1	54.0	53.8	53.9	<0.79
BMI (mean), kg/m^2	28.3	26.3	24.4	24.8	23.6	<**0.001**	22.7	23.8	25.6	26.8	28.9	<**0.001**
Age at menarche (mean), y	12.7	13.2	13.2	13.3	13.2	**0.03**	13.3	13.1	13.3	13.2	13.0	0.21
Nulliparous, %	14.9	16.2	29.7	12.2	33.8	**0.03**	20.3	26.0	16.0	21.6	23.0	**0.94**
Number of children (median)	1.8	1.8	1.5	1.9	1.4	0.14	1.7	1.6	1.8	1.6	1.7	**0.15**
Age at first delivery (mean),[a] y	24.5	24.6	26.3	26.3	28.1	<**0.001**	25.8	25.4	26.0	26.8	25.3	<**0.85**
Postmenopausal, %	62.2	58.1	56.8	43.2	33.8	<**0.001**	44.6	57.5	56.0	44.6	51.4	<**0.001**
Age at menopause (mean),[b] y	47.8	48.7	47.1	49.6	46.6	0.20	45.7	49.3	48.7	47.6	49.9	0.89
Ever HT use, %	32.9	24.4	33.8	31.1	30.1	0.92	24.3	30.6	28.0	38.4	34.2	0.43
Ever pill use, %	86.3	91.9	87.8	90.5	86.5	0.93	87.8	89.0	90.7	91.8	83.8	0.25
First-degree family history of breast cancer, %	14.9	20.3	17.6	14.9	14.9	0.69	20.3	16.4	17.3	14.9	13.5	0.77

[a]Parous women only.
[b]Postmenopausal women only.

Table 3. Absolute density: Distribution of breast cancer risk factors by quintiles of threshold and volumetric methods

	Threshold method, absolute density						Volumetric method, absolute density					
	1 ($N = 74$)	2 ($N = 74$)	3 ($N = 74$)	4 ($N = 74$)	5 ($N = 74$)	P_{trend}	1 ($N = 74$)	2 ($N = 74$)	3 ($N = 74$)	4 ($N = 74$)	5 ($N = 74$)	P_{trend}
Age at examination (mean), y	55.2	54.3	53.9	54.3	52.0	<**0.001**	54.0	54.1	54.0	53.8	53.9	0.79
BMI (mean), kg/m^2	28.5	26.3	24.4	24.8	23.6	<**0.001**	22.7	23.8	25.6	26.8	28.9	<**0.001**
Age at menarche (mean), y	12.7	13.2	13.2	13.3	13.2	**0.03**	13.3	13.1	13.3	13.0	13.0	0.21
Nulliparous, %	14.9	16.2	29.7	12.2	33.8	**0.03**	20.3	26.0	16.0	21.6	23.0	0.94
Number of children (median)	1.8	1.8	1.5	1.9	1.4	0.14	1.7	1.6	1.8	1.6	1.7	0.15
Age at first delivery (mean)[a], y	24.7	24.6	26.3	26.3	28.1	<**0.001**	25.8	25.4	26.0	26.8	25.3	0.85
Postmenopausal, %	62.2	58.1	56.8	43.2	33.8	<**0.001**	44.6	57.5	56.0	44.6	51.4	0.97
Age at menopause (mean),[b] y	47.8	48.7	47.1	49.6	49.6	0.20	45.7	49.3	48.7	47.6	49.9	**0.04**
Ever HT use, %	32.9	27.4	33.8	31.1	30.1	0.92	24.3	30.6	28.0	38.4	34.2	0.11
Ever pill use, %	86.3	91.9	87.8	90.5	86.5	0.93	87.8	89.0	90.7	91.8	83.8	0.64
First-degree family history of breast cancer, %	14.9	20.3	17.6	14.9	14.9	0.69	20.3	16.4	17.3	14.9	13.5	0.27

[a]Parous women only.
[b]Postmenopausal women only.

Table 4. Standardized percent density and absolute density are adjusted for age at examination and BMI

		Percent density				Absolute density			
		Threshold		Volumetric		Threshold, cm^2		Volumetric, cm^3	
		β	95% CI	β	95% CI	β	95% CI	β	95% CI
Age at examination[a]	Per year	**−0.056**	**−0.077 to −0.036**	**−0.060**	**−0.082 to −0.038**	**−0.049**	**−0.071 to −0.026**	−0.005	−0.027 to 0.017
BMI[b]	Per 2-kg/m^2 increase	**−0.206**	**−0.241 to −0.170**	**−0.144**	**−0.182 to −0.105**	**−0.137**	**−0.176 to −0.097**	**0.191**	**0.153 to 0.230**
Nulliparous	Yes	0.137	−0.072 to 0.346	**0.260**	**0.038 to 0.482**	0.118	−0.112 to 0.348	0.073	−0.152 to 0.297
Postmenopausal	Yes	**−0.201**	−0.389 to −0.012	−0.133	−0.334 to 0.069	**−0.223**	**−0.430 to −0.016**	−0.043	−0.246 to 0.160
Age at menarche	Per year	0.045	−0.012 to 0.102	0.013	−0.049 to 0.075	0.044	−0.018 to 0.107	−0.008	−0.070 to 0.054
Age at menopause	Per year	0.016	−0.008 to 0.041	0.015	−0.010 to 0.040	**0.024**	**0.000 to 0.048**	**0.029**	**0.005 to 0.053**
Age at first delivery	Per 2 year	**0.045**	**0.004 to 0.086**	**0.052**	**0.009 to 0.096**	**0.050**	**0.005 to 0.094**	0.033	−0.011 to 0.078
Ever HT use	Yes	0.134	−0.061 to 0.329	0.193	−0.016 to 0.402	0.186	−0.029 to 0.400	**0.215**	**0.006 to 0.424**
Ever pill use	Yes	−0.095	−0.362 to 0.172	−0.221	−0.507 to 0.064	−0.106	−0.073 to 0.028	−0.068	−0.355 to 0.220
Family history	Yes	0.101	−0.132 to 0.335	0.077	−0.172 to 0.327	0.111	−0.146 to 0.367	0.052	−0.198 to 0.302

NOTE: β is the number of SD change in breast density.

[a] β_{age} is adjusted for BMI.

or breast cancer risk. Both Ding et al. and Aitken et al. showed that the threshold method gives stronger relations with breast cancer risk than the volumetric method. A possible explanation for the weaker relation with the volumetric method can be the automatic segmentation of the breast in the volumetric method that might be more sensitive to errors than the manual segmentation (8). Another study, using a different volumetric method on film screen mammograms, did not show a better performance of the volumetric approach in relation with breast cancer risk either (9).

Volumetric methods for MRI and ultrasound have also been developed. Both seem to give high correlations with the Breast Imaging Reporting and Data System breast density classification (22, 23) and the computer-assisted threshold method (24), but yet only 1 study examined the relation between these measures and breast cancer risk factors (25). In this study, the MRI volumetric method and the computer-assisted threshold method gave approximately equally strong results in relation with established anthropometric and hormonal factors, but also in this study higher BMI was related to a higher dense volume, although this relation was weak. A limitation of this method is that, due to the high costs of MRI, it can only be used in restricted groups of women.

In our study, mammographic information has been routinely collected through a population based screening program and information on breast cancer risk factors through comprehensive questionnaires. Through the selection of a younger and an older group of participants, we enlarged the variation in breast density in our study population. Data for these groups have been collected in different time periods. Nevertheless, the results were the same when we did separate analyses for the younger and older groups (results not shown).

The median percent density in our study population was 15% for subjects with a median age of 57 years. This is low in comparison with previous studies on breast density. This could be explained by the fact that we measured density on digital mammograms whereas most previous studies measured density on film screen mammograms. As digital mammography is designed to make density less obstructive, average density is expected to be lower. We had expected to find stronger relationships with breast cancer risk factors for the FFDM volumetric method than for the computer-assisted threshold method, but this was not confirmed by our results. Several issues may have played a role. First, it is known that for extremely dense breasts the volumetric method tends to underestimate the volume of dense tissue. van Engeland et al. uses an internal calibration, which relies on the pixel value of purely fatty tissue. In extremely dense breasts it is very hard to obtain a reliable calibration location that contains only fatty tissue (5). Second, the volumetric method was developed and tested on mammograms that were acquired with a GE Senographe 2000D, whereas in this study the images were acquired with a Hologic Selenia FFDM system. A major difference between both mammography systems is the compression paddle that is used to compress the breast during image acquisition. The Hologic compression paddle is designed to tilt during compression, whereas the compression paddle that is used in the GE Senographe 2000D is much more rigid. The usage of a flexible paddle results in variation in breast thickness up to 2 cm from the chest wall to the breast margin. This variation in breast thickness introduces a source of error in the volumetric breast density estimation (26, 27). It is therefore possible that the volumetric measurements are less accurate for the Hologic mammograms used in this study than for the GE images of the study of van Engeland et al. Another possible reason why the volumetric method did not find stronger relations might be that variability of the percent density and the dense area is limited. This was also found by McCormack et al. and Aitken et al. (8, 14).

Despite the positive first results described by van Engeland et al., the volumetric method used is still not perfect and will be further developed, tested, and validated in breast cancer patients and controls to gain even more precise results.

In summary, percent density measured with the FFDM volumetric method is strongly related to well-known breast cancer risk factors, but not more strongly than percent density measured with a computer-assisted threshold method. Absolute dense volume is less strongly related to breast cancer risk factors that the dense area using the threshold method. This indicates that the method needs further improvements. On the other hand, the positive relationship between BMI and dense volume could give new insights in the influence of BMI on the composition of the breasts and breast cancer risk. This study is a first step to measure the validity of the volumetric approach, but as mentioned earlier, the threshold method has limitations as well and cannot be considered a true golden standard. Therefore, it is important to examine whether the volumetric measurements from FFDM are more strongly related to breast cancer risk than the threshold measurements.

Disclosure of Potential Conflicts of Interest

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