Mammographic density over time among women who have participated in BreastScreen Norway

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ABSTRACT

Background

We analyzed the consistency in absolute and percent density using an automated method for estimating volumetric breast density among women who attended BreastScreen Norway 2007-2015.

Material and Methods

We used information from 33,711 women aged 50-69 who underwent two to five full field digital screening examinations biennially, 2007-2015. BMI and HT-use was obtained from a self-administered questionnaire, sent together with the invitation to screening. BMI was categorized into <21.0; 21.0-24.9; ≥25.0 kg/m^2, while use of HT was defined as ever versus never used. An automated method estimated fibroglandular volume (cm^3), breast volume (cm^3) and volumetric breast density (%) for each screening examination. We applied mixed-effects linear models to estimate associations between age, fibroglandular volume, breast volume and volumetric breast density over time including data on BMI and HT.

Results

The results models indicated age to be associated with decreased fibroglandular volume and volumetric breast density, and increased breast volume. BMI <21 kg/m^2 was associated with higher volumetric breast density, but lower fibroglandular and breast volume. Contrary, BMI ≥25 kg/m^2 was associated with lower volumetric breast density and higher fibroglandular and breast volumes. Variation in volumetric breast density and fibroglandular volume within women was rather subtle: this variance did not exceed 10% for either volumetric breast density, fibroglandular volume or breast volume.

Conclusion

Automated measures of volumetric breast density and fibroglandular volume software decreased with age among women screened in BreastScreen Norway. Absolute and percent density varied with a maximum of 10% over time, from first to last screening examination.

Key words: mammographic density, breast cancer screening, longitudinal trends

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1. INTRODUCTION

Mammographic density (MD) is considered an independent risk factor for breast cancer[1]. Further, high MD is shown to mask tumors and thus decrease the sensitivity of screening mammography[2,3]. Age is currently the main factor associated with invitation to organized breast cancer screening programs[4]. Further stratification of breast cancer screening based on risk factors could be seen as expedient and justifiable[5]. Studies have shown that age, parity, menopausal status, body mass index (BMI) and hormonal interventions are factors of influence for MD[6-11]. For women targeted by screening, some of these factors might change over time. In order to consider implementation of breast cancer screening stratified by MD, there is a need to understand what factors considerably affect changes in MD. However, there are a limited number of studies on the topic, and the results are inconsistent[9,12,13]. Most of the studies are performed with BI-RADS density measurements, which is shown to have a substantial inter-reader variability[14,15].

Several studies have investigated changes in MD and factors related to these changes[8,16]. Boyd et al. showed a decline in MD among postmenopausal compared with premenopausal women[8]. Other studies have reported a slower decline in density over time among women with a high body mass index, late age at first birth and use of hormonal therapy (HT)[16,17]. Further studies based on a large number of women, longer follow-up period and objective MD measurements are thus needed.

As of today, automated methods of MD assessment are available. BreastScreen Norway has collected information on automated density measures for women screened in two counties, Rogaland and Hordaland, from 2014. In addition, density information was extracted from the DICOM header and run through the automated density assessment software retrospectively for the period 2007-2014. In this study, we examined the consistency in absolute and percent MD estimated by the automated software, among women attended two, three, four or five regular screening examinations in BreastScreen Norway by age, body mass index (BMI) and HT.

2. MATERIAL AND METHODS

The Regional Committee for Medical and Health Research Ethics approved the study. We used solely de-identified data from the Cancer Registry database for analyses.

2.1 Study population and information on breast cancer risk factors

We used information from 94,597 full field digital screening examinations performed among 33,711 women who had participated in BreastScreen Norway two (n=14,473), three (n=12,192), four (n=6,155) and five (n=891) times, 2007-2015. BreastScreen Norway invites women aged 50-69 years to two-view mammography biennially. The program started in 1996 and became nationwide in 2005. The participation rate among the invited women have been stable around 75%. The target population of the program was about 600,000 women in 2015. The program has been described further elsewhere[18].

2.2 Mammographic density measurement

The automated software, Volpara[TM19,20] produced measurements of fibroglandular volume (cm^3), breast volume (cm^3) and the ratio between the two, volumetric breast density (%), for each screening examination as average values for the mammograms (four mammograms per examination).

2.3 Questionnaire on breast cancer risk factors

Women who participated in BreastScreen Norway completed a self-administered questionnaire that asked about several risk factors for breast cancer including demographic information, weight and height, and use of HT. Women received the questionnaire together with the invitation to screening and handed it in at the time of screening examination. BMI was calculated as kg/m^2 and divided into three categories: < 21; 21-24.9; ≥25 kg/m^2 for analyses. According to the data obtained, use of HT was classified as never or ever used. The latter category included women who responded that they were currently using estrogen (ET) or combined estrogen-progesterone therapy (EPT), or had used these types of HT in the past.

2.4 Statistical analysis

Descriptive information included means, medians and interquartile distributions and percentages for all screening examinations combined. To compare distributions of fibroglandular and breast volume, and volumetric breast density and by risk factor information for different periods, we analyzed the data at examination level. Mean, median and range of volumetric breast density, fibroglandular volume and breast volume were computed for four-year age groups. Absolute differences in means of volumetric breast density, fibroglandular volume and breast volume between two-year screening intervals were depicted by hormonal therapy status and BMI. We applied mixed-effects linear models to estimate the association of age and volumetric breast density, fibroglandular volume and breast volume over time. These models included data on BMI and use of hormonal therapy. Random intercepts and slopes were applied to reflect individual-specific, time-dependent trends in density and fibroglandular and breast volume, while an unstructured correlation structure was used to account for varied time intervals between repeated measurements as about 5% of women participated in screening irregularly. The final model was identified from backward selection. The results represent a cross-sectional, age specific average based on all of the observed values of volumetric breast density and fibroglandular and breast volume, constrained to reflect individual-specific trends present in the data provided by each woman. We applied natural logarithm transformation to normalize the distributions of volumetric breast density and fibroglandular volume and square root transformation to normalize the distribution of breast volume. The transformed outcome variables were used in mixed-effects models. All analyses were performed with Stata (version 14, *Stata*Corp, College Station, TX, USA).

3. RESULTS

Among the 33,711 women included in the study population, 43% (n=14,473) had participated in the program two times, 36% (n=12,192) three times, 18% (n=6,155) four and 3% (n=891) five times. Mean age at time for the 94,597 screening examinations was 58.6 years and average BMI was 24.9 kg/m^2.

The majority of the screening examinations (34%, 16,081/94,597) were performed among women aged 55-59 years. Among all screening examinations, 64% (60,542/94,597) were obtained among never users of HT while 36% (34,055/94,597) reported ever use of HT (Figure 1). About 7% (6,622/94,597) of screening examinations were obtained among women with BMI <21 kg/m^2, while about 36% (34,055/94,597) had BMI ≥ 25 kg/m^2.

Table 1. Descriptive information for volumetric breast density, fibroglandular volume and breast volume by age groups for 94,597 screening examinations performed in BreastScreen Norway, 2007-2015

Age	Volumetric breast density (%)			Fibroglandular volume (cm^3)			Breast volume (cm^3)		
(years)	Mean (SD)*	Median	Range	Mean (SD)*	Median	Range	Mean (SD)*	Median	Range
50-54	8.0 (4.8)	6.6	1.5-51.2	51.2 (26.4)	44.9	6.6-359.5	780.9 (424.2)	700.8	37.4-3897.6
55-59	6.7 (4.0)	5.5	1.4-45.6	46.4 (22.7)	41.0	4.8-316.2	838.4 (435.1)	763.7	29.6-3567.1
60-64	6.0 (3.5)	4.9	1.5-35.9	44.2 (20.8)	39.4	5.3-270.9	884.1 (433.9)	815.7	28.6-3540.9
65-69	5.7 (3.3)	4.7	1.4-27.9	43.8 (19.9)	39.5	4.7-274.1	921.9 (445.8)	857.6	46.2-3559.5
Total	6.7 (4.1)	5.4	1.4-51.2	46.6 (22.9)	41.1	4.7-359.5	849.3 (436.4)	777.9	28.6-3897.6

*P-value <0.001 for the differences between mean values of volumetric breast density and fibroglandular and breast volume for different age groups

The differences between mean values of volumetric breast density and fibroglandular and breast volume were statistically significant, implying the trend of decreasing volumetric breast density and fibroglandular volume by age and increasing breast volume by age (Table 1).

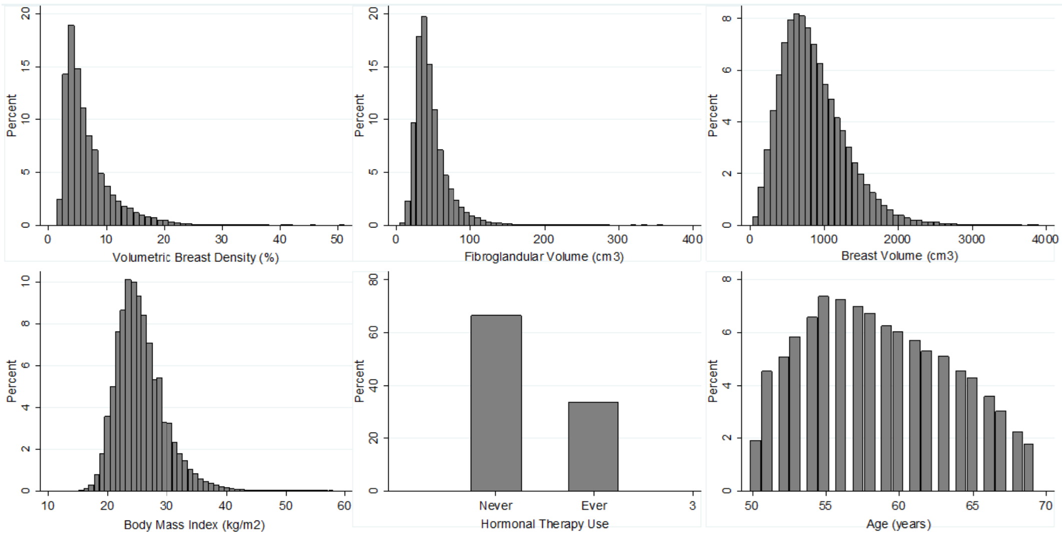

Figure 1. Distribution of screening examinations by volumetric breast density, fibroglandular volume, breast volume, body mass index, use of hormonal therapy and age

For never users of HT, the mean difference in volumetric breast density, fibroglandular volume and breast volume gradually increased with increasing screening interval for all BMI categories (Table 2). Similar trends were observed for HT users; however, the changes in fibroglandular volume for women with BMI<21 kg/m^2 were inconsistent.

Table 2. Changes in volumetric breast density, fibroglandular volume and breast volume (mean, standard deviation (SD) in percent) by screening interval, use of hormonal therapy (ever, never) and body mass index (BMI) for 94,597 screening examinations performed in BreastScreen Norway, 2007-2015

	Never used hormonal therapy			Ever used hormonal therapy		
	BMI			BMI		
Years after first screening examination	<21 kg/m^2	21-24.9 kg/m^2	≥25 kg/m^2	<21 kg/m^2	21-24.9 kg/m^2	≥25 kg/m^2
Changes in volumetric breast density, mean (SD), %						
2 years	-1.3 (2.8)	-1.0 (2.1)	-0.4 (1.4)	-1.0 (2.7)	-0.7 (1.8)	-0.4 (1.4)
4 years	-2.2 (3.2)	-1.6 (2.5)	-0.7 (1.7)	-1.7 (3.0)	-1.1 (2.1)	-0.5 (1.7)
6 years	-2.5 (10.3)	- 1.9 (2.4)	-0.9 (1.8)	-2.4 (3.0)	-1.6 (2.3)	-0.8 (1.8)
8 years	-3.0 (3.7)	-2.4 (3.2)	-1.1 (1.7)	-3.4 (4.5)	-2.2 (2.4)	-1.3 (1.8)
Changes in fibroglandular volume, mean (SD), cm^3						
2 years	-1.5 (9.5)	-2.5 (10.7)	-2.1 (11.3)	-0.01 (9.1)	-1.7 (9.8)	-1.1 (11.7)
4 years	-1.8 (12.0)	-3.6 (12.4)	-2.8 (12.9)	0.1 (11.7)	-1.9 (11.3)	-1.3 (13.3)
6 years	-2.4 (11.5)	-4.2 (11.8)	-3.9 (14.2)	-1.9 (9.9)	-3.4 (12.7)	-3.1 (14.2)
8 years	-3.0 (11.5)	-7.4 (17.0)	-6.1 (15.4)	-3.3 (14.2)	-5.2 (13.4)	-4.3 (14.0)
Changes in breast volume, mean (SD), cm^3						
2 years	30.5 (110.0)	42.4 (136.8)	38.6 (207.6)	28.6 (109.9)	36.7 (134.2)	43.8 (190.4)
4 years	58.1 (121.7)	71.5 (147.8)	67.4 (232.9)	56.6 (121.2)	63.4 (149.3)	59.9 (226.6)
6 years	62.0 (121.0)	96.7 (151.9)	79.2 (235.2)	67.5 (126.8)	81.4 (153.2)	89.2 (227.8)
8 years	63.7 (200.9)	89.5 (158.9)	97.6 (214.5)	58.2 (101.1)	101.9 (152.3)	129.3 (257.9)

The results of the mixed-effects models indicated that age was associated with decreased volumetric breast density and fibroglandular volume and an increased in breast volume (Table 3). BMI <21 kg/m^2 was associated with higher volumetric breast density, but lower fibroglandular and breast volume. Contrary, BMI ≥25 kg/m^2 was associated with lower volumetric breast density and higher fibroglandular and breast volume. Ever use of HT was associated with an increase in volumetric breast density and fibroglandular volume, and a decrease in breast volume. The models showed that variation in volumetric breast density and fibroglandular volume within women was rather subtle. The proportion of the changes due to variation between women for both volumetric breast density and fibroglandular and breast volume did not exceed 10%.

Table 3. Predictors of volumetric breast density, fibroglandular volume and breast volume in the mixed effects models for 94,597 screening examinations (n=33,711 women) performed in BreastScreen Norway, 2007-2015

	Volumetric breast density (%)		Fibroglandular volume (cm^3)		Breast volume (cm^3)	
Variable	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Intercept (cons)	2.11	2.11;2.12	3.84	3.83;3.85	24.81	24.72;24.91
Age						
Linear term centered at 50 years	-0.50	-0.05; -0.04	-0.02	-0.03; -0.02	0.34	0.33;0.35
Quadratic term	0.001	0.0012; 0.0013	0.001	0.006; 0.007	-0.007	-0.007; -0.006
Body mass index, kg/m^2						
<21	0.2	0.19; 0.21	-0.07	-0.08; -0.07	-2.71	-2.80; -2.63
21-24.9	ref	ref	ref	ref	ref	ref
≥25	-0.19	-0.19; -0.18	0.06	0.05; 0.06	3.13	2.07; 3.18
Use of hormonal therapy						
Never	ref	ref	ref	ref	ref	ref
Ever	0.03	0.03;0.04	0.02	0.01;0.02	-0.22	-0.29; -0.15

4. DISCUSSION

In our study, volumetric breast density and fibroglandular volume decreased with age. Use of HT was associated with a slight increase in volumetric breast density and fibroglandular volume. Increasing BMI was associated with lower volumetric breast density, but higher fibroglandular volume over time.

The results are in line with the results of previous studies. As such, a recent study from the UK, assessing MD changes over time by comparing two methods of breast density measurement, concluded that percent and absolute density decreased over time, and higher BMI was associated with lower mean percent density[21]. Kelemen et al, using data from the Minnesota Breast Cancer Family Study, reported that change in MD over time appeared to be influenced by age, baseline density, BMI, and use of HT[16]. Another study from the U.S. showed that for women who did developed breast cancer, MD decreased with age[22]. The study by Maskarinec et al., investigating longitudinal trends in MD for the Multiethnic Cohort of Hawaii, reported that the size of dense areas decreased by 34% with age[17]. Use of HT has been shown to be associated with a lower decrease in MD over time compared with no use[23,24], while increase in BMI has been shown to be inversely associated with decreasing MD[11].

The decrease in volumetric breast density and fibroglandular volume by increased age is associated with involution of the glandular tissue, due to the decline in circulating ovarian-produced estrogens, which is typically found after menopause. On the other hand, the increased breast volume might be related to subsequent increase in the amount of adipose tissue in the breast, as it replaces the fibroglandular tissue after menopause. Weight gain might also influence the amount of adipose tissue and thus breast volume over time.

The strengths of our study include the large sample of examinations obtained from women who attended two to five regular screening examinations in a population based screening program, and the use of the automated method for density assessment, producing values of volumetric breast density and fibroglandular volume.

However, the study also had limitations. Women who are concerned about their health are probably more likely to participate in mammographic screening and answer the questionnaire related to breast cancer risk factors compared to women without such concern. The study sample does not represent the entire population. Furthermore, we did not have information about several important breast cancer risk factors as menopausal status, parity, age at menarche, etc. and the mixed-effect models were thus incomplete in terms of explanation of changes in density over time. The data on HT and BMI were self-reported implying possibilities for misclassification. We used solely descriptive approach with regard to density, we did not have information about cancer cases and the study population included both cancer-free women and women who were diagnosed with breast cancer.

5. CONCLUSION

Our study showed that MD estimated as volumetric breast density and fibroglandular volume decreased with age among women screened in BreastScreen Norway. Higher BMI was associated with lower volumetric breast density, while use of HT was associated with a slight increase in volumetric breast density. Further studies are needed to identify possible changes for women diagnosed with breast cancer and thus determine if changes in MD over time could influence the risk of breast cancer.

Conflict of interest

The authors declare no conflict of interest.

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