Research Article

Cancer Epidemiology, Biomarkers & Prevention

# Volumetric Mammographic Density, Age-Related Decline, and Breast Cancer Risk Factors in a National Breast Cancer Screening Program

Kirsti Vik Hjerkind[1], Merete Ellingjord-Dale[1,2], Anna L.V. Johansson[1,3], Hildegunn Siv Aase[4], Solveig Roth Hoff[5], Solveig Hofvind[1,6], Siri Fagerheim[7], Isabel dos-Santos-Silva[8], and Giske Ursin[1,9,10]

## Abstract

**Background:** Volumetric mammographic density (VMD) measures can be obtained automatically, but it is not clear how these relate to breast cancer risk factors.

**Methods:** The cohort consisted of 46,428 women (ages 49–71 years) who participated in BreastScreen Norway between 2007 and 2014 and had information on VMD and breast cancer risk factors. We estimated means of percent and absolute VMD associated with age, menopausal status, body mass index (BMI), and other factors.

**Results:** The associations between VMD and most breast cancer risk factors were modest, although highly significant. BMI was positively associated with absolute VMD, whereas inversely associated with percent VMD. Percent VMD was inversely associated with a 5-year older age at screening in premenopausal and postmenopausal women (−0.18% vs. −0.08% for percent VMD and −0.11 $cm^3$ vs. −0.03 $cm^3$ for absolute VMD). This difference was largest among postmenopausal women with BMI < 25 $kg/m^2$ ($P$ for interaction with percent VMD < 0.0001), never users of postmenopausal hormone therapy ($P$ for interaction < 0.0001), and premenopausal women with a family history of breast cancer ($P$ for interaction with absolute VMD = 0.054).

**Conclusions:** VMD is associated with several breast cancer risk factors, the strongest being BMI, where the direction of the association differs for percent and absolute VMD. The inverse association with age appears modified by menopausal status and other breast cancer risk factors.

**Impact:** Because VMD methods are becoming widely available in screening and clinical settings, the association between VMD measures and breast cancer risk factors should be investigated further in longitudinal studies. *Cancer Epidemiol Biomarkers Prev; 27(9); 1065–74. ©2018 AACR.*

## Introduction

Mammographic density describes the relative amounts of radiolucent fatty tissue versus radiodense fibroglandular tissue in the breast (1). High density is a strong independent risk factor for breast cancer, with risk increasing with increasing density (2, 3). Women with a very high percentage of the breast occupied by dense tissue have a 4- to 6-fold increased risk of breast cancer compared with women who have predominately fatty breasts (3).

Traditionally, mammographic density assessment methods are based on a two-dimensional area-based projection of the breast. Such methods estimate area-based absolute density (i.e., the area occupied by dense tissue in $cm^2$) as well as percent density (i.e., the percentage of the total breast area occupied by dense tissue). Although the latter is the most frequently used area-based measure of mammographic density, both percent density and absolute density have been shown to be strong risk factors for breast cancer (4–9). The breast imaging reporting and data system (BI-RADS) is a commonly used ordinal density scale which provides a standardized classification for mammographic density (10).

Several automated methods have been developed for assessment of volumetric mammographic density (VMD) on digital images during the last decade. These methods assess the breast volume by multiplying the breast area on a two-dimensional mammogram by the compressed thickness of the breast. They determine the amount of dense tissue in the breast, absolute density, by integration of the thickness of dense tissue at each pixel over the mammogram. Percent VMD is obtained from the ratio absolute VMD divided by breast volume. VMD measures have produced reasonably strong associations with breast cancer risk when validated against visual assessment and computer-assisted methods (11). As VMD methods are becoming increasingly used

[1]Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway. [2]Imperial College London, School of Public Health, Department of Epidemiology and Biostatistics, London, United Kingdom. [3]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. [4]Haukeland University Hospital, Bergen, Norway. [5]Helse Møre og Romsdal HF, Ålesund, Norway. [6]Oslo Metropolitan University, Oslo, Norway. [7]Stavanger University Hospital, Stavanger, Norway. [8]Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom. [9]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California. [10]Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway.

**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

**Corresponding Author:** Kirsti Vik Hjerkind, Cancer Registry of Norway, 0304 Oslo, Norway. Phone: 47-95-28-35-06; Fax: 47-22-45-13-70; E-mail: kirsti.vik.hjerkind@kreftregisteret.no

**doi:** 10.1158/1055-9965.EPI-18-0151

in epidemiologic studies of density (12–18), it becomes important to understand not only how VMD measures are associated to breast cancer risk, but also how they relate to established breast cancer risk factors.

We have much knowledge on the association between breast cancer risk factors and area-based mammographic density measures. Such measures of mammographic density are positively associated with late age at first birth, nulliparity, and postmenopausal hormone therapy (19–22). Alcohol intake has also been positively associated with mammographic density in area-based studies, whereas physical activity and smoking have been inversely or not associated (23–25). Body mass index (BMI) is strongly inversely associated with percent mammographic density (16); however, the association with absolute mammographic density is less clear, with an inverse association mostly reported (6, 16, 26).

To what extent these breast cancer risk factors affect similarly absolute and percent VMD is less clear. There is also less understanding of how the magnitude of VMD differs between women with different risk factor profiles. Although a 5% arithmetic difference in percent density in area-based studies is indicative of an effect similar to that of postmenopausal hormone therapy (27), it is not yet clear what represents a "large" effect on VMD.

Area-based measures have shown that mammographic density declines with increasing age and during the menopausal transition (28, 29). It is, however, less clear whether similar age- and menopause-related declines occur with VMD and, if so, which factors may modify the rate of such declines.

We decided to take advantage of a large collection of VMD measures from women participating in BreastScreen Norway to better understand how volumetric and area-based mammographic density measures are correlated, how various risk factors are associated with both percent and absolute VMD, and the extent to which those risk factors modify age- and menopause-related differences.

## Materials and Methods

### Study population

BreastScreen Norway (the Norwegian screening program for breast cancer) is administered by the Cancer Registry of Norway and invites women within a targeted age range of 50 to 69 years to a bilateral two-view mammogram biennially. It has a participation rate of about 84% (30). From August 2006, women who underwent mammographic screening were asked to complete a questionnaire on a number of standard breast cancer risk factors and a second questionnaire on current exposures to risk factors. At subsequent screenings, they were asked to complete only the second questionnaire (31). Our cohort consisted of women who participated in BreastScreen Norway in the four counties where VMD measures were registered (Hordaland, Rogaland, Akershus, and Trøndelag), who had information on VMD from their first mammographic screening between 2007 and 2014, and had completed both questionnaires ($n = 63{,}544$). We excluded 1,194 women who had a diagnosis of breast cancer or ductal carcinoma *in situ* previous or up to 6 months after the screening date, and 622 women who had incomplete data on the VMD variables, leaving information from a total of 61,728 women. Further, we excluded the following due to missing information on the confounding variables BMI ($n = 6{,}785$), education ($n = 1{,}425$), menopausal status ($n = 1{,}595$), and number of pregnancies ($n = 5{,}689$). This left us with 46,234 women for analyses. In analyses of associations between age, menopausal status, and breast cancer risk factors, we excluded pre/perimenopausal women above the age of 55 years, leaving 45,448 women for these analyses.

The study was approved by the Regional Committee for Medical and Health Research Ethics in the South-East Health Region of Norway.

### Mammographic density measures

All women in the study had standard two-view (mediolateral oblique and craniocaudal) full-field mammography of each breast with Senographe DS or Senographe Essential machines (GE Healthcare) in Hordaland and Rogaland, MDM L50 (Philips) in Akershus, and MDM L30 (Philips) in Trøndelag. VMD was read using the fully automated system Volpara v1.5.0 (Volpara Health Technologies Limited). Volpara is shown to be associated with BI-RADS [i.e., in a study by van der Waal and colleagues, BI-RADS category A (fatty) is equivalent to a median dense volume of 3.6%, category B (scattered density) 5.3%, category C (heterogeneously dense) 10.2%, and category D (extremely dense) 19.3%; ref. 32].

Volpara computes the thickness of dense tissue at each individual pixel in the mammogram, using a fatty region as an internal reference. To do the calculation, it is assumed that the pixel value is linearly related to the energy imparted to the x-ray detector, so that the difference in the pixel values between each pixel and the reference point can be related directly to the thickness of dense tissue between the pixel and the x-ray source. Absolute VMD ($cm^3$) is estimated by integrating the dense thickness at each pixel over the whole mammogram and multiplying by the known pixel size. The total breast volume ($cm^3$) is derived by multiplying the breast area ($cm^2$) by breast thickness with a correction for the breast edge. Percent VMD (%) is obtained from the ratio of these two measures (33). In the analyses, we have used the mean VMD from both breasts of the mediolateral oblique view and of the craniocaudal view. Correlation between measures across breasts and views was high, with $r > 0.89$, $P < 0.0001$ for percent VMD and $r > 0.82$, $P < 0.0001$ for absolute VMD. The main reason for using the average value across the four images is to reduce random measurement errors and hence to increase precision.

### Exposure information

The breast cancer risk factors of interest included reproductive factors (age at menarche, age at first birth, number of pregnancies lasting at least 6 months, and duration of breastfeeding), menopausal status (whether a woman still had her menstrual period or whether she menstruated regularly, yes = premenopausal, uncertain = perimenopausal, no = postmenopausal), age at menopause (the age at which her menstrual periods stopped), and hormone use (oral contraceptives and postmenopausal hormone therapy). We also examined self-reported height and BMI ($kg/m^2$) at the time of the mammography, and other risk factors such as education (no education/primary school, high school, university bachelor, university master), current physical activity (no exercise, 1–2.5 hours/week, 2.5–4.5 hours/week, 4.5–6 hours/week, >6 hours/week), alcohol intake (never, 1 glass/week, 2 glasses/week, 3–4 glasses/week, 5–6 glasses/week, >6 glasses/week), and smoking habits (never, past, current). Women with a family history of breast

cancer had answered "yes" to the question "Have your mother/sister/daughter had breast cancer (yes, no, do not know)" and/or "yes" to the question "Have your grandmother or your mother's sister had breast cancer (yes, no, do not know)." Information on current exposures was collected from the questionnaire belonging to the screening round from which we have density measures, and if the questionnaire or certain values were missing, information from the questionnaire completed at a previous screening round was used (approximately 16.5%).

### Statistical analyses

We evaluated the agreement by side (left vs. right) and view (mediolateral oblique vs. craniocaudal) in correlation analyses, calculating Pearson correlation coefficients. We estimated marginal means of percent and absolute VMD associated with the above-mentioned breast cancer risk factors using generalized linear models with the postestimation Stata-command –margins- (34), with a normal error distribution and a log link, to account for the skewed distribution of percent and absolute VMD. We further applied robust standard errors to account for additional under- or overdispersion and relax the assumption of log-normality. The delta method was used to calculate 95% confidence intervals (CI; ref. 35). Effects are presented in actual percentage units for percent VMD and in $cm^3$ for absolute VMD, in marginal means as predicted from the model. Based on *a priori* information from area-based studies, as well as based on trends and effect estimates observed in our analyses, we included the following variables as potential confounders: age at screening, BMI at screening, education, number of pregnancies, and menopausal status. In additional analyses, we adjusted for age at menarche, age at first birth, duration of breastfeeding in months, use of postmenopausal hormone therapy, and family history of breast cancer. We also mutually adjusted for smoking, alcohol, and physical activity in analyses with those variables. Women with missing information on an exposure variable were excluded from analyses including that variable. Tests for trend were conducted by modeling the exposures as continuous variables.

We estimated differences in percent and absolute VMD per a 5-year increment in age at screening in pre/perimenopausal and postmenopausal women separately, overall and by subgroups of breast cancer risk factors. We also included an interaction term of menopausal status and age and tested if interaction was present using the Wald test. If an interaction was present, we estimated means of percent and absolute VMD per a 2-year increment in age stratified by the breast cancer risk factor. We examined whether a nonlinear model (i.e., cubic spline regression with five degrees of freedom) of VMD with age was a better fit than the linear model and compared the two models using a likelihood-ratio test. Analyses were carried out using Stata version 15 (36).

## Results

The characteristics of the women in the study cohort are summarized in Table 1. Their mean age was 56.1 years, and their mean BMI was 25.6 $kg/m^2$. A total of 73.5% of the women reported to be postmenopausal, and their mean age at menopause was 49.1 years. Note that 33.5% of the women were ever users of postmenopausal hormone therapy, 79.2% current alcohol consumers, 23.1% current smokers, and 11.5% currently physically inactive. Crude (unadjusted for BMI and other factors) mean percent VMD was 7.2%, and absolute VMD was 49.3 $cm^3$.

**Table 1.** Characteristics of the study population ($N = 46{,}234$)

| Characteristic | Mean (SD), unless stated | Range |
|---|---|---|
| Age at mammography, years | 56.1 (5.6) | 49.1–71.0 |
| Height, cm | 166.3 (5.7) | 130–198 |
| BMI, $kg/m^2$ | 25.6 (4.2) | 10.0–54.5 |
| Age at menarche, years | 13.3 (1.4) | 9–18 |
| Number of pregnancies | 2.6 (1.6) | 0–20 |
| Age at first birth, years | 23.6 (4.6) | 13–50 |
| Duration breastfeeding, months | 16.9 (12.9) | 0–80 |
| Age at menopause, years | 49.1 (4.7) | 25–67 |
| Age at start of oral contraceptives, years | 21.6 (5.2) | 11–50 |
| University bachelor/master | 36.3% | |
| Nulliparous | 9.3% | |
| Postmenopausal | 73.5% | |
| Family history of breast cancer | 23.3% | |
| Hormone therapy use ever | 33.5% | |
| Current smokers | 23.1% | |
| Alcohol consumers (≥1 glass per week) | 79.2% | |
| Inactive | 11.5% | |
| Mammographic measures | | |
| Percent VMD | 7.2 (4.5) | 1.5–41.6 |
| Percent VMD, median | 5.8 | |
| Absolute VMD $cm^3$ | 49.3 (25.2) | 5.7–334.9 |
| Absolute VMD $cm^3$, median | 43.0 | |
| Percent VMD, left CC view | 7.5 (4.9) | 1.4–51.6 |
| Percent VMD, left CC view, median | 5.9 | |
| Percent VMD, left MLO view | 6.9 (4.3) | 1.1–50.8 |
| Percent VMD, left MLO view, median | 5.6 | |
| Absolute VMD, left CC view | 46.6 (25.8) | 5.1–504.6 |
| Absolute VMD, left CC view, median | 40.1 | |
| Absolute VMD, left MLO view | 51.6 (28.1) | 3.6–464.0 |
| Absolute VMD, left MLO view, median | 44.8 | |

Abbreviations: CC, craniocaudal; MLO, mediolateral oblique.

Table 2 shows a strong and inverse association between BMI and percent VMD, with women with BMI < 20 $kg/m^2$ having on average a 3-fold higher percent VMD than those with BMI > 33 $kg/m^2$ [12.9% (95% CI, 12.7%–13.2%) vs. 3.9% (95% CI, 3.9%–4.0%)]. In contrast, BMI was positively associated with absolute VMD, with 1.5 times higher VMD in women in the highest, relative to those in the lowest, BMI category [58.4 $cm^3$ (95% CI, 57.4–59.5 $cm^3$] vs. 37.9 $cm^3$ (95% CI, 37.1–38.8 $cm^3$)]. Both percent and absolute VMD were lower in postmenopausal compared with premenopausal women, and decreased with increasing age. Women who reported a family history of breast cancer had slightly higher percent and absolute VMD than women with no family history.

Table 3 shows mean percent and absolute VMD by age at menarche, age at first birth, age at menopause, education, height and number of pregnancies. We found increasing percent and absolute VMD with increasing age at menarche, increasing age at first birth, increasing age at menopause, and with increasing educational level. Both percent and absolute VMD decreased with increasing number of pregnancies. We observed a weak positive association between height and percent VMD in unadjusted (i.e., adjusted for age only) analyses, but this association diminished upon adjustment for BMI and the other covariates. The positive association between height and absolute VMD, however, persisted after adjustment.

Table 4 shows mean percent and absolute VMD by duration of breastfeeding, age at start of oral contraceptives and duration of oral contraceptives, and use and duration of postmenopausal hormone therapy. We found increasing percent and

**Table 2.** Unadjusted and adjusted mean (95% CI) percent and absolute VMD by selected breast cancer risk factors ($n = 46{,}234$)

| | | Percent VMD | | Absolute VMD | |
|---|---|---|---|---|---|
| | ***n*** | **Age-adjusted[a]** | **Multiadjusted[b] (95% CI)** | **Age-adjusted[a]** | **Multiadjusted[b] (95% CI)** |
| Age | | | | | |
| <50 | 1,760 | 9.1 | 8.2 (8.0–8.4) | 56.9 | 52.5 (51.3–53.8) |
| 50 | 5,365 | 8.8 | 8.1 (8.0–8.2) | 56.1 | 52.7 (52.0–53.5) |
| 51 | 6,113 | 8.2 | 7.7 (7.6–7.8) | 52.8 | 50.5 (49.9–51.2) |
| 52–53 | 6,880 | 7.9 | 7.7 (7.6–7.8) | 51.4 | 50.7 (50.1–51.3) |
| 54–55 | 4,940 | 7.1 | 7.2 (7.1–7.3) | 48.3 | 49.2 (48.5–49.8) |
| 56–57 | 4,482 | 6.7 | 7.0 (6.9–7.1) | 46.5 | 47.8 (47.2–48.5) |
| 58–59 | 3,777 | 6.5 | 6.8 (6.7–6.9) | 45.9 | 47.4 (46.7–48.1) |
| 60–61 | 3,480 | 6.2 | 6.5 (6.4–6.7) | 45.5 | 47.1 (46.4–47.9) |
| 62–63 | 2,991 | 6.0 | 6.5 (6.4–6.6) | 45.1 | 46.7 (45.9–47.5) |
| 64–65 | 2,591 | 5.9 | 6.3 (6.2–6.5) | 45.2 | 47.2 (46.3–48.3) |
| 66–67 | 2,114 | 5.7 | 6.1 (6.0–6.3) | 44.1 | 46.5 (45.6–47.4) |
| ≥68 | 1,741 | 5.7 | 6.1 (5.9–6.3) | 43.1 | 45.5 (44.6–46.4) |
| *P* trend | | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| BMI (kg/m$^2$) | | | | | |
| <20 | 2,284 | 13.0 | 12.9 (12.7–13.2) | 38.1 | 37.9 (37.1–38.8) |
| 20 | 2,583 | 11.2 | 11.1 (10.9–11.3) | 42.4 | 42.2 (41.3–43.0) |
| 21 | 3,770 | 9.8 | 9.7 (9.6–9.9) | 44.4 | 44.3 (43.5–45.1) |
| 22 | 4,738 | 8.8 | 8.8 (8.6–8.9) | 46.9 | 46.9 (46.2–47.6) |
| 23 | 5,038 | 7.9 | 7.9 (7.7–8.0) | 48.2 | 48.3 (47.6–49.0) |
| 24 | 5,352 | 7.2 | 7.2 (7.1–7.3) | 49.2 | 49.3 (48.6–50.0) |
| 25 | 4,515 | 6.4 | 6.4 (6.3–6.5) | 50.1 | 50.3 (49.5–51.0) |
| 26 | 3,863 | 5.9 | 5.9 (5.8–6.0) | 50.5 | 50.8 (50.1–51.6) |
| 27 | 3,138 | 5.6 | 5.6 (5.5–5.7) | 52.9 | 53.0 (52.1–53.9) |
| 28–30 | 6,270 | 4.9 | 4.9 (4.9–5.0) | 53.0 | 52.9 (52.3–53.5) |
| 31–32 | 2,190 | 4.3 | 4.3 (4.2–4.4) | 54.3 | 54.3 (53.2–55.3) |
| ≥33 | 2,493 | 3.9 | 3.9 (3.9–4.0) | 58.9 | 58.4 (57.4–59.5) |
| *P* trend | | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Menopausal status | | | | | |
| Pre- | 7,602 | 8.3 | 8.3 (8.2–8.4) | 56.1 | 56.3 (55.6–57.1) |
| Peri- | 4,660 | 7.4 | 7.6 (7.4–7.7) | 51.8 | 51.5 (50.7–52.3) |
| Post- | 33,972 | 6.9 | 6.9 (6.9–7.0) | 47.2 | 47.2 (47.0–47.5) |
| *P* trend | | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Family history of BC | | | | | |
| No | 34,456 | 7.2 | 7.2 (7.1–7.2) | 48.8 | 48.9 (48.6–49.1) |
| Yes | 10,447 | 7.5 | 7.4 (7.3–7.5) | 50.8 | 50.7 (50.2–51.2) |
| *P* trend | | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

Abbreviation: BC, breast cancer.
[a]Adjusted for age at mammography.
[b]Additionally adjusted for BMI, education, menopausal status, and pregnancies.

absolute VMD with increasing duration of breastfeeding, in current postmenopausal hormone therapy users, and with duration of postmenopausal hormone therapy. Neither percent nor absolute VMD was affected by use of oral contraceptives ($P$ for trend > 0.38).

Table 5 shows mean percent and absolute VMD by selected lifestyle factors, and both percent and absolute VMD were slightly lower among current smokers. A dose–response-positive association was observed between amount of alcohol consumed and percent and absolute VMD. There was an inverse association between physical activity and absolute VMD, and increased percent VMD in women exercising more than 6 hours a week.

Although most of these associations were highly significant ($P < 0.001$), the magnitude of the effect was modest. We found differences in percent and absolute VMD between the lowest and highest exposure categories (with an absolute magnitude of ≥1.0% and ≥5.0 cm$^3$, respectively) for age, BMI, number of pregnancies, menopausal status, and duration of breastfeeding.

The results were essentially unchanged when the analyses were additionally adjusted for age at menarche, age at first birth, duration of breastfeeding in months, use of postmenopausal hormone therapy, and family history of breast cancer. We mutually adjusted for smoking, alcohol, and physical activity in analyses with those variables, and results were unchanged.

When examining the association between age and menopausal status with percent and absolute VMD, we found a larger difference in VMD per 5-year increase in age at screening in pre/perimenopausal women compared with postmenopausal women, that this difference was present in women of different risk factor levels, and that this difference was modified by BMI, postmenopausal hormone therapy, and family history of breast cancer (Supplementary Table S1).

Figure 1 shows associations between age and menopausal status with VMD, stratified by BMI, postmenopausal hormone therapy, and family history of breast cancer. We found the largest difference in percent VMD among postmenopausal women with a BMI < 25 kg/m and no apparent difference in postmenopausal women with a BMI ≥ 30 kg/m$^2$ ($P_{int}$ <

**Table 3.** Unadjusted and adjusted mean (95% CI) percent and absolute VMD by selected breast cancer risk factors ($n = 46{,}234$)

| | | Percent VMD | | Absolute VMD | |
|---|---|---|---|---|---|
| | ***n*** | **Age-adjusted[a]** | **Multiadjusted[b] (95% CI)** | **Age-adjusted[a]** | **Multiadjusted[b] (95% CI)** |
| Age at menarche (years) | | | | | |
| 9–12 | 13,136 | 6.7 | 7.1 (7.0–7.1) | 49.0 | 48.1 (47.7–48.5) |
| 13 | 12,571 | 7.2 | 7.2 (7.2–7.3) | 49.5 | 49.4 (49.0–49.9) |
| 14 | 10,844 | 7.5 | 7.3 (7.2–7.4) | 49.2 | 49.7 (49.2–50.1) |
| 15–18 | 7,831 | 7.8 | 7.4 (7.3–7.5) | 49.3 | 50.2 (49.7–50.8) |
| *P* trend | | <0.0001 | <0.0001 | 0.526 | <0.0001 |
| Age at first birth (years) Height (cm)[c] | | | | | |
| 13–20 | 11,380 | 6.6 | 6.9 (6.8–7.0) | 47.0 | 47.5 (47.1–48.0) |
| 21–22 | 7,445 | 6.9 | 7.0 (7.0–7.1) | 47.4 | 47.9 (47.3–48.4) |
| 23–25 | 10,473 | 7.3 | 7.2 (7.2–7.3) | 48.7 | 48.9 (48.4–49.4) |
| 26–30 | 8,395 | 7.7 | 7.4 (7.3–7.4) | 49.7 | 49.3 (48.7–49.8) |
| 31–50 | 3,260 | 7.9 | 7.5 (7.3–7.6) | 53.3 | 51.2 (50.2–52.1) |
| *P* trend | | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Age of menopause (years)[d] | | | | | |
| <47 | 7,164 | 6.4 | 6.5 (6.4–6.6) | 45.7 | 45.4 (44.9–45.9) |
| 47–49 | 7,025 | 6.7 | 6.6 (6.5–6.7) | 45.5 | 45.7 (45.2–46.2) |
| 50–52 | 11,658 | 6.8 | 6.8 (6.7–6.8) | 46.6 | 46.8 (46.4–47.2) |
| >52 | 6,393 | 6.8 | 6.9 (6.8–7.0) | 48.5 | 48.3 (47.7–48.9) |
| *P* trend | | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Education | | | | | |
| Lower sec. | 9,302 | 6.7 | 6.9 (6.8–7.0) | 47.8 | 47.9 (47.4–48.4) |
| Upper sec. | 20,146 | 7.0 | 7.1 (7.0–7.1) | 48.9 | 48.8 (48.5–49.2) |
| Bachelor | 10,331 | 7.7 | 7.5 (7.4–7.6) | 50.2 | 50.3 (49.8–50.7) |
| Master | 6,455 | 8.1 | 7.7 (7.6–7.8) | 50.7 | 50.7 (50.1–51.4) |
| *P* trend | | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Height | | | | | |
| <159 | 3,844 | 7.0 | 7.3 (7.2–7.4) | 46.7 | 46.2 (45.4–46.9) |
| 160–164 | 12,934 | 7.1 | 7.2 (7.1–7.3) | 47.7 | 47.8 (47.4–48.2) |
| 165–169 | 15,038 | 7.3 | 7.2 (7.2–7.3) | 49.7 | 49.8 (49.4–50.2) |
| 170–174 | 10,025 | 7.4 | 7.3 (7.2–7.4) | 50.7 | 50.6 (50.1–51.1) |
| 175–179 | 2,945 | 7.5 | 7.3 (7.1–7.4) | 52.5 | 52.5 (51.5–53.4) |
| ≥180 | 524 | 7.2 | 7.1 (6.7–7.4) | 53.1 | 52.7 (50.3–55.1) |
| *P* trend | | <0.0001 | 0.707 | <0.0001 | <0.0001 |
| Number of pregnancies | | | | | |
| Never | 4,287 | 7.9 | 8.0 (7.9–8.2) | 55.5 | 55.3 (54.5–56.2) |
| 1 | 4,065 | 7.6 | 7.6 (7.5–7.7) | 53.3 | 53.5 (52.6–54.3) |
| 2 | 17,704 | 7.4 | 7.3 (7.3–7.4) | 49.7 | 49.8 (49.4–50.2) |
| 3 | 14,251 | 7.0 | 7.0 (6.9–7.0) | 47.2 | 47.2 (46.8–47.5) |
| ≥4 | 5,927 | 6.7 | 6.8 (6.7–6.9) | 45.5 | 45.3 (44.7–45.8) |
| *P* trend | | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

Abbreviation: sec, secondary.
[a]Adjusted for age at mammography.
[b]Additionally adjusted for BMI, education, menopausal status, and pregnancies.
[c]Excluding nulliparous women.
[d]Excluding pre/perimenopausal women.

0.0001). Associations stratified by use of postmenopausal hormone therapy showed a larger difference in percent and absolute VMD with increasing age at screening in never users of postmenopausal hormone therapy, compared with past and current users ($P_{int} < 0.0001$), and associations stratified by a family history of breast cancer showed that premenopausal women with a family history had a larger difference in absolute VMD with age at screening compared with premenopausal women with no family history ($P_{int} = 0.054$).

Further examination of VMD with age using cubic spline regression revealed that the nonlinear model was not a better fit than the linear model in pre/perimenopausal women (percent VMD $P = 0.792$ and absolute VMD $P = 0.963$); however, there could be a plateauing of VMD in postmenopausal women (percent VMD $P < 0.0001$ and absolute VMD $P = 0.008$). For these women, the overall VMD–age associations from Supplementary Fig. S1 were modestly stronger when we excluded women over 65 years (the coefficient for percent VMD changed from −0.08 to −0.09 and for absolute VMD from −0.03 to −0.04).

## Discussion

We found associations between VMD and several breast cancer risk factors in this largely postmenopausal cohort, with the strongest associations between BMI and percent and absolute VMD. BMI was positively associated with absolute VMD, but inversely associated with percent VMD. Further, we found modest differences in percent and absolute VMD between the highest and lowest categories of the following risk factors: age, height (only absolute), number of pregnancies, menopausal

**Table 4.** Unadjusted and adjusted mean (95% CI) percent and absolute VMD by selected breast cancer risk factors ($n = 46,234$)

| | | Percent VMD | | Absolute VMD | |
|---|---|---|---|---|---|
| | ***n*** | **Age-adjusted[a]** | **Multiadjusted[b] (95% CI)** | **Age-adjusted[a]** | **Multiadjusted[b] (95% CI)** |
| Duration breastfeeding (months) | | | | | |
| Parous no breastfeeding | 37 | 6.8 | 6.2 (5.2–7.2) | 44.6 | 44.3 (40.1–48.6) |
| 1–6 | 8,455 | 6.9 | 6.9 (6.8–7.0) | 48.1 | 45.9 (45.3–46.4) |
| 7–12 | 8,996 | 7.1 | 7.1 (7.0–7.2) | 49.0 | 47.7 (47.1–48.2) |
| 13–20 | 8,642 | 7.5 | 7.4 (7.3–7.5) | 49.5 | 49.2 (48.7–49.7) |
| 21–30 | 6,537 | 7.5 | 7.5 (7.4–7.6) | 49.7 | 50.5 (49.8–51.1) |
| >30 | 4,321 | 7.5 | 7.7 (7.5–7.8) | 48.4 | 50.5 (49.7–51.3) |
| *P* trend | | <0.0001 | <0.0001 | 0.025 | <0.0001 |
| Age at start of OC (years)[c] | | | | | |
| <19 | 6,769 | 7.1 | 7.2 (7.1–7.3) | 49.6 | 49.2 (48.6–49.8) |
| 19–20 | 5778 | 7.4 | 7.2 (7.1–7.3) | 49.5 | 49.5 (48.8–50.1) |
| 21–24 | 6,118 | 7.5 | 7.3 (7.2–7.4) | 49.3 | 49.4 (48.8–50.1) |
| >24 | 5,179 | 7.4 | 7.3 (7.2–7.4) | 48.8 | 48.8 (48.1–49.5) |
| *P* trend | | 0.001 | 0.068 | 0.113 | 0.395 |
| Duration of OC (years) | | | | | |
| Never users | 19,855 | 7.2 | 7.2 (7.2–7.3) | 49.2 | 49.3 (48.9–49.6) |
| <2 | 3,498 | 7.3 | 7.3 (7.1–7.4) | 49.3 | 49.4 (48.6–50.3) |
| 2–5 | 8,269 | 7.3 | 7.3 (7.2–7.4) | 49.1 | 49.2 (48.6–49.7) |
| 6–10 | 5,378 | 7.3 | 7.3 (7.2–7.4) | 49.6 | 49.4 (48.7–50.1) |
| >10 | 4,803 | 7.4 | 7.2 (7.1–7.3) | 49.1 | 48.8 (48.1–49.5) |
| *P* trend | | 0.001 | 0.916 | 0.755 | 0.379 |
| Postmenopausal hormone therapy | | | | | |
| Never | 26,774 | 7.2 | 7.3 (7.2–7.3) | 49.7 | 49.5 (49.2–49.8) |
| Past | 6,588 | 7.1 | 7.2 (7.1–7.3) | 48.5 | 48.9 (48.3–49.5) |
| Estrogen current | 3,986 | 7.6 | 7.5 (7.3–7.6) | 49.2 | 49.9 (49.1–50.7) |
| EP current | 2,938 | 8.1 | 7.8 (7.6–7.9) | 52.4 | 52.4 (51.3–53.4) |
| *P* trend | | <0.0001 | <0.0001 | 0.005 | <0.0001 |
| Duration of EP therapy (years) | | | | | |
| Never | 26,774 | 7.3 | 7.3 (7.3–7.4) | 49.9 | 49.7 (49.4–50.0) |
| <3 | 2,629 | 7.3 | 7.4 (7.2–7.5) | 49.0 | 49.7 (48.6–50.7) |
| 3–5 | 2,188 | 7.7 | 7.6 (7.4–7.7) | 50.0 | 50.5 (49.4–51.6) |
| 6–10 | 1,640 | 7.8 | 7.6 (7.4–7.8) | 49.3 | 49.8 (48.6–51.0) |
| >10 | 2,002 | 8.2 | 7.8 (7.6–8.0) | 50.5 | 50.9 (49.7–52.0) |
| *P* trend | | <0.0001 | <0.0001 | 0.882 | 0.061 |

Abbreviations: EP, estrogen and progestin; OC, oral contraceptives.
[a]Adjusted for age at mammography.
[b]Additionally adjusted for BMI, education, menopausal status, and pregnancies.
[c]Excluding women who never used oral contraceptives.

status, and duration of breastfeeding. Lower percent and absolute VMD were observed with increasing age at screening, and with being postmenopausal compared with pre/perimenopausal. The inverse association with age appears modified not only by menopausal status at baseline, but also by BMI (percent VMD in postmenopausal women), use of postmenopausal hormone therapy, and family history of breast cancer (absolute VMD in premenopausal women).

When comparing the observed associations between VMD and breast cancer risk factors with results from area-based mammographic density studies (12, 17, 37–44), the observed direction of the associations between VMD and breast cancer risk factors was mostly similar. An exception was BMI, which has been inversely associated with mammographic density in area-based studies. This study found BMI to be inversely associated with percent VMD, but positively associated with absolute VMD, consistent with other studies using volumetric methods (16–18, 45, 46). We have no strong explanation for the difference between volumetric and area-based methods when it comes to BMI except that the two methods capture different variations in breast tissue composition, and that volumetric methods may be more accurate (46).

BMI is associated with breast size and amount of fatty tissue in the breast. It is expected that women with high BMI often have larger breasts and larger amount of fatty tissue, i.e., they have lower percent VMD; however, they also often have more breast tissue in total, and more dense volume, and therefore higher absolute VMD compared with women with smaller breasts (18, 47). It is not clear whether percent or absolute VMD is the most important measure biologically (48), and which measure to use, especially in models including BMI, has implications for the consistency of the estimates. Because BMI is inversely associated with percent VMD, it can reduce the overall effect whenever BMI is positively associated with the exposure, and it is therefore important to adjust for BMI especially in analyses with percent VMD.

The underlying distribution of VMD is more left-skewed than the distribution of area-based mammographic density measures, with a smaller range of possible values in VMD. When comparing the differences across categories of age and BMI with a previous area-based study in the same population (41), results suggest that the difference across categories is 2.5–4 times lower for VMD. This implies that a difference of 1.5% to 2% in VMD is similar to a clinically relevant 5% difference in area-based

**Table 5.** Unadjusted and adjusted mean (95% CI) percent and absolute VMD by smoking, alcohol use, and physical activity level ($n$ = 46,234)

| | | Percent VMD | | Absolute VMD | |
|---|---|---|---|---|---|
| | ***n*** | **Age-adjusted[a]** | **Multiadjusted[b] (95% CI)** | **Age-adjusted[a]** | **Multiadjusted[b] (95% CI)** |
| Smoking | | | | | |
| Never | 19,780 | 7.4 | 7.3 (7.3–7.4) | 49.9 | 49.8 (49.4–50.1) |
| Former | 14,741 | 7.1 | 7.3 (7.2–7.3) | 50.5 | 49.9 (49.5–50.3) |
| Current | 10,377 | 7.2 | 7.0 (7.0–7.1) | 46.3 | 47.2 (46.8–47.7) |
| *P* trend | | 0.055 | <0.0001 | <0.0001 | <0.0001 |
| Alcohol | | | | | |
| Never drinkers | 9,177 | 6.9 | 7.3 (7.2–7.4) | 49.1 | 49.1 (48.5–49.6) |
| 1 glass/week | 10,929 | 7.0 | 7.1 (7.1–7.2) | 49.0 | 48.9 (48.4–49.3) |
| 2 glass/week | 8,563 | 7.3 | 7.2 (7.1–7.3) | 48.5 | 48.8 (48.3–49.3) |
| 3–4 glasses week | 10,094 | 7.5 | 7.3 (7.2–7.4) | 49.8 | 49.8 (49.3–50.3) |
| 5–6 glasses week | 3,389 | 7.7 | 7.3 (7.2–7.5) | 50.4 | 50.2 (49.4–51.1) |
| >6 glasses week | 2,072 | 8.2 | 7.5 (7.4–7.7) | 51.6 | 51.3 (50.1–52.0) |
| *P* trend | | <0.0001 | 0.001 | <0.0001 | <0.0001 |
| Physical activity | | | | | |
| No exercise | 5,266 | 6.5 | 7.2 (7.0–7.3) | 51.2 | 50.2 (49.5–50.9) |
| 1–2.5 hours/week | 16,031 | 6.9 | 7.2 (7.1–7.3) | 50.1 | 49.7 (49.4–50.1) |
| 2.5–4.5 hours/week | 15,281 | 7.4 | 7.3 (7.2–7.4) | 48.9 | 49.0 (48.6–49.4) |
| 4.5–6 hours/week | 8,621 | 7.8 | 7.2 (7.2–7.3) | 47.5 | 48.4 (47.9–49.0) |
| 6+ hours/week | 664 | 8.3 | 7.4 (7.1–7.6) | 45.0 | 46.5 (44.9–48.2) |
| *P* trend | | <0.0001 | 0.074 | <0.0001 | <0.0001 |

[a]Adjusted for age at mammography.
[b]Additionally adjusted for BMI, education, menopausal status, and pregnancies.

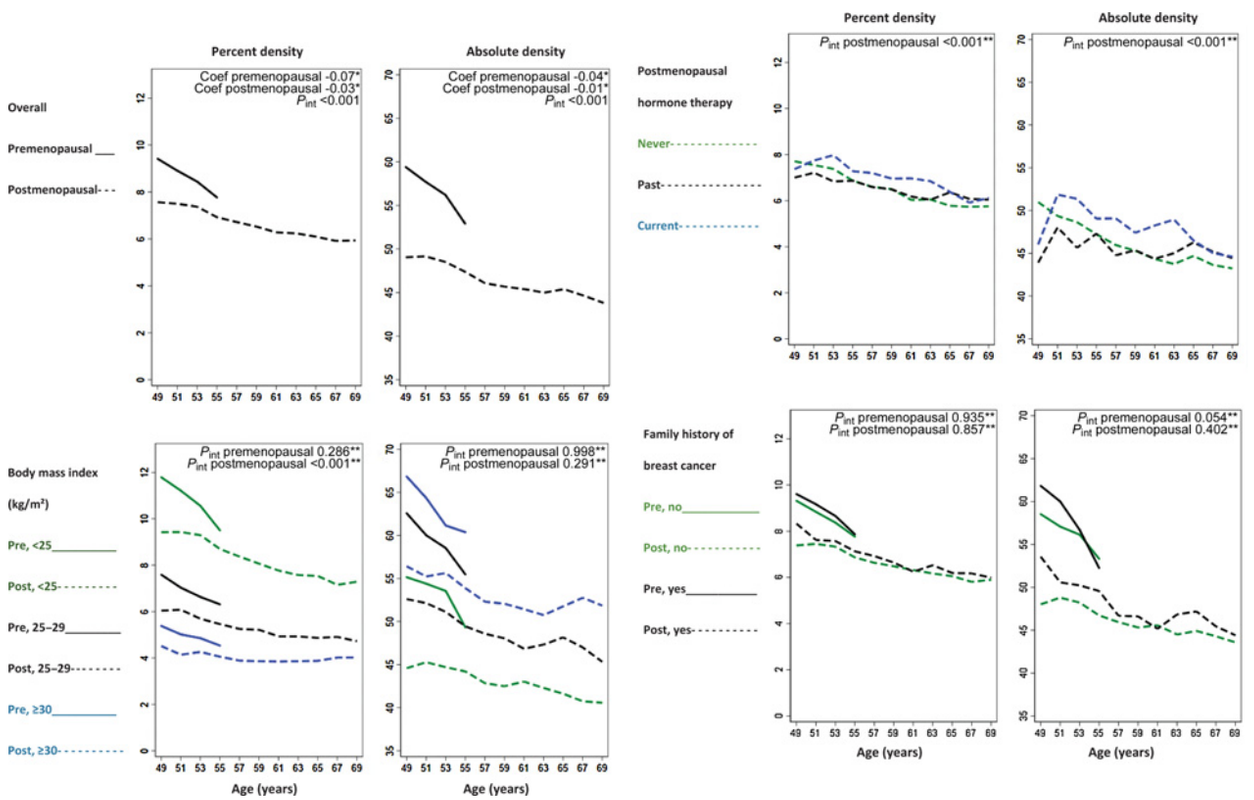


**Figure 1.**
Associations of percent and absolute VMD with age (in 2-year age groups) and menopausal status, overall and by subgroups. All models are adjusted for BMI, education, and number of pregnancies. Premenopausal women above the age of 55 years are excluded. Pre, premenopausal and perimenopausal women; post, postmenopausal women; coef, coefficient; $P_{int}$, $P$ for interaction. *, Rate of decline per a 5-year increment in age. **, Interaction between age and the exposure.

density. Although area-based methods assume that dark areas of a mammogram are composed of fat, and each pixel in the mammogram is either dense or nondense, volumetric methods estimate the relative amount of dense tissue in each individual pixel. A recent validation study comparing VMD to MRI indicated that Volpara may slightly underestimate the true density as measured by MRI (49). However, although the associations may be weaker, the overall associations and the usually accepted determinants of mammographic density seem to be similar for VMD.

Breastfeeding is associated with reduced breast cancer risk (50), but not in a case–control study nested within the same screening population as the present study (51). This could be because the protective effect of breastfeeding is time-limited and may be seen predominately in younger women (52, 53). Consequently, the positive association we observed between breastfeeding and VMD should not be given too much significance and may simply reflect the age of our cohort or be a chance finding. Physical activity protects against breast cancer (54), and we found an inverse association between physical activity and absolute VMD. The positive association between percent VMD and exercising more than 6 hours a week may reflect residual confounding by BMI.

It is well-known that women experience both a reduction in dense tissue and an increase in fatty tissue with increasing age (29). We found lower percent and absolute VMD to be associated with older age at screening in both pre/perimenopausal and postmenopausal women, where the largest age-associated differences were found in pre/perimenopausal women. This may reflect the reduction in circulating sex hormones during the menopausal transition (55). Several risk factors that influence breast cancer and mammographic density could modify this age–VMD association, through modification of breast cell involution or breast tissue composition changes over time (15). We found that the magnitude of the age-related differences in percent VMD was modified by BMI in postmenopausal women, the differences in both percent and absolute VMD by use of postmenopausal hormone therapy, and the difference in absolute VMD by family history of breast cancer in pre/perimenopausal women. The age-associated differences in percent VMD was smaller among postmenopausal women that were overweight and obese than in those with a BMI $< 25$ kg/m$^2$. This finding is consistent with that of Maskarinec and colleagues (19). Hormonal or reproductive events could be less influential in women with a BMI $\geq 30$ kg/m$^2$ whose circulating estrogen levels may be elevated by peripheral conversion in adipose tissue of androgens produced by the supra-renal glands (39). We found larger age-associated differences in VMD in never users of postmenopausal hormone therapy, compared with current and past users, which has been described previously (19, 56). Never users may consist of a unique group of women because they have not experienced menopausal symptoms (57). The larger age-associated difference in absolute VMD by family history of breast cancer in pre/perimenopausal women could perhaps reflect genetic risk factors that are mediated by hormones linked to the menopausal transition (58).

### Strengths and limitations

Strengths of our study include detailed information on breast cancer risk factors and VMD measures using a fully automated volumetric method. Another strength is the population-based screening cohort and its very large size, albeit the latter means that differences of small magnitude can reach statistical significance even if they are of no clinical significance. We therefore considered the absolute magnitude of the observed differences.

The most important limitation of the study is that it is cross-sectional rather than longitudinal. The observed age and menopausal differences may reflect true declines with age and menopausal status, but also differences in density across different cohorts of women, without disentangling between the two. Another limitation is that Volpara tends to underestimate VMD in very dense breasts (49, 59, 60). The selection of internal reference is more complex in dense breasts, i.e., finding an area of the breast that is entirely fat, which affects the calibration of fatty tissue attenuation. This misclassification, which is likely to be nondifferential, could have underestimated the magnitude of exposure–VMD associations in our data. Self-reported height and weight measures could lead to misclassification and inability in adjusting completely for the confounding effect of BMI. However, a recent study found that women attending BreastScreen Norway consistently reported weight and height within 1 kg/cm (31). The cohort included women between 49 and 71 years of age. A wider age range would have been beneficial, especially the inclusion of women of younger ages.

### Conclusions

This large study has added important knowledge concerning VMD: (1) volumetric and area-based mammographic density share similar correlates, (2) the strongest association was found for BMI, with the direction of the association differing for percent (negative association) and absolute (positive association) VMD, (3) percent and absolute VMD were inversely associated with age at screening in both pre/perimenopausal and postmenopausal women; however, larger age-associated differences were observed among pre/perimenopausal women, and (4) the magnitude of the age-associated differences in percent VMD was modified by BMI in postmenopausal women, the differences in both percent and absolute VMD by use of postmenopausal hormone therapy, and the difference in absolute VMD by family history of breast cancer in pre/perimenopausal women. Because VMD methods are becoming widely available in screening and clinical settings, the association between VMD measures and breast cancer risk factors should be investigated further in longitudinal studies.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Authors' Contributions

**Conception and design:** S. Hofvind, I. dos-Santos-Silva, G. Ursin

**Development of methodology:** K.V. Hjerkind, A.L.V. Johansson, S. Hofvind, I. dos-Santos-Silva

**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** S. Fagerheim

**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** K.V. Hjerkind, M. Ellingjord-Dale, A.L.V. Johansson, S. Hofvind, I. dos-Santos-Silva, G. Ursin

**Writing, review, and/or revision of the manuscript:** K.V. Hjerkind, M. Ellingjord-Dale, A.L.V. Johansson, H.S. Aase, S.R. Hoff, S. Hofvind, S. Fagerheim, I. dos-Santos-Silva, G. Ursin

**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** S. Hofvind, G. Ursin
**Study supervision:** G. Ursin

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

## Acknowledgments

This study was supported by the Norwegian Cancer Society (grant reference numbers 698320 and 161326).

Received February 2, 2018; revised April 25, 2018; accepted June 15, 2018; published first June 20, 2018.

## References

1. Boyd NF, Martin LJ, Bronskill M, Yaffe MJ, Duric N, Minkin S. Breast tissue composition and susceptibility to breast cancer. J Natl Cancer Inst 2010; 102:1224–37.
2. Boyd NF, Rommens JM, Vogt K, Lee V, Hopper JL, Yaffe MJ, et al. Mammographic breast density as an intermediate phenotype for breast cancer. Lancet Oncol 2005;6:798–808.
3. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2006;15:1159–69.
4. Byrne C, Schairer C, Wolfe J, Parekh N, Salane M, Brinton LA, et al. Mammographic features and breast cancer risk: effects with time, age, and menopause status. J Natl Cancer Inst 1995;87:1622–9.
5. Ursin G, Ma H, Wu AH, Bernstein L, Salane M, Parisky YR, et al. Mammographic density and breast cancer in three ethnic groups. Cancer Epidemiol Biomarkers Prev 2003;12:332–8.
6. Haars G, van Noord PA, van Gils CH, Grobbee DE, Peeters PH. Measurements of breast density: no ratio for a ratio. Cancer Epidemiol Biomarkers Prev 2005;14:2634–40.
7. Baglietto L, Krishnan K, Stone J, Apicella C, Southey MC, English DR, et al. Associations of mammographic dense and nondense areas and body mass index with risk of breast cancer. Am J Epidemiol 2014;179: 475–83.
8. Pettersson A, Graff RE, Ursin G, Santos Silva ID, McCormack V, Baglietto L, et al. Mammographic density phenotypes and risk of breast cancer: a meta-analysis. J Natl Cancer Inst 2014;106.
9. Kato I, Beinart C, Bleich A, Su S, Kim M, Toniolo PG. A nested case-control study of mammographic patterns, breast volume, and breast cancer (New York City, NY, United States). Cancer Causes Control 1995;6:431–8.
10. Eberl MM, Fox CH, Edge SB, Carter CA, Mahoney MC. BI-RADS classification for management of abnormal mammograms. J Am Board Fam Med 2006;19:161–4.
11. Eng A, Gallant Z, Shepherd J, McCormack V, Li J, Dowsett M, et al. Digital mammographic density and breast cancer risk: a case-control study of six alternative density assessment methods. Breast Cancer Res 2014;16:439.
12. Brand JS, Czene K, Shepherd JA, Leifland K, Heddson B, Sundbom A, et al. Automated measurement of volumetric mammographic density: a tool for widespread breast cancer risk assessment. Cancer Epidemiol Biomarkers Prev 2014;23:1764–72.
13. Rajaram N, Mariapun S, Eriksson M, Tapia J, Kwan PY, Ho WK, et al. Differences in mammographic density between Asian and Caucasian populations: a comparative analysis. Breast Cancer Res Treat 2017;161: 353–62.
14. Shepherd JA, Kerlikowske K, Ma L, Duewer F, Fan B, Wang J, et al. Volume of mammographic density and risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2011;20:1473–82.
15. Hart V, Reeves KW, Sturgeon SR, Reich NG, Sievert LL, Kerlikowske K, et al. The effect of change in body mass index on volumetric measures of mammographic density. Cancer Epidemiol Biomarkers Prev 2015;24: 1724–30.
16. Lokate M, Kallenberg MG, Karssemeijer N, Van den Bosch MA, Peeters PH, Van Gils CH. Volumetric breast density from full-field digital mammograms and its association with breast cancer risk factors: a comparison with a threshold method. Cancer Epidemiol Biomarkers Prev 2010;19:3096–105.
17. McCormack VA, Highnam R, Perry N, dos Santos Silva I. Comparison of a new and existing method of mammographic density measurement: intramethod reliability and associations with known risk factors. Cancer Epidemiol Biomarkers Prev 2007;16:1148–54.
18. Aitken Z, McCormack VA, Highnam RP, Martin L, Gunasekara A, Melnichouk O, et al. Screen-film mammographic density and breast cancer risk: a comparison of the volumetric standard mammogram form and the interactive threshold measurement methods. Cancer Epidemiol Biomarkers Prev 2010;19:418–28.
19. Maskarinec G, Pagano I, Lurie G, Kolonel LN. A longitudinal investigation of mammographic density: the multiethnic cohort. Cancer Epidemiol Biomarkers Prev 2006;15:732–9.
20. Reeves KW, Stone RA, Modugno F, Ness RB, Vogel VG, Weissfeld JL, et al. Longitudinal association of anthropometry with mammographic breast density in the Study of Women's Health Across the Nation. Int J Cancer 2009;124:1169–77.
21. Vachon CM, Pankratz VS, Scott CG, Maloney SD, Ghosh K, Brandt KR, et al. Longitudinal trends in mammographic percent density and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2007;16:921–8.
22. Gram IT, Funkhouser E, Tabar L. Reproductive and menstrual factors in relation to mammographic parenchymal patterns among perimenopausal women. Br J Cancer 1995;71:647–50.
23. Brand JS, Czene K, Eriksson L, Trinh T, Bhoo-Pathy N, Hall P, et al. Influence of lifestyle factors on mammographic density in postmenopausal women. PLoS One 2013;8:e81876.
24. Qureshi SA, Ellingjord-Dale M, Hofvind S, Wu AH, Ursin G. Physical activity and mammographic density in a cohort of postmenopausal Norwegian women; a cross-sectional study. Springerplus 2012;1:75.
25. Bremnes Y, Ursin G, Bjurstam N, Gram IT. Different measures of smoking exposure and mammographic density in postmenopausal Norwegian women: a cross-sectional study. Breast Cancer Res 2007;9:R73.
26. Ursin G, Lillie EO, Lee E, Cockburn M, Schork NJ, Cozen W, et al. The relative importance of genetics and environment on mammographic density. Cancer Epidemiol Biomarkers Prev 2009;18:102–12.
27. McTiernan A, Martin CF, Peck JD, Aragaki AK, Chlebowski RT, Pisano ED, et al. Estrogen-plus-progestin use and mammographic density in postmenopausal women: Women's Health Initiative randomized trial. J Natl Cancer Inst 2005;97:1366–76.
28. Boyd N, Martin L, Stone J, Little L, Minkin S, Yaffe M. A longitudinal study of the effects of menopause on mammographic features. Cancer Epidemiol Biomarkers Prev 2002;11:1048–53.
29. Burton A, Maskarinec G, Perez-Gomez B, Vachon C, Miao H, Lajous M, et al. Mammographic density and ageing: a collaborative pooled analysis of cross-sectional data from 22 countries worldwide. PLoS Med 2017;14:e1002335.
30. Hofvind S, Tsuruda K, Mangerud G, Ertzaas AK, Holen ÅS, Pedersen K, et al. The Norwegian Breast Cancer Screening Program 1996–2016: celebrating 20 years of organised mammographic screening. Norway, Oslo: Cancer Registry of Norway; 2017.
31. Tsuruda KM, Sagstad S, Sebuodegard S, Hofvind S. Validity and reliability of self-reported health indicators among women attending organized mammographic screening. Scand J Publig Health 2018:1403494817749393. doi:10.1177/1403494817749393 (Epub ahead of print).
32. van der Waal D, den Heeten GJ, Pijnappel RM, Schuur KH, Timmers JM, Verbeek AL, et al. Comparing visually assessed BI-RADS breast density and automated volumetric breast density software: a cross-sectional study in a breast cancer screening setting. PLoS One 2015;10:e0136667.
33. Highnam R, Brady SM, Yaffe MJ, Karssemeijer N, Harvey J. Robust breast composition measurement - VolparaTM. In: Martí J, Oliver A, Freixenet J, Martí R, editors. Digital mammography: 10th International Workshop, IWDM 2010, Girona, Catalonia, Spain, June 16–18, 2010 Proceedings. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010. p. 342–9.

34. Mitchell MN. Interpreting and visualizing regression models using Stata. College Station, Texas: Stata Press; 2012.
35. Harden J, Hilbe J. Generalized linear models and extensions. 3rd ed. College Station, TX: StataCorp LP; 2012.
36. StataCorp. Stata Statistical Software: Release 15. College Station, TX: Statacorp LP; 2015.
37. Boyd NF, Lockwood GA, Martin LJ, Knight JA, Byng JW, Yaffe MJ, et al. Mammographic densities and breast cancer risk. Breast Dis 1998;10:113–26.
38. Martin LJ, Boyd NF. Mammographic density. Potential mechanisms of breast cancer risk associated with mammographic density: hypotheses based on epidemiological evidence. Breast Cancer Res 2008;10:201.
39. Titus-Ernstoff L, Tosteson AN, Kasales C, Weiss J, Goodrich M, Hatch EE, et al. Breast cancer risk factors in relation to breast density (United States). Cancer Causes Control 2006;17:1281–90.
40. El-Bastawissi AY, White E, Mandelson MT, Taplin SH. Reproductive and hormonal factors associated with mammographic breast density by age (United States). Cancer Causes Control 2000;11:955–63.
41. Qureshi SA, Couto E, Hofvind S, Wu AH, Ursin G. Alcohol intake and mammographic density in postmenopausal Norwegian women. Breast Cancer Res Treat 2012;131:993–1002.
42. Ellingjord-Dale M, dos-Santos-Silva I, Grotmol T, Sakhi AK, Hofvind S, Qureshi S, et al. Vitamin D intake, month the mammogram was taken and mammographic density in Norwegian women aged 50–69. PLoS One 2015;10:e0123754.
43. Couto E, Qureshi SA, Hofvind S, Hilsen M, Aase H, Skaane P, et al. Hormone therapy use and mammographic density in postmenopausal Norwegian women. Breast Cancer Res Treat 2012;132:297–305.
44. Jeffreys M, Warren R, Highnam R, Smith GD. Initial experiences of using an automated volumetric measure of breast density: the standard mammogram form. Br J Radiol 2006;79:378–82.
45. Jeffreys M, Warren R, Highnam R, Davey Smith G. Breast cancer risk factors and a novel measure of volumetric breast density: cross-sectional study. Br J Cancer 2008;98:210–6.
46. Gierach GL, Geller BM, Shepherd JA, Patel DA, Vacek PM, Weaver DL, et al. Comparison of mammographic density assessed as volumes and areas among women undergoing diagnostic image-guided breast biopsy. Cancer Epidemiol Biomarkers Prev 2014;23:2338–48.
47. Chen Z, Wu AH, Gauderman WJ, Bernstein L, Ma H, Pike MC, et al. Does mammographic density reflect ethnic differences in breast cancer incidence rates? Am J Epidemiol 2004;159:140–7.
48. Ursin G, Hovanessian-Larsen L, Parisky YR, Pike MC, Wu AH. Greatly increased occurrence of breast cancers in areas of mammographically dense tissue. Breast Cancer Res 2005;7:R605–8.
49. Gubern-Merida A, Kallenberg M, Platel B, Mann RM, Marti R, Karssemeijer N. Volumetric breast density estimation from full-field digital mammograms: a validation study. PLoS One 2014;9:e85952.
50. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet. Lancet 2002;360:187–95.
51. Ellingjord-Dale M, Vos L, Tretli S, Hofvind S, Dos-Santos-Silva I, Ursin G. Parity, hormones and breast cancer subtypes - results from a large nested case-control study in a national screening program. Breast Cancer Res 2017;19:10.
52. Byers T, Graham S, Rzepka T, Marshall J. Lactation and breast cancer. Evidence for a negative association in premenopausal women. Am J Epidemiol 1985;121:664–74.
53. McTiernan A, Thomas DB. Evidence for a protective effect of lactation on risk of breast cancer in young women. Results from a case-control study. Am J Epidemiol 1986;124:353–8.
54. Lynch BM, Neilson HK, Friedenreich CM. Physical activity and breast cancer prevention. Recent Results Cancer Res 2011;186:13–42.
55. Burger HG, Hale GE, Dennerstein L, Robertson DM. Cycle and hormone changes during perimenopause: the key role of ovarian function. Menopause 2008;15:603–12.
56. Sterns EE, Zee B. Mammographic density changes in perimenopausal and postmenopausal women: is effect of hormone replacement therapy predictable? Breast Cancer Res Treat 2000;59:125–32.
57. Kelemen LE, Pankratz VS, Sellers TA, Brandt KR, Wang A, Janney C, et al. Age-specific trends in mammographic density: the Minnesota Breast Cancer Family Study. Am J Epidemiol 2008;167:1027–36.
58. Yaghjyan L, Colditz GA, Rosner B, Tamimi RM. Mammographic breast density and breast cancer risk by menopausal status, postmenopausal hormone use and a family history of breast cancer. Cancer Causes Control 2012;23:785–90.
59. van Engeland S, Snoeren PR, Huisman H, Boetes C, Karssemeijer N. Volumetric breast density estimation from full-field digital mammograms. IEEE Trans Med Imaging 2006;25:273–82.
60. Kallenberg MG, van Gils CH, Lokate M, den Heeten GJ, Karssemeijer N. Effect of compression paddle tilt correction on volumetric breast density estimation. Phys Med Biol 2012;57:5155–68.