Automated Measurement of Volumetric Mammographic Density: A Tool for Widespread Breast Cancer Risk Assessment

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Abstract

Introduction: Mammographic density is a strong risk factor for breast cancer and an important determinant of screening sensitivity, but its clinical utility is hampered due to the lack of objective and automated measures. We evaluated the performance of a fully automated volumetric method (Volpara).

Methods: A prospective cohort study included 41,102 women attending mammography screening, of whom 206 were diagnosed with breast cancer after a median follow-up of 15.2 months. Percent and absolute dense volumes were estimated from raw digital mammograms. Genotyping was performed in a subset of the cohort (N = 2,122). We examined the agreement by side and view and compared density distributions across different mammography systems. We also studied associations with established density determinants and breast cancer risk.

Results: The method showed good agreement by side and view, and distributions of percent and absolute dense volume were similar across mammography systems. Volumetric density was positively associated with nulliparity, age at first birth, hormone use, benign breast disease, and family history of breast cancer, and negatively with age and postmenopausal status. Associations were also observed with rs10995190 in the ZNF365 gene (P < 1.0 × 10^{-5}) and breast cancer risk [HR for the highest vs. lowest quartile, 2.93; 95% confidence interval, 1.73–4.96 and 1.63 (1.10–2.42) for percent and absolute dense volume, respectively].

Conclusions: In a high-throughput setting, Volpara performs well and in accordance with the behavior of established density measures.

Impact: Automated measurement of volumetric mammographic density is a promising tool for widespread breast cancer risk assessment. Cancer Epidemiol Biomarkers Prev; 23(9); 1764–72. ©2014 AACR.
limitations, several automated volumetric methods for FFDM have been developed which could potentially work in high-throughput settings. Volpara is one of these methods with multivendor clearance from the FDA. Volpara has already been validated against breast MRI data and seems to be robust to changes in imaging conditions (13). However, no studies to date have evaluated Volpara based on established properties of mammographic density including the association with breast cancer risk.

Because the widespread application of mammographic density is highly dependent on the accuracy and reliability of its measurement, we studied the performance of Volpara in a large prospective cohort study. The importance of an accurate method is also underlined by recent legislative activities, as several U.S. states have passed laws requiring radiologists to inform patients about their mammographic density including the association with breast cancer risk.

The study population

KARMA (KArolinska MAmmography project for risk prediction of breast cancer) is a prospective cohort study initiated in January 2011 and comprises 70,866 women attending mammography screening or clinical mammography at four hospitals in Sweden (15). Upon study entry, participants donated blood and filled out a detailed Web-based questionnaire. In addition, permission was asked for storage of both "for processing" (raw) and "for presentation" (processed) FFDM and linkage to Swedish national registers on inpatient care and cancer. All participants provided written informed consent and the study was approved by the ethical review board at Karolinska Institutet.

For the present analysis, we selected women who attended the mammography screening program (40–74 years) with raw mammograms stored at baseline (N = 50,461). We excluded women with previous cancers other than nonmelanoma skin cancer (N = 3,015), women who underwent breast enlargements/reductions/surgery (N = 2,191), women who did not give information on age and body mass index (BMI; N = 3,908), and women pregnant 12 months before study entry (N = 40), leaving 41,307 women in the study. Of these, 41,102 women had craniocaudal mammograms. Follow-up on malignant breast cancer was performed through linkage to the Swedish national breast cancer registry, Information Network for Cancer Care (INCA) (16).

Mammographic density assessment

Digital mammography was performed using five different models from three manufacturers [General Electric (GE) Medical Systems, Philips Healthcare, and Sectra Imtec AB]. According to our records, women were not selectively referred to one of these mammography systems except for the GE Senograh DS 53-40 model, which was used for screening women with small breasts.

Volumetric mammographic density was measured using Volpara (version 1.4.3). Technical details of the software have been described elsewhere (13). In brief, the algorithm computes the thickness of dense tissue at each pixel using the X-ray attenuation of an entirely fatty region as an internal reference. The absolute dense volume (cm$^3$) is measured by integrating the dense thickness at each pixel over the whole mammogram, and the total breast volume (cm$^3$) is derived by multiplying the breast area by the recorded breast thickness, with an appropriate correction for the breast edge. Percent dense volume (%) is then obtained from the ratio of these two volumetric measures.

To compare Volpara volumetric measures with area-based measures, 77 digital MLO mammograms were processed for measurement with the user-assisted threshold method Cumulus (12). A trained observer (J. Li) set the appropriate gray-scale thresholds to define the breast and dense area (cm$^2$), after which the percent dense area (%) was calculated. The mammograms were selected from two manufacturers (GE Medical Systems: N = 28 and Sectra Imtec AB: N = 49) in such a way that their density measures covered the full range of possible values. All mammograms were measured in duplicate to assess the intraobserver reliability, which was high (R = 0.93).

Questionnaire data

Participants were asked to report on reproductive history, use of oral contraceptives (OC) and hormone replacement therapy (HRT), previous benign breast disease, and family history of breast cancer. A positive family history was defined as a diagnosis of breast cancer in at least one first-degree relative (i.e., sister, mother, or daughter).

Menopausal status was defined according to information on menstruation status, previous oophorectomy, and age at study entry. Postmenopausal women were defined as those who had no periods during the last year, a history of oophorectomy, or age 55 or older. Women were classified as perimenopausal/unknown when they had menses during the past year but were no longer menstruating during the last 3 months or when they had missing data on menstruation status and were between 46 and 55 years of age. Women were considered premenopausal when they reported having periods during the past 3 months or age <46 years if they had missing data on menstruation status. BMI was calculated based on self-reported height and weight.

Genotyping data

A subset of the study population (N = 2,122) was genotyped using a custom Illumina iSelect genotyping array (iCOGS) as has been described in detail elsewhere (17). For the present analysis, we focused on rs10995190 in the zinc finger protein 365 (ZNF365) gene, an SNP that has previously been associated with percent dense area (18).

Statistical analyses

All four standard views were stored, but the main analyses were based on the MLO view, as this is the
Results

The mean age at study entry was 55.0 years, and 56.5% of the women were postmenopausal at baseline (Table 1). All mammographic measures showed a positively skewed distribution, and the medians (interquartile range, IQR) for total breast volume, absolute dense volume, and percent dense volume were 760 (493–1,106) cm³, 57 (42–77) cm³, and 7.7 (5.3–11.7)% respectively (Fig. 1). Density distributions were similar across manufacturers, but significant differences in age-and-BMI-adjusted geometric means were observed across manufacturer models and X-ray detectors (P < 0.001; Table 2; Supplementary Table S1). These differences, however, were mainly driven by the GE Senograph DS 53.40 model (Table 2), due to selective referral of women with small breasts (and thus higher mammographic density) to this specific model. For the other mammography systems, differences were only

Table 1. Baseline characteristics of the study population (N = 41,102)

<table>
<thead>
<tr>
<th>Participant characteristic</th>
<th>N</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>55.0</td>
<td>9.8</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>25.4</td>
<td>4.2</td>
</tr>
<tr>
<td>Age at menarche (years), mean (SD)</td>
<td>13.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Parity, % (N)</td>
<td>0</td>
<td>12.1 (4,979)</td>
</tr>
<tr>
<td>1</td>
<td>14.1</td>
<td>(5,792)</td>
</tr>
<tr>
<td>2</td>
<td>48.4</td>
<td>(19,901)</td>
</tr>
<tr>
<td>≥3</td>
<td>25.2</td>
<td>(10,363)</td>
</tr>
<tr>
<td>Menopausal status, % (N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenopausal</td>
<td>40.2</td>
<td>(16,506)</td>
</tr>
<tr>
<td>Perimenopausal/unknown</td>
<td>3.3</td>
<td>(1,349)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>56.5</td>
<td>(23,247)</td>
</tr>
<tr>
<td>Ever OC use, % (N)</td>
<td>79.3</td>
<td>(32,602)</td>
</tr>
<tr>
<td>HRT use, % (N)</td>
<td>74.9</td>
<td>(30,791)</td>
</tr>
<tr>
<td>Never</td>
<td>14.5</td>
<td>(5,945)</td>
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<tr>
<td>Current</td>
<td>3.7</td>
<td>(1,521)</td>
</tr>
<tr>
<td>Missing</td>
<td>6.9</td>
<td>(2,845)</td>
</tr>
<tr>
<td>Benign breast disease, % (N)</td>
<td>21.7</td>
<td>(8,919)</td>
</tr>
<tr>
<td>Missing</td>
<td>2.0</td>
<td>(811)</td>
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<tr>
<td>Family history breast cancer, % (N)</td>
<td>12.7</td>
<td>(5,236)</td>
</tr>
<tr>
<td>Missing</td>
<td>3.6</td>
<td>(1,471)</td>
</tr>
<tr>
<td>Total breast volume (cm³), median (IQR)</td>
<td>760 (493–1,106)</td>
<td></td>
</tr>
<tr>
<td>Absolute dense volume (cm³), median (IQR)</td>
<td>57 (42–77)</td>
<td></td>
</tr>
<tr>
<td>Percent dense volume (%)</td>
<td>7.7</td>
<td>(5.3–11.7)</td>
</tr>
</tbody>
</table>
minor, with the largest percentage deviation being observed for X-ray detectors PL197_02 (GE Senograph Essential 53.40) and KM070400 (Sectra L30). The relative difference in percent dense volume was 3% for these two models when taking the largest category of X-ray detectors (PL678_04) as a reference (Supplementary Table S1).

Agreement by side and view was high in correlation analyses including all mammograms (Supplementary Table S2). The left–right correlations were equally high for the craniocaudal and MLO view, but the craniocaudal/MLO agreement was slightly higher for total breast volume and percent dense volume than for the absolute dense volume.

The correlation between total breast area and total breast volume was high ($R$, 0.91; 95% confidence interval, CI, 0.87–0.94), as was the correlation between percent dense area and percent dense volume ($R$, 0.93; 95% CI, 0.89–0.96; Supplementary Fig. S1). The correlation between absolute dense area and absolute dense volume, however, was weak ($R$, 0.55; 95% CI, 0.38–0.69).

All known determinants of mammographic density were associated with percent and absolute dense volume in a similar way, except for BMI (Table 3 and Supplementary Table S3). Postmenopausal and older women had a lower percent and absolute dense volume, whereas nulliparity, older age at first birth, current HRT use, benign breast disease, and a family history of breast cancer were all associated with a larger amount of dense tissue. By contrast, women with a high BMI had a lower percent dense volume but a larger absolute dense volume. Overall, the strength of associations was comparable between the two volumetric measures, although the effect of parity seemed to be stronger for the absolute dense volume, whereas age and BMI had a larger impact on percent

### Table 2. Geometric means of volumetric mammographic measures stratified by manufacturer model

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Model</th>
<th>$N$</th>
<th>Age, mean (SD)</th>
<th>BMI, mean (SD)</th>
<th>Total breast volume (cm³)</th>
<th>Absolute dense volume (cm³)</th>
<th>Percent dense volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE</td>
<td>Senograph Essential 53.40</td>
<td>15,926</td>
<td>55.0 (9.6)</td>
<td>26.0 (4.4)</td>
<td>729 (724–733)</td>
<td>57.0 (56.6–57.4)</td>
<td>7.8 (7.8–7.9)</td>
</tr>
<tr>
<td></td>
<td>Senograph Essential 53.10</td>
<td>397</td>
<td>55.2 (9.6)</td>
<td>25.4 (4.1)</td>
<td>751 (723–781)</td>
<td>60.6 (58.1–63.3)</td>
<td>8.1 (7.8–8.4)</td>
</tr>
<tr>
<td>Philips</td>
<td>Senograph DS 53.40</td>
<td>2,743</td>
<td>52.8 (9.6)</td>
<td>22.8 (2.5)</td>
<td>499 (492–506)</td>
<td>44.3 (43.6–45.1)</td>
<td>8.9 (8.8–9.0)</td>
</tr>
<tr>
<td></td>
<td>MammDiagnost DR</td>
<td>809</td>
<td>55.8 (9.7)</td>
<td>25.3 (4.1)</td>
<td>723 (713–752)</td>
<td>56.9 (55.2–58.6)</td>
<td>7.8 (7.6–8.0)</td>
</tr>
<tr>
<td></td>
<td>L30</td>
<td>14,929</td>
<td>55.2 (10.1)</td>
<td>25.1 (4.1)</td>
<td>744 (740–749)</td>
<td>58.1 (57.7–58.5)</td>
<td>7.8 (7.8–7.9)</td>
</tr>
<tr>
<td>Sectra</td>
<td>L30</td>
<td>6,298</td>
<td>55.1 (9.4)</td>
<td>25.4 (4.2)</td>
<td>766 (758–773)</td>
<td>61.3 (60.7–62.0)</td>
<td>8.0 (7.9–8.1)</td>
</tr>
</tbody>
</table>

**NOTE:** Age- and BMI-adjusted geometric means of volumetric mammographic measures per manufacturer model. All mammographic measures were derived from the mediolateral oblique view.
<table>
<thead>
<tr>
<th>Age (years), mean</th>
<th>59.1</th>
<th>57.9</th>
<th>55.9</th>
<th>52.7</th>
<th>49.3</th>
<th>&lt;0.001</th>
<th>56.6</th>
<th>56.8</th>
<th>55.7</th>
<th>54.2</th>
<th>51.6</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²), mean</td>
<td>29.2</td>
<td>26.6</td>
<td>25.0</td>
<td>23.7</td>
<td>22.4</td>
<td>&lt;0.001</td>
<td>23.2</td>
<td>25.0</td>
<td>25.8</td>
<td>26.3</td>
<td>26.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at menarche (years), mean</td>
<td>13.0</td>
<td>13.1</td>
<td>13.1</td>
<td>13.2</td>
<td>13.2</td>
<td>&lt;0.001</td>
<td>13.2</td>
<td>13.2</td>
<td>13.1</td>
<td>13.1</td>
<td>13.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parity, %</td>
<td>0</td>
<td>11.8</td>
<td>10.9</td>
<td>11.5</td>
<td>12.1</td>
<td>14.3</td>
<td>8.7</td>
<td>10.0</td>
<td>11.7</td>
<td>13.7</td>
<td>16.6</td>
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<td>13.6</td>
<td>13.9</td>
<td>14.0</td>
<td>14.9</td>
<td>12.6</td>
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<td>14.9</td>
<td>16.8</td>
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<tr>
<td>2</td>
<td>47.2</td>
<td>47.6</td>
<td>48.0</td>
<td>50.0</td>
<td>47.7</td>
<td>48.5</td>
<td>50.2</td>
<td>48.8</td>
<td>48.0</td>
<td>47.1</td>
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<tr>
<td>≥3</td>
<td>26.8</td>
<td>27.9</td>
<td>26.7</td>
<td>23.9</td>
<td>21.0</td>
<td>30.2</td>
<td>27.5</td>
<td>25.7</td>
<td>23.4</td>
<td>19.5</td>
<td></td>
<td></td>
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<tr>
<td>Age at first birth (years), mean</td>
<td>25.6</td>
<td>26.1</td>
<td>26.9</td>
<td>27.8</td>
<td>28.9</td>
<td>&lt;0.001</td>
<td>26.9</td>
<td>26.7</td>
<td>26.7</td>
<td>27.0</td>
<td>28.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Menopausal status, %</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>21.5</td>
<td>26.3</td>
<td>34.7</td>
<td>50.1</td>
<td>68.3</td>
<td>32.5</td>
<td>31.3</td>
<td>35.9</td>
<td>44.0</td>
<td>57.2</td>
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<tr>
<td>Perimenopausal/unknown</td>
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<td>3.3</td>
<td>3.5</td>
<td>3.6</td>
<td>3.1</td>
<td>2.7</td>
<td>2.9</td>
<td>3.3</td>
<td>3.6</td>
<td>3.8</td>
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<tr>
<td>Postmenopausal</td>
<td>75.7</td>
<td>70.4</td>
<td>61.8</td>
<td>46.3</td>
<td>28.6</td>
<td>64.8</td>
<td>65.8</td>
<td>60.8</td>
<td>52.4</td>
<td>39.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever OC use, %</td>
<td>74.3</td>
<td>78.3</td>
<td>80.4</td>
<td>82.2</td>
<td>83.3</td>
<td>&lt;0.001</td>
<td>78.8</td>
<td>79.4</td>
<td>79.5</td>
<td>79.8</td>
<td>81.2</td>
<td>0.003</td>
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<tr>
<td>HRT use, %a</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>Never</td>
<td>70.1</td>
<td>69.1</td>
<td>68.4</td>
<td>67.7</td>
<td>69.3</td>
<td>69.1</td>
<td>69.0</td>
<td>69.4</td>
<td>69.1</td>
<td>67.9</td>
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<td></td>
</tr>
<tr>
<td>Former</td>
<td>26.0</td>
<td>26.2</td>
<td>25.5</td>
<td>24.4</td>
<td>21.6</td>
<td>25.5</td>
<td>25.7</td>
<td>25.1</td>
<td>25.2</td>
<td>24.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>4.0</td>
<td>4.6</td>
<td>6.1</td>
<td>8.0</td>
<td>9.1</td>
<td>0.001</td>
<td>5.4</td>
<td>5.3</td>
<td>5.5</td>
<td>5.7</td>
<td>7.9</td>
<td></td>
</tr>
<tr>
<td>Benign breast disease, %</td>
<td>17.8</td>
<td>20.6</td>
<td>22.0</td>
<td>24.0</td>
<td>26.4</td>
<td>&lt;0.001</td>
<td>20.7</td>
<td>21.2</td>
<td>20.8</td>
<td>22.9</td>
<td>25.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history breast cancer, %</td>
<td>12.7</td>
<td>13.0</td>
<td>13.1</td>
<td>13.6</td>
<td>13.7</td>
<td>0.03</td>
<td>12.3</td>
<td>12.9</td>
<td>13.4</td>
<td>13.3</td>
<td>14.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*aIn postmenopausal women only. Percent and absolute dense volumes were derived from the mediolateral oblique view.
Table 4. Associations of percent and absolute dense volume with breast cancer risk

<table>
<thead>
<tr>
<th>N/cases</th>
<th>Crudea</th>
<th>Model 1a</th>
<th>Model 2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent dense volume (in quartiles)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;5.3)</td>
<td>10,276/37</td>
<td>1.27 (1.10–1.47)</td>
<td>1.51 (1.26–1.81)</td>
</tr>
<tr>
<td>Q2 (5.3–7.6)</td>
<td>10,276/44</td>
<td>1.20 (0.96–1.49)</td>
<td>1.38 (1.10–1.72)</td>
</tr>
<tr>
<td>Q3 (7.7–11.7)</td>
<td>10,276/55</td>
<td>1.15 (0.96–1.37)</td>
<td>1.27 (1.02–1.59)</td>
</tr>
<tr>
<td>Q4 (&gt;11.7)</td>
<td>10,276/206</td>
<td>1.12 (0.93–1.35)</td>
<td>1.21 (1.02–1.42)</td>
</tr>
<tr>
<td>P trend</td>
<td>0.01</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Percent dense volume (per SD increase)b 41,102/206 1.27 (1.10–1.47) 1.51 (1.26–1.81) 1.46 (1.22–1.76)

Absolute dense volume (in quartiles) |        |          |          |
| Q1 (<42) | 10,276/47 | 1.59 (1.28–1.99) | 1.71 (1.40–2.08) | 1.56 (1.24–1.95) |
| Q2 (42–56) | 10,275/33 | 1.18 (0.93–1.49) | 1.32 (1.07–1.63) | 1.24 (0.98–1.56) |
| Q3 (57–77) | 10,276/55 | 1.16 (0.97–1.38) | 1.28 (1.07–1.54) | 1.21 (0.99–1.48) |
| Q4 (>77) | 10,275/206 | 1.12 (0.91–1.37) | 1.22 (1.00–1.47) | 1.14 (0.92–1.40) |
| P trend | 0.001 | <0.001 | 0.002 |

Absolute dense volume (per SD increase)b 41,102/206 1.30 (1.13–1.50) 1.33 (1.15–1.54) 1.30 (1.12–1.51)

NOTE: Model 1: adjusted for age (years) and BMI (kg/m²). Model 2: adjusted for age (years), BMI (kg/m²), menopausal status (premenopausal, perimenopausal/unknown, postmenopausal), parity and age at first birth (nulliparous, 1 child age at first birth ≥ 25 years, 2 children age at first birth ≥ 25 years, 2 children age at first birth ≥ 25 years, 3 children age at first birth ≥ 25 years, ≥ 3 children age at first birth ≥ 25 years), HRT status (never, former, current), benign breast disease (yes vs. no), and family history of breast cancer (yes vs. no). Volumetric percent and absolute dense volumes were derived from the mediolateral oblique view.

aCox proportional hazards models stratified by manufacturer.
bBased on log-transformed mammographic measures.

dense volume (Supplementary Table S3). SNP rs10995190 in the ZNF365 gene was associated with both percent and absolute dense volume (Supplementary Table S4), with betas in the same direction to those reported for percent dense volume and 1.63 (95% CI, 1.10–2.24) for absolute dense volume when comparing the highest versus lowest quartile. Results were similar when taking the contralateral mammogram for incident breast cancer cases and a randomly assigned view for those without breast cancer at the end of follow-up (data not shown).

Discussion

In this study, we demonstrate the potential of automated volumetric mammographic measures in widespread breast cancer risk assessment. Percent and absolute dense volumes as obtained with Volpara are associated with established determinants of mammographic density as well as breast cancer risk. The method itself showed good agreement by side and view, and distributions of both density measures were similar across mammography systems. In the past decade, several volumetric methods have been developed for measuring mammographic density in an automated fashion, but only few of these are specifically designed for FFDM (22–27). The main advantage of FFDM-based methods is that they can account for unique acquisition parameters that are automatically stored in the image header. For film mammography, these parameters are not easily retrievable. Another advantage is that pixel values from raw digital mammograms are linearly related to X-ray exposure, resulting in more robust mathematical models. A distinct feature of Volpara is the use of a relative rather than absolute physics model, which makes the method less dependent on accurate physics data provided from the X-ray detector. Therefore, Volpara density distributions are expected to be more or less comparable across mammography systems. In our study, density distributions were similar across manufacturers, but a statistically significant difference was observed between manufacturer models. However, given the size of our study (N > 40,000), any difference can reach statistical significance without being clinically significant. It is therefore important to consider the magnitude of the differences observed. The model that deviated most from the
others was GE Senograph DS 53.40, but this was due to
selective referral of women with small breasts. Differences
between other X-ray systems were only minor (for percent
dense volume the largest percentage deviation observed
was 3%). Moreover, it should be noted that any deviation
could also reflect interindividual differences and/or sys-
tem-related differences (i.e., differences in paddle size).
We therefore conclude that the differences are of such a
small magnitude that their impact will be minimal in a
clinical setting. We also found high correlation coefficients
by side and view, which are comparable with those
reported for Cumulus area-based measures (28) and
higher than those of volumetric measures obtained from
film mammograms (29, 30).

Risk factors for breast cancer influence mammographic
density in a similar way with only two exceptions (age and
menopausal status) for which associations are in the
opposite direction (31). In our study, both percent and
absolute dense volumes were associated with all known
density determinants in the expected direction (Table 3
and Supplementary Table S4). The contrasting effect of
BMI on percent and absolute dense volume has been
described previously (29, 32–34) and underscores the
notion that the inverse association with percent density
is mainly due to the positive correlation between BMI and
the amount of nondense fatty tissue. Mammographic
density is not only influenced by reproductive and hor-
monal factors, but is also genetically determined. Twin
studies estimate that approximately two third of the
residual variance in percent dense area is attributable to
genetic factors (35, 36), but apart from some nominally
significant SNP density associations (37, 38), rs10995190 in
the ZNF365 gene is the only established SNP with
genome-wide significance (18). The observed association
between rs10995190 and percent and absolute dense vol-
ume suggests that volumetric and area-based measures
also share genetic determinants.

The underlying distribution of percent dense volume
is different from that of percent dense area, being more
left-skewed with a smaller range of possible values (0% to
40% vs. 0% to 100% for area-based percent density).
Our findings about the correlation with Cumulus agree
with those from earlier reports on volumetric methods
(29, 30, 32–34, 39), showing a strong correlation for total
breast volume and percent dense volume, but a weak
correlation for the absolute dense volume. This differ-
ce in correlation for the absolute dense tissue is not
expected as volumetric and area-based methods mea-
sure different aspects of mammographic density. Area-
based methods reduce mammographic density to pro-
tected areas where pixels represent either dense or
nondense tissue, whereas volumetric methods account
for breast thickness by estimating the relative amount of
dense tissue in each individual pixel. The incorporation
of breast thickness is also reflected in the differential
association with BMI. BMI is inversely related to the
absolute dense area, but shows a positive association
with absolute dense volume (29, 32–34). Because volu-
metric methods are better at capturing the actual
amount of fibroglandular tissue in the breast, their mea-
sures are expected to show a stronger association with
breast cancer risk than area-based measures. Neverthe-
less, results so far have demonstrated the opposite, as
volumetric measures from film mammograms are
weaker predictors of breast cancer risk than area-based
measures (30, 33). This discrepancy is often attributed to
the lower accuracy of volumetric methods for film
mammograms. Although direct comparisons are diffi-
cult to make due to differences in study design and
follow-up period, the observed HR for percent dense
volume (HR highest vs. lowest quartile = 2.9) is similar
to the risk estimate reported by Vachon and colleagues
(40) for percent dense area (OR highest vs. lowest
quartile = 3.1). When comparing the HRs for percent
and absolute dense volume, the HR seemed to be
weaker for the latter. This would be in line with results
from correlation analyses, suggesting that volumetric
and area-based percent densities behave similarly,
whereas the absolute dense volume may have some
unique features, which in turn explain the different
association with breast cancer risk. However, the poten-
tial difference in HRs needs to be interpreted with
care, given the relatively small number of incident
cases and overlapping CIs.

Our study has several strengths, including the large
screening-based cohort, the comprehensive information
on breast cancer risk factors, and the availability of SNP
data in a subset of the study population. Furthermore, we
were able to compare the performance of the method
across a wide range of manufacturer models and X-ray
detectors. However, analyses were restricted to three
manufacturers, and further studies are needed to confirm
the generalizability of our findings. Another limitation is
that Cumulus measurements were only available for a
small subset of the study population, which prevented us
from comparing area- versus volumetric-based measures
in their association with breast cancer risk.

In conclusion, our results suggest that automated mea-
surement of volumetric mammographic density can be
used as part of screening programs to provide risk and
masking information that could be used to alter women’s
clinical management in terms of tumor detection and
breast cancer prevention.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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