Mammographic density and interval cancers in mammographic screening: Moving towards more personalized screening

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ABSTRACT

Purpose: The European Society on Breast Imaging has recommended supplemental magnetic resonance imaging (MRI) every two to four years for women with mammographically dense breasts. This may not be feasible in many screening programs. Also, the European Commission Initiative on Breast Cancer suggests not implementing screening with MRI. By analyzing interval cancers and time from screening to diagnosis by density, we present alternative screening strategies for women with dense breasts.
Methods: Our BreastScreen Norway cohort included 508 536 screening examinations, including 3125 screen-detected and 945 interval breast cancers. Time from screening to interval cancer was stratified by density measured by an automated software and classified into Volpara Density Grades (VDGs) 1–4. Examinations with volumetric density ≤3.4% were categorized as VDG1, 3.5%–7.4% as VDG2, 7.5%–15.4% as VDG3, and ≥15.5% as VDG4. Interval cancer rates were also determined by continuous density measures.
Results: Median time from screening to interval cancer was 496 (IQR: 391–587) days for VDG1, 500 (IQR: 350–616) for VDG2, 482 (IQR: 309–595) for VDG3 and 427 (IQR: 266–577) for VDG4. A total of 35.9% of the interval cancers among VDG4 were detected within the first year of the biennial screening interval. For VDG2, 26.3% were detected within the first year. The highest annual interval cancer rate (2.7 per 1000 examinations) was observed for VDG4 in the second year of the biennial interval.
Conclusions: Annual screening of women with extremely dense breasts may reduce the interval cancer rate and increase program-wide sensitivity, especially in settings where supplemental MRI screening is not feasible.

1. Introduction

Organized mammographic screening has been shown to reduce breast cancer specific mortality [1]. However, there are tradeoffs between the benefits and harms of screening based on frequency and diagnostic accuracy, and it is well known that mammographic screening has limitations for women with dense breasts. Density is an independent risk factor for breast cancer, but dense tissue also masks tumors making interpretation of mammograms challenging [2,3]. Consequently, sensitivity of mammographic screening is lower and the odds of interval cancers are higher for women with dense versus non-dense breasts.

In March 2022, European Society of Breast Imaging (EUSOBI) published screening recommendations for women with extremely dense breasts [4]. Later that same year, several EU groups began supporting and promoting these risk-based screening recommendations [5,6]. According to the EUSOBI recommendations, women with extremely dense breasts should be offered supplemental screening with breast MRI every two to four years [4]. This signals a transition to a more personalized screening approach than what we have today. The European Commission guidelines on breast cancer does not however currently suggest

implementing screening with MRI for asymptomatic women [7].

Under the guidance of the 5th edition of the BI-RADS atlas, about 10% of screened women are categorized as having extremely dense breasts, category d, and should thus be offered supplemental MRI screening [8–10]. However, performing MRI on 10% of the screened women is not feasible in most European screening programs with current resource limitations. Despite lower sensitivity of mammography in women with dense breasts, an alternative personalized approach to supplemental MRI screening may be to offer women with extremely dense breasts more frequent (annual rather than biennial) mammography screening with standard digital mammography or digital breast tomosynthesis. Another alternative approach may be to have a stricter classification of extremely dense breasts so that a lower proportion of women will be offered supplemental MRI screening.

In the DENSE trial, a reduction in the interval cancer rate was used as a short-term indicator for a beneficial effect of supplementary MRI for women with extremely dense breasts [11]. Following this philosophy, we investigated the potential impact on the interval cancer rate of annual versus biennial mammography screening by analyzing time from screening to interval cancer by density. We also explored mammographic density as a continuous, quantitative measure with the aim of establishing acceptable cut-off values for offering supplemental MRI screening or shorter screening intervals.

2. Materials and methods

This study has legal basis in accordance with Articles 6 (1) (e) and 9 (2) (j) of the GDPR. The data was disclosed with legal basis in the Cancer Registry Regulations section 3-1 and the Personal Health Data Filing System Act section 19 a to 19 h [12]. All data were de-identified by the Cancer Registry of Norway prior to analyses.

2.1. Study sample

BreastScreen Norway is the national breast cancer screening program for Norway, inviting women aged 50–69 to two-view biennial mammography screening [13]. The program targets about 650 000 women and is administered by the Cancer Registry of Norway. All information about screening invitation, attendance, and outcomes, including cancer cases, is stored in databases at the Cancer Registry. Reporting to the Cancer Registry has been mandatory by law since 1953, and the registration of breast cancer cases is nearly 100% complete [14]. The mammograms are independently interpreted by two radiologists and examinations classified as suspicious by either or both radiologists are discussed at consensus to determine if a woman should be recalled. From 2007 to 2019, four of the 17 breast centers in BreastScreen Norway had an automated software installed measuring quantitative breast fibroglandular volume, breast volume, and volumetric breast density (Volpara, versions 1.5.0, 1.5.1, 1.5.4, 1.5.5.1, Volpara Solutions, Wellington, New Zealand).

Quantitative mammographic density values from 585 949 screening examinations between 2007 and 2019 were included in this study (Fig. 1). Women screened in 2019 were followed for two years for interval cancers. Examinations from Bergen performed 2016–2019 were excluded due to participation in the digital breast tomosynthesis randomized controlled trial. The final study sample included 508 536 screening examinations performed among 213 105 women, including 504 466 negative examinations, 3125 screen-detected cancers and 945 interval cancers.

2.2. Variables of interest

From the automated software, we obtained information on mammographic density both as a categorical and continuous variable. The average volumetric density value was used to classify examinations into Volpara density grade (VDG) (Volpara, version 1.5.0) or the maximum value for each examination (other versions of Volpara). Examinations with volumetric density ≤3.4% were categorized as VDG1, those with 3.5%–7.4% as VDG2, 7.5%–15.4% as VDG3, and ≥15.5% as VDG4. These categories are considered analogous to the BI-RADS 5th edition density categories [8]. We also explored percentile cut-off values for the classification of extremely dense breasts, 1%–10%, with the
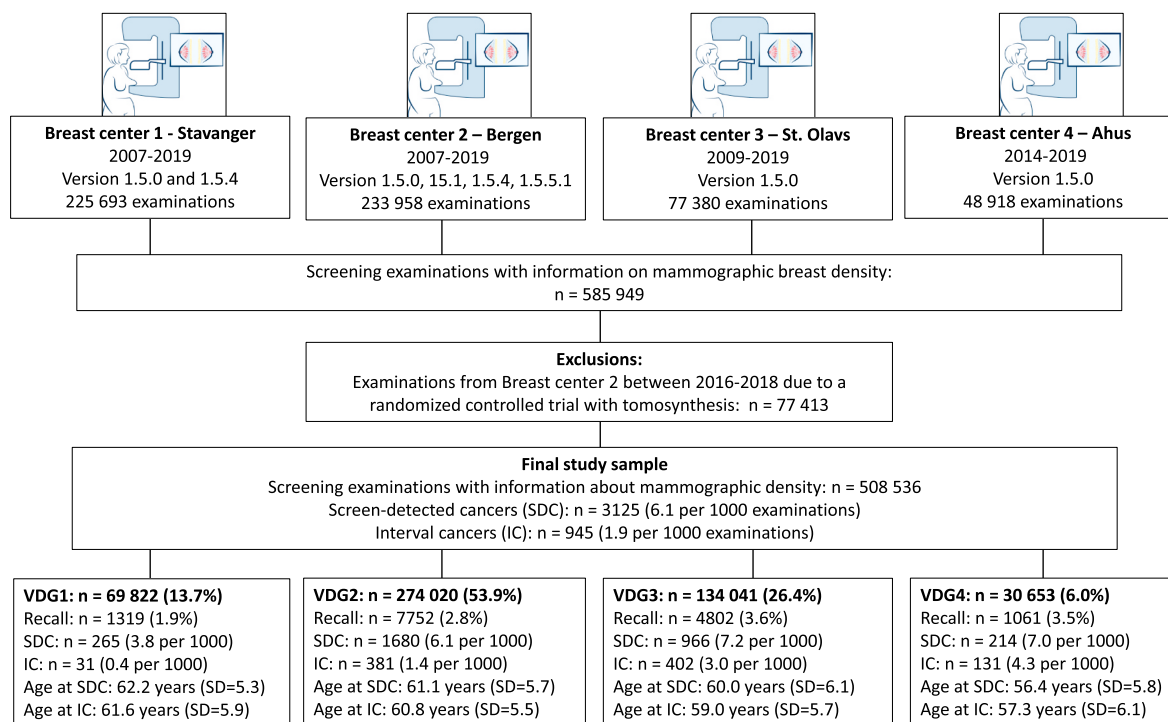

Fig. 1. Flow chart and final study sample stratified by Volpara density grade (VDG 1–4). Age is reported as mean with standard deviation (SD). All women were followed for two years after screening for interval cancer.

highest continuous density values. Density measurements from women with interval cancer were recorded from the most recent screening examination prior to diagnosis.

Screen-detected cancer was defined as breast cancer diagnosed after a recall and within 6 months after a screening examination. Interval cancer was defined as a breast cancer diagnosed within 24 months of a negative screening mammogram or within 6–24 months after a false-positive screening result [13]. A false positive screening result was defined as a recall not resulting in a screen-detected cancer. Time to interval cancer was calculated from date of screening examination to date of histopathological diagnosis.

For invasive cancers, we recorded histopathological tumor characteristics, including tumor diameter in mm, histologic grade 1–3, lymph node status, and immunohistochemical subtypes. Subtypes were based on estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (Her2) status, given as Luminal A–like, Luminal B–like Her2−, Luminal B–like Her2+, Her2+, and triple negative [15].

2.3. Statistical analysis

We describe rates of screen-detected and interval cancers, time (days and months) from screening to interval cancer and histopathological tumor characteristics. Frequencies and percentages are presented for categorical variables and mean and standard deviation (SD) or median and interquartile range (IQR) are presented for continuous variables due to normal/non-normal distributions. Rates were defined as the number of events divided by number of screening examinations. Time to interval cancer and histopathological tumor characteristics are stratified by mammographic density; VDG1-4 or extremely dense/not extremely dense according to different cut-off values (i.e., extremely dense, VDG4, versus not extremely dense, VDG1-3). In addition, interval cancers as outcome and volumetric breast density as a quantitative exposure are analyzed with logistic regression with cubic splines. Results are presented in a figure as predicted probabilities with 95% confidence intervals (CI).

3. Results

A total of 13.7% (69 822/508 536) of the screening mammograms were classified as VDG1, 53.9% (274 020/508 536) as VDG2, 26.4% (134 041/508 536) as VDG3 and 6.0% (30 653/508 536) as VGD4 (Fig. 1).

Of the screen-detected cancers, 8.5% (265/3125) were detected among women with VDG1, 53.8% (1680/3125) among women with VDG2, 30.9% (966/3125) among women with VDG3, and 6.8% (214/3125) with women VDG4 (Fig. 1). The rate of screen-detected cancers were 3.8 (265/69 822) per 1000 examinations for women with VDG1, 6.1 per 1000 (1680/274 020) for VDG2, 7.2 per 1000 (966/134 041) for VDG3, and 7.0 per 1000 (214/30 653) for VDG4.

We found 3.3% (31/945) of the interval cancers among women classified with VDG1, 40.3% (381/945) among VDG2, 42.5% (402/945) among VDG3 and 13.9% (131/945) among VDG4. The interval cancer rates were 0.4 per 1000 (31/69 822) for women with VDG1, 1.4 per 1000 (381/274 020) for VDG2, 3.0 per 1000 (402/134 041) for VDG3, and 4.3 per 1000 (131/30 653) for women with VDG4. A total of 27.5% (36/131) of the interval cancers among women with VDG4 were diagnosed on prevalent screening examinations in BreastScreen Norway. This corresponded to a rate of 4.1 (36/8768) per 1000 baseline examinations. Overall rates, sensitivity, specificity, and false positives are presented in Supplementary Table 1.

We found that 29.5% (279/945) of interval cancers were diagnosed within the first year of the screening interval; 19.4% (6/31) of those among women with VDG1, 26.3% (100/381) among VDG2, 31.3% (126/402) among VDG3, and 35.9% (47/131) among VDG4 (Table 1, Fig. 2). Consequently, the

Table 1

Volumetric breast density, time to interval cancers and proportion of interval cancers detected in the first year after screening stratified by Volpara density grade (VDG, 1–4).

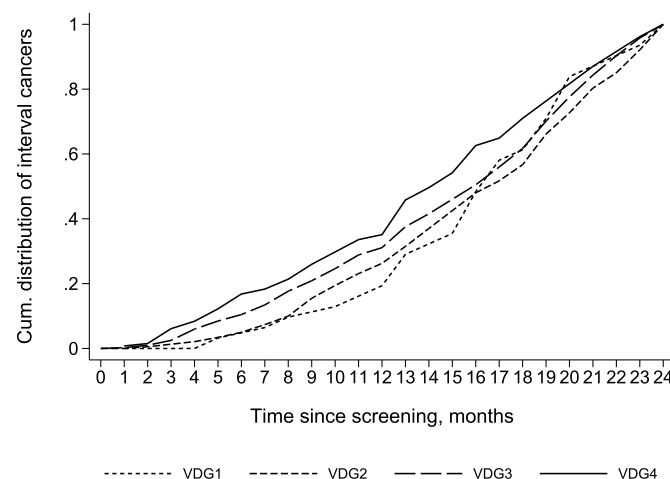| Volpara density grade	Volumetric breast density	Time to interval cancer, median (IQR) days	Interval cancers detected within the first year, n (%)
VDG1	≤3.4%	496 (391–587)	6/31 (19.4)
VDG2	3.5–7.4%	500 (350–616)	100/381 (26.3)
VDG3	7.5–15.4%	482 (309–595)	126/402 (31.3)
VDG4	≥15.5%	427 (266–577)	47/131 (35.9)
Total	–	482 (323–602)	279/945 (29.5)

Fig. 2. Cumulative distribution of interval cancers by time since screening for Volpara density grade (VDG) 1–4.

interval cancer rates during the first year after negative screening were 0.5 per 1000 (279/508 536) in total, 0.09 per 1000 (6/69 822) for VDG1, 0.4 per 1000 (100/274 020) for VDG2, 0.9 per 1000 (126/134 041) for VDG3 and 1.5 per 1000 (47/30 653) for VDG4 (Supplementary Table 1). For the second year after negative screening, the rates were 1.3 (666/508 536) per 1000 in total, 0.4 per 1000 (25/69 822), 1.0 per 1000 (281/274 020), 2.1 per 1000 (296/134 041), and 2.7 per 1000 (84/30 653) for VDG1, VDG2, VDG3 and VDG4, respectively.

In a hypothetical setting of offering women with extremely dense breasts annual mammography screening, we calculated the expected interval cancer rate over two years to compare with the usual biennial setting to estimate an assumed rate reduction. If we assume that the interval cancer rate over two years in annual screening setting would equal two times the interval cancer rate for the first year in biennial screening (2*(279/508 536), a change from biennial to annual screening would reduce the total interval cancer rate by 40.9% (Supplementary Table 1). The relative reduction would be 59.1% for VDG1, 48.2% for VDG2, 37.3% for VDG3 and 28.2% for VDG4, respectively.

3.1. Time from screening to interval cancer

The median time from screening to cancer diagnosis for the 945 interval cancers was 482 days (IQR: 323–602) (Table 1). Median time was 496 days (IQR: 391–587) for VDG1, 500 days (IQR: 350–616) for VDG2, 482 days (IQR: 309–595) for VDG3 and 427 days (IQR: 266–577) for VDG4.

We investigated different continuous volumetric density cut-off values and their impact on the interval cancer rate and the median time to diagnosis for biennial screening. We examined cut-off values for the highest 10% down to the highest 1% of screening examinations based on volumetric density. For the highest 10% of screening

examinations based on volumetric density, the continuous density cut-off value was >12.9%, thus including all VDG4 cases and some VDG3 cases. Among these examinations, 207 interval cancers were diagnosed, equivalent to an interval cancer rate of 4.1 per 1000 (207/508 536) (Table 3). The median time from screening to diagnosis was 444 days (IQR: 271–580). For the highest 4–10% of screening examinations based on volumetric density, the interval cancer rates remained similar (between 4.1 and 4.3 per 1000), as did the median time to interval cancer diagnosis (which varied from 435 to 448 days). However, in the highest 3% of screening examinations based on volumetric density, the interval cancer rate was 4.6 per 1000 and the median time to diagnosis 384 days. More than 40% of the interval cancers among the 3% highest density were diagnosed within the first year of the two-year interval. Considering all 945 interval cancers in the biennial screening setting, 7.4% (70/945) were diagnosed among the 3% with highest volumetric density. To detect these cancers, 250 women would need to be screened to detect one interval cancer (as screen-detected) compared to about 170 women screened to detect one screen-detected cancer.

Using volumetric breast density as a continuous measure, the risk of interval cancers had a steeper slope for volumetric breast density values <12% compared to higher volumetric density values (Fig. 3). Higher density values were associated with great uncertainty due to low numbers.

3.2. Histopathological tumor characteristics

Invasive cancers comprised 94.1% (766/814) of interval cancers among women with VDG1-3 compared to 93.1% (122/131) for VDG4 (Table 2a). The median invasive tumor diameter was 20 mm (IQR: 14–28) for VDG1-3 and 18 mm (IQR: 14–28) for VDG4. A total of 38.3% (44/115) of the invasive tumors were histologic grade 3 for VDG1-3 and 40.3% (290/720) for VDG4.

Among interval cancers of women with VDG4, 91.5% (43/47) were invasive and diagnosed within the first year after screening versus 94.1% (79/94) diagnosed within the second year after screening (Table 2b). 35.0% (14/40) of interval invasive cancers among women with VDG4 found during the first year were histologic grade 3, compared to 40.0% (30/75) found during the second year after negative screening. Lymph node involvement was observed for 36.6% (14/41) in interval invasive cancers found during the first year versus 29.1% (23/79) of interval invasive tumors found during the second year.
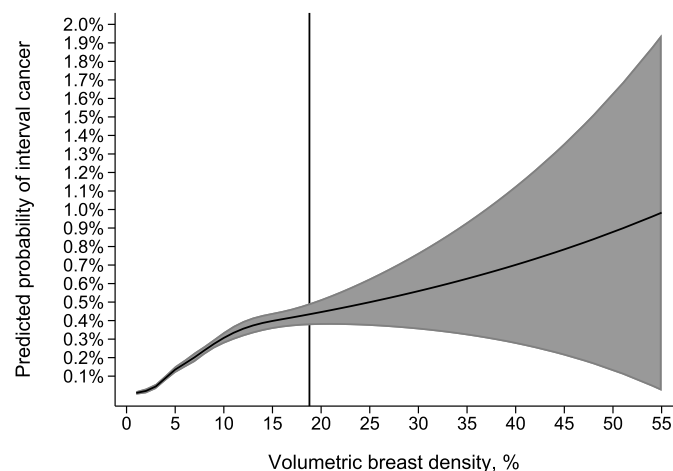

Fig. 3. Predicted probability of interval cancer by volumetric breast density. The vertical line corresponds to the cut-off (18.8%) for the 3% with the highest volumetric breast density.

Table 2a

Tumor characteristics of invasive interval cancers stratified by Volpara Density Grade 1–3 (VDG, not extremely dense) and VDG4 (extremely dense).

	VDG1-3	VDG4
Interval cancers (n)	814	131
Invasive interval cancers, n (%)	766 (94.1)	122 (93.1)
Characteristics of invasive interval cancers		
Tumor diameter, median (IQR) mm	20 (14–28)	18 (14–28)
Information not available (n)	63	9
Histologic grade, n (%)		
Grade 1	100 (13.9)	19 (16.5)
Grade 2	330 (45.8)	52 (45.2)
Grade 3	290 (40.3)	44 (38.3)
Information not available	46	7
Lymph node positive, n (%)	250 (34.8)	38 (32.7)
Information not available (n)	47	2
Immunohistochemical subtypes, n (%)		
Luminal A–like (ER+/PR+/Her2−)	193 (30.8)	33 (32.7)
Luminal B–like Her2− (ER+/PR−/Her2−)	179 (28.6)	26 (25.7)
Luminal B–like Her2+ (ER+/PR±/Her2+)	116 (18.5)	20 (19.8)
Her2+ (ER−/PR−/Her2+)	40 (6.4)	6 (5.9)
Triple negative (ER−/PR−/Her2−)	99 (15.8)	16 (15.8)
Information not available (n)	139	21

Table 2b

Tumor characteristics of invasive interval cancers in the first and second years of the screening interval for women with Volpara Density Grade 4 (VDG, extremely dense).

	VDG4 First year	VDG4 Second year
Interval cancers (n)	47	84
Invasive interval cancers, n (%)	43 (91.5)	79 (94.1)
Characteristics of invasive interval cancers		
Tumor diameter, median (IQR) mm	19 (14–30)	18 (14–25)
Information not available (n)	4	5
Histologic grade, n (%)		
Grade 1	5 (12.5)	14 (18.7)
Grade 2	21 (52.5)	31 (41.3)
Grade 3	14 (35.0)	30 (40.0)
Information not available (n)	3	4
Lymph node positive, n (%)	14 (36.6)	23 (29.1)
Information not available (n)	2	0
Immunohistochemical subtypes		
Luminal A–like (ER+/PR+/Her2−)	12 (34.3)	21 (31.8)
Luminal B–like Her2− (ER+/PR−/Her2−)	12 (34.3)	14 (21.2)
Luminal B–like Her2+ (ER+/PR±/Her2+)	6 (17.1)	14 (21.2)
Her2+ (ER−/PR−/Her2+)	2 (5.7)	4 (6.1)
Triple negative (ER−/PR−/Her2−)	3 (8.6)	13 (19.7)
Information not available (n)	8	13

4. Discussion

In our analysis using over a decade's worth of data from BreastScreen Norway, we found the highest rate of interval cancers among women with extremely dense breasts (4.33 per 1000 for VDG4 versus 0.4–3.0 per 1000 for VDG1-3). While women with extremely dense breasts (VDG4) constitute only about 6% of the screening population, they accounted for 14% of all interval cancers. This supports the recent EUSOBI recommendations for more intensive screening regimens for this subgroup of women.

We found that women with extremely dense breasts also experienced shorter times from screening to diagnosis of interval cancer compared to women with other density categories (median 427 days for VDG4 versus 482–496 days for VDG1-3). Median time to interval cancer for women with extremely dense breasts was also closer to an annual screening interval compared to the more protracted median time to interval cancer for other density categories, supporting more intensive screening regimens for the former subgroup. Annual mammography screening may benefit women with extremely dense breasts. While the recent EUSOBI

Table 3

Frequency and rate of interval cancers for different cut-off for defining extremely dense breasts. Volumetric breast density cut-off values, interval cancers, interval cancer rates, and median times from screening to date of diagnosis for the 10%–1% of screening examinations with the highest volumetric breast density.

Cut-off	Volumetric breast density	Interval cancers, n (per 1000) for extremely dense	Interval cancers, n (per 1000) for not extremely dense	Median time (IQR), days for extremely dense	Median time (IQR), days for not extremely dense	Interval cancers diagnosed within the first year, n (%)
10%	>12.9%	207/4.1 per 1000	738/1.6 per 1000	444 (271–580)	494 (336–605)	75 (36.2)
9%	>13.4%	191/4.2 per 1000	754/1.6 per 1000	448 (273–577)	494 (331–606)	67 (35.1)
8%	>14.0%	166/4.1 per 1000	779/1.7 per 1000	443 (253–572)	494 (332–608)	61 (36.8)
7%	>14.7%	149/4.2 per 1000	796/1.7 per 1000	443 (258–567)	494 (331–607)	54 (36.2)
6%	>15.5%	130/4.3 per 1000	815/1.7 per 1000	435 (273–577)	493 (329–605)	46 (35.4)
5%	>16.4%	108/4.2 per 1000	837/1.7 per 1000	443 (281–588)	491 (328–603)	39 (36.1)
4%	>17.5%	87/4.3 per 1000	858/1.8 per 1000	443 (300–586)	485 (327–603)	30 (34.5)
3%	>18.8%	70/4.6 per 1000	875/1.8 per 1000	384 (258–567)	491 (328–603)	28 (40.0)
2%	>20.3%	42/4.1 per 1000	903/1.8 per 1000	370 (258–540)	485 (327–603)	19 (45.2)
1%	>22.8%	26/5.1 per 1000	919/1.8 per 1000	397 (213–628)	484 (325–602)	11 (42.3)

recommendations suggest adding MRI every 2–4 years for this subgroup, annual mammography screening may be more feasible in low MRI-resource settings and potentially more cost-effective.

A combination of the more intensive mammography screening approach suggested above along with the EUSOBI recommendation for supplemental MRI screening could also be considered. As 40% of the interval cancers among the 3% with highest density were diagnosed within the first year after screening, MRI could be offered to this subgroup of women. Women in the top X% (but not in the top 3%) could be offered annual screening where X is to be determined based on MRI capacity, as well as cost-effectiveness analyses weighing benefits and harms. In our study cohort, the top 3% measured by volumetric density corresponded to continuous volumetric density measures of >18.8%. This threshold may be different for populations outside of Norway. If a continuous cut-off is used, automated density measures would be a prerequisite for adopting such a strategy.

In addition to not suggesting screening with MRI, the European Commission Initiative on Breast Cancer does not suggest digital breast tomosynthesis for prevalently screened women with extremely dense breasts [7]. However, among women with extremely dense breasts, we found over one-fourth (27.5%) of interval cancers among the prevalently screened women. Thus, in low MRI capacity settings, an alternative strategy could be offering supplemental MRI or annual mammography screening for women found to have extremely dense breasts at their first or prevalent screening (versus women with extremely dense breasts undergoing subsequent screening).

We also examined interval cancer rates by different continuous density measure cut-off values for women with extremely dense breasts to help inform alternative future approaches for density-driven risk-based supplemental screening in limited MRI resource settings. We found that interval cancer rates increased with more strict cut-off values for categorizing women as having extremely dense breasts. For instance, while the current categorization for VDG4 (volumetric density >15.5%) leads to 6% of the screened population, a stricter cut-off of volumetric density >22.8% would lead to just 1% of the screened population categorized to the highest density group with a higher interval cancer rate (4.1 per 1000 vs 5.1 per 1000, respectively). Thus, MRI could be offered to just the 1% of the screened population with the highest interval cancer rate based on continuous volumetric density.

It is unclear why women with extremely dense breasts experienced shorter times to interval cancer. It may be due to the masking effect at the time of imaging interpretation. With a median time to interval cancer still within the second year after screening (427 days) but closer to an annual screening interval time point (365 days) compared to other density groups, some of the masked interval cancers may be visible on an intermittent annual screening mammogram. Our descriptive analysis thus supports the consideration of annual screening for women with extremely dense breasts in programs currently offering biennial mammography screening.

Considering the proportion of invasive tumors as well as results on

histopathological grade, and subtypes, invasive interval cancer diagnosed within the first year appear subjectively less aggressive than cancer detected the second year for VDG4. For women with extremely dense breasts, triple negative interval breast cancers accounted for double the proportion of interval cancers found in the second (19.7%) versus the first (8.6%) year after negative screening. While we did not have the statistical power to conclude if there were significant differences based on tumor subtypes across groups, this finding suggests that earlier detection of second year interval cancers with an intervening annual screening mammogram has the potential to improve outcomes for women with extremely dense breasts.

Early results from AI cancer detection algorithms have shown promising results for earlier cancer detection, and thus a decrease in interval cancers [16–18]. Future studies should focus on the use of AI on the subgroup of women with extremely dense breasts and if AI can effectively identify those women who should be offered supplemental MRI based on risk for interval cancer.

Limitations of our study are related to the relatively small number of interval cancers for women with extremely dense breasts, leading to a lack of statistical power to demonstrate statistically significant differences in tumor characteristics across density groups. However, our study included a large sample of data spanning more than a decade involving a large national screening program with robust cancer outcomes linkages. Our study also involved an automated quantitative measure of mammographic density, allowing for evaluation of density as both a categorical and continuous variable without any reader or interpretation bias.

In summary, our descriptive analysis adds to the body of evidence on potential risk-based stratification of women for more intensive screening regimens based on mammographic density. We demonstrated that women with the highest quantitative breast density volume measurements were at the highest risk of interval cancer and may benefit from annual mammography screening and/or MRI rather than the usual biennial screening with mammography alone. Our proposed alternative risk-based stratification approach for offering annual mammography screening to women with extremely dense breasts may be beneficial in settings where MRI access is restricted.

Declaration of competing interest

CIL, SH, KL and ML have no conflicts of interest directly related to this work. CIL has received personal fees from Grail for service on a data and safety monitoring board, personal fees from the ACR for journal editorial board work, and textbook royalties from McGraw-Hill, Oxford University Press, and UpToDate, all outside the submitted work. SH is head of Breast Screen Norway. She has a fixed position at the Cancer Registry of Norway independent of the job as the leader.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2023.03.010.

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