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FULL PAPER

Breast tissue density change after oophorectomy in BRCA mutation carrier patients using visual and volumetric analysis

^{1,2}AUGUSTIN LECLER, MD, MSc, ³ARIANE DUNANT, MD, ⁴SUZETTE DELALOGUE, MD, ⁵DELPHINE WEHRER, MD, ²TANIA MOUSSA, MD, ⁵OLIVIER CARON, MD and ^{2,6}CORINNE BALLEYGUIER, MD, PhD

¹Department of Radiology, Fondation Ophtalmologique Rothschild, Paris, France

²Department of Radiology, Gustave Roussy, Villejuif, France

³Department of Biostatistic and Epidemiology, Gustave Roussy, Villejuif, France

⁴Department of Medical Oncology, Gustave Roussy, Villejuif, France

⁵Department of Genetics, Gustave Roussy, Villejuif, France

⁶Department of Radiology, University Paris-Sud, Orsay, France

Address correspondence to: Dr Augustin Lecler

E-mail: alecler@for.paris

Objective: BRCA1/2 mutations account for 30–50% of hereditary breast cancers and bilateral oophorectomy is associated with a reduced risk of breast cancer in these patients. Breast density is a well-established breast cancer risk factor and is also associated with increased risk in BRCA carriers. The aim of the study was to evaluate the impact of oophorectomy on mammographic breast density and to assess which method of breast density assessment is more sensitive to change over time.

Methods: Retrospective study of 50 BRCA1/2 patients who underwent bilateral oophorectomy and had at least a baseline and post-surgery mammogram. Mammographic breast density was determined by Volpara and consensus visual assessment by two radiologists. The primary endpoint was change in density between baseline and the first mammogram post-surgery.

Results: At baseline, there was a non-significant trend for decreased density with increasing age. Volumetric breast density (VBD) significantly decreased after oophorectomy from a median VBD of 12.5% at baseline to 10.2% post-surgery which was driven by a reduction

in fibroglandular volume. There was a higher absolute decrease in VBD in patients aged between 40–50 ($p < 0.01$). Using Volpara Density Grades (analogous to BI-RADS 4th edition density categories), 84% of females displayed a decrease in density category over the study period compared to only 76% using the radiologists' visual classification ($p < 0.001$).

Conclusion: Oophorectomy is associated with a decrease in breast density and younger patients exhibit a larger absolute decrease. Volpara is more sensitive to identify change over time compared to visual assessment.

Advances in knowledge: Oophorectomy is associated with a significant decrease in VBD in patients with BRCA mutations and Volpara Density Grades were more sensitive to identify decreases in density compared to visually assessed BI-RADS categories. Decreases in breast density following oophorectomy surgery in BRCA patients may be one of the mechanisms contributing to the observed decreased breast cancer risk after surgery. However, further studies are needed to investigate the relationship between breast density, oophorectomy and breast cancer risk in BRCA patients.

INTRODUCTION

Breast density has been demonstrated in multiple studies as a strong independent risk factor for breast cancer; with reported increases in risk up to 6 times for females with very dense breasts compared to females with very fatty breasts.^{1–3} Breast density is also linked to decreased performance and decreased diagnostic accuracy of mammography. In addition to a single time-point assessment of breast density, abnormal temporal change in breast density

has also been identified to be associated with an increased risk of developing breast cancer.⁴

BRCA1 and BRCA2 mutations account for 30 to 50% of hereditary breast cancers), which represent approximately 5% of all breast cancers diagnosed.⁵ HBC families show a high incidence of both breast and ovarian cancer. The risk of breast cancer in females with BRCA1 or BRCA2 mutations range from 54 to 87%.^{6–8} Although prophylactic

Table 1. Population demographics at baseline

	<i>N</i> = 50
Oophorectomy year	2007 (2003–2012)
Mean/median age (range)	46/47 (40–60)
Age 40–45	15 (30%)
Age 45–50	17 (34%)
Age 50–55	10 (20%)
Age 55–60	8 (16%)
Menarche Age	13 (10–16)
Number of pregnancies	
0	4 (8%)
1	4 (8%)
2	15 (30%)
>2	14 (28%)
Unknown	13 (26%)
BRCA mutation type	
1	29 (58%)
2	21 (42%)
Breast cancer history	
No	13 (26%)
Yes	37 (74%)
History of unilateral mastectomy	
No	14 (28%)
Yes	21 (42%)
Unknown	15 (30%)
Family history of breast cancer	
No	7 (14%)
Yes	34 (68%)
Unknown	9 (18%)

mastectomy decreases breast cancer risk by 90%,⁹ most females with BRCA mutations decline it and opt for surveillance. Premenopausal bilateral oophorectomy is associated with a reduced risk of breast cancer by 60 and 50% in BRCA1 and BRCA2 carriers, respectively.¹⁰ Two studies have evaluated the relationship between breast density and breast cancer risk in BRCA patients and reported conflicting results.^{11,12} However, the relationship between oophorectomy and breast density has not been investigated and there also lacks evidence around which methods of density assessment are more appropriate.

The most widespread method of evaluating breast density is visually with the 4-point BI-RADS breast density scale. However, this method is fraught with substantial inter- and intrareader variability^{13–15} and is not reliable or reproducible. For breast density to be a suitable indicator of temporal change, the measure must be robust and objective. To meet these criteria, automated measures of breast density have been developed. Volpara Density

is a fully automated volumetric breast density measurement and provides both a quantitative measurement of density and the Volpara Density Grade (VDG), which are analogous to American College of Radiology BI-RADS density scores. This software has been found to have moderate agreement with radiologists visual assessment of density in several studies.^{16,17}

The aim of the study was to evaluate the impact of oophorectomy on mammographic breast density and to assess which method of breast density assessment is more sensitive to change over time. The primary endpoint was the change in volumetric breast density on the first post-surgery mammogram compared to baseline.

METHODS AND MATERIALS

Study population

This study was approved by the Scientific Committee of our institution and was found to conform to scientific principles and research ethics standards. The population was identified within a longitudinal cohort of all the Caucasian patients identified to carry a BRCA 1 and BRCA 2 mutation in our tertiary centre specialized in oncology, between 2001 and 2014. This prospectively maintained database was retrospectively queried to identify all consecutive patients matching the following inclusion criteria: (1) bilateral oophorectomy (2) available “For Processing” mammography images (including mediolateral oblique and craniocaudal) before and after oophorectomy. All patients were followed up until the end of data collection in August 2014. We tried to avoid potential sources of bias by including all patients followed by our institution without any pre selection other than the two inclusion criteria. Baseline characteristics of patients including; age, age at menarche, number of pregnancies, type of BRCA mutation, personal history of breast cancer, personal history of unilateral mastectomy, family history of breast cancer before 50, were recorded. Endocrine therapy use was tracked throughout the study.

Assessment of mammographic breast density

All available mammograms for each patient were collected for breast density analysis. If patients had undergone unilateral mastectomy, the remaining breast was used to assess breast density changes. Two methods were used to assess breast density, BI-RADS density categories (ACR 4th edition definitions) were visually assessed in consensus by two radiologists reading at the same time (AL 1 year mammography experience, CB 20 years mammography experience). Volumetric breast density (VBD), Fibroglandular Volume and Breast Volume were measured using an FDA-cleared, fully-automated tool, VolparaDensity™, (Volpara Algorithm v.1.5.0, Volpara Health Technologies, Wellington, NZ).

The method underlying Volpara Density has been described in detail elsewhere.¹⁸ Briefly, the Volpara algorithm determines the X-ray attenuation between the image detector and the X-ray source, based on the pixel signals in the images. A pixel signal corresponding to purely adipose tissue is used as a reference to which all other pixels are compared, in order to calculate the thickness of adipose versus fibroglandular tissue that must have

Figure 1. No difference in baseline volumetric breast density was observed by number of pregnancies (a), history of breast cancer (b), history of breastfeeding (c), history of mastectomy (d) and age of menarche (e).

been present between the detector and the X-ray source. As the pixel dimensions are reported in the image, the volumes of adipose and fibroglandular tissue are then summed across the entire breast. VBD is calculated as the ratio of fibroglandular tissue volume to total breast volume, expressed as a percentage. This quantitative VBD value is then mapped to a FDA cleared VDG (*i.e.* an automated equivalent of the BI-RADS 4th edition density categories) using preset thresholds (VDG 1: < 4.5%, VDG 2: $\geq 4.5\%$ and < 7.5%, VDG 3: $\geq 7.5\%$ and < 15.5% and VDG 4: $\geq 15.5\%$).

Statistical analysis

Mann-Whitney test and Friedman test were used to compare baseline VBD between demographic variables. *T*-test and Anova were used to compare baseline BI-RADS between categories. Wilcoxon matched pairs analysis was conducted to compare VBD and BI-RADS before and after oophorectomy to investigate

the primary endpoint. This statistical method was also used to investigate the change in Fibroglandular and Breast Volume before and after oophorectomy. Repeated measures Friedman with Dunnett's post hoc test was used for determining changes in VBD over multiple time points. Chi-squared test was used to compare differences between VDG and BI-RADS categories. A *p* value of less than 0.05 was considered statistically significant. Analysis and graphing was conducted using STATA 13.1 and GraphPad Prism 5.0 software packages.

RESULTS

We identified 876 BRCA 1 and BRCA 2 mutated patients followed in our institution between 2001 and 2014. Among them, 150 patients underwent oophorectomy, between October 2001 and January 2014. We excluded 100 patients because of incomplete data sets: 84 patients had only analogic mammograms, 13 patients did not have available mammogram before oophorectomy and 3 patients had an incomplete pre or post oophorectomy mammogram. Thus, the final study population included 50 patients with pre and post oophorectomy mammograms. A summary of the baseline demographics is shown in Table 1. None of the patients included in our study received endocrine therapy.

Figure 2. No difference in baseline volumetric breast density was observed in younger patients (a), patients with a family history of breast cancer (b) and patients with the BRCA 1 mutation compared to BRCA 2 carriers (c).

At baseline there was no significant difference in volumetric breast density for the number of pregnancies (Figure 1, $p = 0.74$), a history of breast cancer (Figure 1, $p = 0.95$), history of breastfeeding (Figure 1, $p = 0.22$), previous mastectomy (Figure 1, $p = 0.59$) or age of menarche (Figure 1, $p = 0.76$).

At baseline there was no significant difference in volumetric breast density for the patient age (Figure 2, $p = 0.08$), a family history of breast cancer (Figure 2, 13.7 vs 9.1%, $p = 0.09$) or BRCA1 mutation vs BRCA2 (Figure 2, 14.9 vs 11.6% respectively, $p = 0.09$). However, BRCA1 patients were significantly younger than BRCA2 patients (44 vs 51, $p < 0.001$) and patients with a family history were also slightly younger (47 vs 51, $p = 0.15$) potentially confounding these results.

Figure 3. Significant decrease in volumetric breast density post-surgery compared to baseline (a) which was greater in younger patients (b), ** $p < 0.01$, *** $p < 0.001$.

All patients had a baseline and at least one post-surgery mammogram as per the inclusion criteria. The majority of the patients had a second mammogram before baseline (88%) and a second mammogram following surgery (88%) and a smaller proportion (38%) had a third mammogram available. The interval between mammograms varied between patients. The median time interval between the first mammogram and baseline was 11.2 months (IQR 7.6–15.6),

4.8 months between the baseline mammogram and surgery (IQR 2.7–10 months) and 8.4 months between surgery and the first post-surgery mammogram (IQR 5.8–11.8). Of the 50 patients, 44 (88%) had a second post-surgery mammogram available for analysis and the median time difference between this mammogram and the first post-surgery mammogram was 12.4 months (IQR 10.4–13.1). There were fewer patients that had 3 post surgery mammograms available (38%), which were taken approximately 13 months following their last mammogram (IQR 12–14).

There was a significant decrease in VBD at the first post-surgery mammogram compared to baseline from a median of 12.5% (IQR 7.4–18.2) to 10.2% (IQR 7.1–14.2, Figure 3, $p < 0.001$). This change in VBD was driven by a significant reduction in fibroglandular volume from a median of 57 cm³ (IQR 44–80) to 45 cm³ (IQR 39–68, Figure 3, $p < 0.001$, Figure 4, $p < 0.001$) as breast volumes did not significantly change post-operatively (519 cm³ vs 502 cm³, Figure 4). The absolute change in VBD was significantly greater in the younger age groups with a median VBD of 15.9% (IQR 7.8–22.1) at baseline in the 40–45 year old group, decreasing to 11.5% (IQR 7.3–19.4) at the first mammogram post-surgery (Figure 3b, $p < 0.001$) and a smaller decrease but still significant in the 45–50 year old group, 13.1% (IQR 10.3–18.2) at baseline to 10.5% (IQR 7.6–15.3) at first post-surgery mammogram ($p < 0.01$). There were small decreases in density at older age groups but they were not statistically significant. Analysis of patients with additional mammograms available demonstrated further decreases in density in the younger patients which were significantly lower compared to baseline (Figure 3, $p < 0.001$), but these were not statistically lower compared to the first post-surgery density values.

Figure 4. No change in breast volume post-surgery compared to baseline (a), whereas fibroglandular volume was significantly reduced (b), *** $p < 0.001$.

An example of density change following surgery is displayed in Figure 5. In patients with a second mammogram before baseline, there were no significant changes in VBD before surgery.

Density was also assessed visually for each mammogram at baseline and post-surgery. Demographic factors and baseline BI-RADS category information are provided in Table 2. There was a significant decrease in BI-RADS at the first post-surgery mammogram compared to baseline from an average of 2.96 to 2.78 ($p = 0.04$). The absolute change in BI-RADS was significantly greater in the younger age groups with an average of 3.21 at baseline in the 40–45 year old group, decreasing to 2.82 at the first mammogram post-surgery ($p < 0.01$). There were small decreases in density at older age groups but they were not statistically significant.

The agreement between visual BI-RADS and Volpara Density Grades ranged from 0.66 to 0.83 (weighted kappa) over the study period. Tracking changes in Volpara Density Grades (VDG) over time, there was significantly more females with a decrease in VDG compared to BI-RADS both immediately following surgery and longer term. Comparing the first mammogram following surgery with baseline, 28% of females had a decrease in density category as assessed by Volpara compared to 16% as assessed by BI-RADS (Table 3, $p < 0.018$). An example of a decrease in VDG following surgery is shown in Figure 5, with a change in VDG from a category 3 (Figure 5) to category 2 at the first post-surgery mammogram (Figure 5). Looking at the whole study period, 84% of females had a decrease in density category after oophorectomy compared to 76% using BI-RADS visual assessment (Table 4, $p < 0.001$).

DISCUSSION

Our study showed a significant decrease in volumetric breast density after oophorectomy in BRCA 1 and BRCA 2 mutated patients. There was a greater decrease in younger patients and the use of Volpara Density Grades were more

Figure 5. Example of density decrease in Volpara Density Grade post-surgery compared to baseline. Right MLO views for baseline mammogram (a), first mammogram post-surgery (b) and second mammogram post-surgery (c). Changes in the density grade are shown in the Volpara scorecards corresponding to the baseline mammogram (d), first mammogram post-surgery (e) and second mammogram post-surgery (f).

sensitive to breast density reductions compared to visual BI-RADS.

We also found higher absolute volumetric breast density in younger patients, BRCA 1 carriers and patients with a family history at baseline. However, these differences were not significant and BRCA 1 carriers and patients with family history were also younger than their comparison, potentially confounding the result. There may be a slight bias to younger patients with a

family history as these patients may be triggered to seek counseling and enter the high risk surveillance system earlier than patients without family members diagnosed with breast cancer. Other studies have also found age is an important confounder in BRCA patients, Gierach et al observed in BRCA1/2 patients that a significant finding of higher breast density compared to the general population disappeared when adjusting for age.¹⁹ The significantly younger BRCA 1 patients may be due to the documented earlier age of disease onset compared to

Table 2. Demographic factors and baseline BI-RADS category information

	Average BI-RADS category	<i>p</i> -value
Age		
40–45	3.2	0.06
45–50	3.2	
50–55	2.7	
55–60	2.3	
Menarche age		
10	2	0.39
11	2	
12	2.5	
13	2.8	
14	3.2	
16	3	
Number of pregnancies		
0	3	0.676
1	3.3	
2	3	
>2	2.8	
BRCA mutation type		
1	3.2	0.07
2	2.8	
Breast feeding		
No	2.8	0.39
Yes	3.3	
Breast cancer history		
No	2.9	0.57
Yes	3.1	
History of unilateral mastectomy		
No	3.1	0.43
Yes	2.8	
Family history of breast cancer		
No	2.3	0.02
Yes	3.1	

BRCA 2 mutation, triggering intervention earlier in those patients.²⁰

After oophorectomy, there was a significant decrease in VBD with a median absolute reduction of 2.3% at the first mammogram post-surgery. As there was no significant change in breast volume between time points and a significant reduction in fibroglandular volume, this reduction in VBD was due to a direct effect on the dense tissue in the breast. This decrease was significantly higher in the younger patients with a median decrease of

Table 3. Change in density category between baseline and the 1st post-surgery mammogram as assessed by Volpara Density Grades and visual BI-RADS

	Density assessed by Volpara Density Grades			
Density assessed by visual BI-RADS		No Change	Decrease	Total
	No Change	33 (66%)	9 (18%)	42 (84%)
	Decrease	3 (6%)	5 (10%)	8 (16%)
	Total	36 (72%)	14 (28%)	50 (100%)

Table 4. Change in density category between baseline and all available post-surgery mammograms as assessed by Volpara Density Grades and visual BI-RADS

	Density assessed by Volpara Density Grades			
Density assessed by visual BI-RADS		No Change	Decrease	Total
	No Change	6 (12%)	6 (12%)	12 (24%)
	Decrease	2 (4%)	36 (72%)	38 (76%)
	Total	8 (16%)	42 (84%)	50 (100%)

4.4% compared to 1.6% in the oldest age group. This trend was also demonstrated in the tamoxifen arm of the IBIS 1 study, with higher density decreases in the younger age groups.²¹ The relationship between increased mammographic breast density and increased breast cancer incidence in females with BRCA mutations remains unclear with contradictory results. A prospective study of 462 patients showed no relationship between breast density and breast cancer, whereas a retrospective study of 206 patients reported an OR of cancer of 2.29 in patients with a breast density of 50% or more.^{11,12}

There have been several studies suggesting decreases in breast density are an early marker of response in prevention trials.^{22,23} The strongest evidence has come from Cuzick *et al*²⁴ who found a reduction of greater than 10% in visually assessed breast density after tamoxifen, resulted in a 63% reduction in breast cancer risk compared to patients whose breast density did not change. The LIBER trial,²⁵ a phase III trial studying letrozole and its ability to prevent breast cancer in BRCA patients, is the only current BRCA specific prospective study to our knowledge and results have yet to be published. Further work is also needed to confirm whether the decrease breast cancer risk following oophorectomy in these patients¹⁰ is directly related to the reduction in breast density, as seen in this study.

In this study two different methods of mammographic breast density assessment were used and the automated measure identified greater changes in breast density. This was the case both immediately following surgery, with 28% of patients experiencing a change in VDG category compared to 16% with visual BI-RADS and at the last available mammogram (84 vs 76% respectively). In the clinical setting, breast density has traditionally been determined by means of visual assessment, but this method only achieves moderate inter-observer agreements.^{13,14} Volpara has shown excellent reproducibility with within-breast

density variability <1% on repeat mammograms.²⁶ In this study, the agreement between Volpara and visual assessment ranged between 0.66 to 0.83 (weighted kappa). This is in line with kappa values of 0.57 reported by Brandt et al¹⁶ but higher than the agreement of 0.43 reported by Youk et al¹⁷ which was conducted in a South Korean population. It is currently not possible to determine which method most accurately reflects “true” breast density. However, as breast density is used more frequently as a biomarker of treatment response and in determining individual breast cancer risk, the ability to have a reproducible automated density measurement becomes increasingly integral to the appropriate management of patients.

Due to the study design there were several limitations that may have impacted the data. As the study only included patients undergoing oophorectomy, we could not compare the impact of surgery on breast density compared to the expected change in breast density with aging. Similarly, as the study was retrospective, the timing of the mammograms before and after surgery were not controlled and may have also impacted our results. The

menopausal status of patients before surgery was not available in the medical notes and therefore we could not factor this in to our analysis. However, the study population is relatively young and we do not think this was impacted our results greatly. The study size was relatively small and reduced our power to identify subtle changes in baseline density.

Oophorectomy is associated with a significant decrease in volumetric breast density in patients with BRCA 1 and BRCA 2 mutations and there was a significantly larger absolute decrease in density in the younger patient groups. The automated Density Grades were also more sensitive to decreases in density compared to the visually assessed BI-RADS categories, both immediately after surgery and at follow-up. Further studies are needed to investigate whether the decrease in breast cancer risk observed after oophorectomy is due to changes in breast density in BRCA 1 and BRCA 2 patients.

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REFERENCES

- Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, et al. Mammographic density and the risk and detection of breast cancer. *N Engl J Med* 2007; **356**: 227–36. doi: <https://doi.org/10.1056/NEJMoa062790>
- 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. doi: <https://doi.org/10.1158/1055-9965.EPI-06-0034>
- 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. doi: <https://doi.org/10.3233/BD-1998-103-412>
- Kerlikowske K, Ichikawa L, Miglioretti DL, Buist DS, Vacek PM, Smith-Bindman R, et al. Longitudinal measurement of clinical mammographic breast density to improve estimation of breast cancer risk. *J Natl Cancer Inst* 2007; **99**: 386–95. doi: <https://doi.org/10.1093/jnci/djk066>
- Marcus JN, Watson P, Page DL, Narod SA, Lenoir GM, Tonin P, et al. Hereditary breast cancer: pathobiology, prognosis, and BRCA1 and BRCA2 gene linkage. *Cancer* 1996; **77**: 697–709. doi: [https://doi.org/10.1002/\(SICI\)1097-0142\(19960215\)77:4<697::AID-CNCR16>3.0.CO;2-W](https://doi.org/10.1002/(SICI)1097-0142(19960215)77:4<697::AID-CNCR16>3.0.CO;2-W)
- Struwing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med* 1997; **336**: 1401–8. doi: <https://doi.org/10.1056/NEJM199705153362001>
- Easton DF, Ford D, Bishop DT. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast cancer linkage consortium. *Am J Hum Genet* 1995; **56**: 265–71.
- Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE. Risks of cancer in BRCA1-mutation carriers. Breast cancer linkage consortium. *Lancet* 1994; **343**: 692–5.
- Hartmann LC, Schaid DJ, Woods JE, Crotty TP, Myers JL, Arnold PG, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N Engl J Med* 1999; **340**: 77–84. doi: <https://doi.org/10.1056/NEJM199901143400201>
- Metcalf K, Lynch HT, Foulkes WD, Tung N, Kim-Sing C, Olopade OI, et al. Effect of oophorectomy on survival after breast cancer in BRCA1 and BRCA2 mutation carriers. *JAMA Oncol* 2015; **1**: 306–13. doi: <https://doi.org/10.1001/jamaoncol.2015.0658>
- Passaperuma K, Warner E, Hill KA, Gunasekara A, Yaffe MJ. Is mammographic breast density a breast cancer risk factor in women with BRCA mutations? *J Clin Oncol* 2010; **28**: 3779–83. doi: <https://doi.org/10.1200/JCO.2009.27.5933>
- Mitchell G, Antoniou AC, Warren R, Peock S, Brown J, Davies R, et al. Mammographic density and breast cancer risk in BRCA1 and BRCA2 mutation carriers. *Cancer Res* 2006; **66**: 1866–72. doi: <https://doi.org/10.1158/0008-5472.CAN-05-3368>
- Lee HN, Sohn YM, Han KH. Comparison of mammographic density estimation by volpara software with radiologists' visual assessment: analysis of clinical-radiologic factors affecting discrepancy between them. *Acta Radiol* 2015; **56**: 1061–8. doi: <https://doi.org/10.1177/0284185114554674>
- Gweon HM, Youk JH, Kim JA, Son EJ. Radiologist assessment of breast density by BI-RADS categories versus fully automated volumetric assessment. *AJR Am J Roentgenol* 2013; **201**: 692–7. doi: <https://doi.org/10.2214/AJR.12.10197>
- Ciatto S, Houssami N, Apruzzese A, Bassetti E, Brancato B, Carozzi F, et al. Categorizing breast mammographic density: intra- and interobserver reproducibility of BI-RADS density categories. *Breast* 2005; **14**: 269–75. doi: <https://doi.org/10.1016/j.breast.2004.12.004>
- Brandt KR, Scott CG, Ma L, Mahmoudzadeh AP, Jensen MR, Whaley DH, et al. Comparison of clinical and automated breast density measurements: implications for risk prediction and supplemental screening. *Radiology* 2016; **279**: 710–9. doi: <https://doi.org/10.1148/radiol.2015151261>
- Youk JH, Gweon HM, Son EJ, Kim JA. Automated volumetric breast density measurements in the era of the BI-RADS fifth edition: a comparison with visual assessment. *AJR Am J Roentgenol* 2016; **206**: 1056–62. doi: <https://doi.org/10.2214/AJR.15.15472>

18. Ng KH, Lau S. Vision 20/20: Mammographic breast density and its clinical applications. *Med Phys* 2015; **42**: 7059–77. doi: <https://doi.org/10.1118/1.4935141>
19. Gierach GL, Loud JT, Chow CK, Prindiville SA, Eng-Wong J, Soballe PW, et al. Mammographic density does not differ between unaffected BRCA1/2 mutation carriers and women at low-to-average risk of breast cancer. *Breast Cancer Res Treat* 2010; **123**: 245–55. doi: <https://doi.org/10.1007/s10549-010-0749-7>
20. Welch PL, King MC. BRCA1 and BRCA2 and the genetics of breast and ovarian cancer. *Hum Mol Genet* 2001; **10**: 705–13. doi: <https://doi.org/10.1093/hmg/10.7.705>
21. Cuzick J, Warwick J, Pinney E, Warren RM, Duffy SW. Tamoxifen and breast density in women at increased risk of breast cancer. *J Natl Cancer Inst* 2004; **96**: 621–8. doi: <https://doi.org/10.1093/jnci/djh106>
22. Warren R. Hormones and mammographic breast density. *Maturitas* 2004; **49**: 67–78. doi: <https://doi.org/10.1016/j.maturitas.2004.06.013>
23. Sala E, Warren R, McCann J, Duffy S, Luben R, Day N. High-risk mammographic parenchymal patterns, hormone replacement therapy and other risk factors: a case-control study. *Int J Epidemiol* 2000; **29**: 629–36. doi: <https://doi.org/10.1093/ije/29.4.629>
24. Cuzick J, Warwick J, Pinney E, Duffy SW, Cawthorn S, Howell A, et al. Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. *J Natl Cancer Inst* 2011; **103**: 744–52. doi: <https://doi.org/10.1093/jnci/djr079>
25. Pujol P, Lasset C, Berthet P, Dugast C, Delaloge S, Fricker JP, et al. Uptake of a randomized breast cancer prevention trial comparing letrozole to placebo in BRCA1/2 mutations carriers: the LIBER trial. *Fam Cancer* 2012; **11**: 77–84. doi: <https://doi.org/10.1007/s10689-011-9484-4>
26. Alonzo-Proulx O, Mawdsley GE, Patrie JT, Yaffe MJ, Harvey JA. Reliability of automated breast density measurements. *Radiology* 2015; **275**: 366–76. doi: <https://doi.org/10.1148/radiol.15141686>