Cancer Causes & Control (2022) 33:1207–1213
https://doi.org/10.1007/s10552-022-01590-x

BRIEF REPORT

Mammographic breast density and survival in women with invasive breast cancer

Margherita Pizzato[1] · Greta Carioli[1] · Stefano Rosso[2] · Roberto Zanetti[2,3] · Carlo La Vecchia[1]

Received: 24 May 2021 / Accepted: 9 May 2022 / Published online: 13 June 2022

Abstract

Purpose We explored the under-debate association between mammographic breast density (MBD) and survival.

Methods From the Piedmont Cancer Registry, we identified 693 invasive breast cancer (BC) cases. We analyzed the overall survival in strata of MBD through the Kaplan–Meier method. Using the Cox proportional hazards model, we estimated the hazard ratios (HRs) of death; using the cause-specific hazards regression model, we estimated the HRs of BC-related and other causes of death. Models included term for Breast Imaging-Reporting and Data System (BI-RADS) MBD (categorized as BI-RADS 1 and BI-RADS 2–4) and were adjusted for selected patient and tumour characteristics.

Results There were 102 deaths, of which 49 were from BC. After 5 years, the overall survival was 69% in BI-RADS 1 and 88% in BI-RADS 2–4 ($p < 0.01$). Compared to BI-RADS 2–4, the HRs of death for BI-RADS 1 were 1.65 (95% CI 1.06–2.58) in the crude model and 1.35 (95% CI 0.84–2.16) in the fully adjusted model. Compared to BI-RADS 2–4, the fully adjusted HRs for BI-RADS 1 were 1.52 (95% CI 0.74–3.13) for BC-related death and 1.83 (95% CI 0.84–4.00) for the other causes of death.

Conclusion Higher MBD is one of the strongest independent risk factors for BC, but it seems not to have an unfavorable impact on survival.

Keywords Invasive breast cancer · Breast density · Survival · Breast cancer prognostic factors · Population-based data

Introduction

Mammographic breast density (MBD) reflects breast tissue composition as projected on a two-dimensional mammographic image. MBD is routinely classified, on the basis of the fibroglandular tissue proportion, into almost entirely fat (Breast Imaging-Reporting and Data System [BI-RADS] (1), scattered areas of fibroglandular density (BI-RADS (2), heterogeneously dense (BI-RADS (3), and extremely dense (BI-RADS (4) [1]. While the role of MBD on breast cancer (BC) risk has been widely assessed (with a 2 to 6-fold increase in risk between the highest and the lowest MBD category according to meta-analyses [2, 3]), the prognostic effect of MBD on BC patients is still undefined [4, 5].

We therefore analyzed the impact of MBD on survival using data from the Piedmont Cancer Registry (Registro Tumori Piemonte—RTP).

Materials and methods

Study population and data collection

Using the RTP dataset, we identified 693 primary invasive BCs (International Classification of Disease for Oncology, 3rd edition, (ICD-O-3) site codes C50.0–50.9 [6]), diagnosed between 2009 and 2014, and treated at AOU (Azienda Ospedaliera Universitaria) Città della Salute e della Scienza, in Turin, Italy.

We retrieved information from the RTP, hospital discharge forms, and reports. For each cancer case included in this study, we collected data on age at diagnosis, education (we defined primary and middle school as low education, and high school

✉ Greta Carioli
greta.carioli@gmail.com

[1] Department of Clinical Sciences and Community Health, University of Milan, Via Celoria 22, 20133 Milan, Italy

[2] Piedmont Cancer Registry, A.O.U, Citta` della Salute e della Scienza di Torino, Turin, Italy

[3] Fondo Elena Moroni for Oncology, Turin, Italy

and university as high education), parity, menopausal status, BC history in first- or second-degree relatives, tobacco smoking, diabetes, marital status, and the body mass index (BMI) at the time of diagnosis. MBD was assessed from the preoperative mammogram report closest to the time of diagnosis. Density measurement was performed by a single radiologist from diagnostic digital mammograms of the unaffected breast and classified according to the BI-RADS reporting system. From pathology reports, we extracted information on Estrogen (ER) and Progesterone (PR) receptors, HER2 and Ki67 status, and we classified them on the basis of St. Gallen criteria and ASCO-CAP guidelines [7–9]. We defined BC subtypes as luminal A (ER + and/or PR +, HER2-, low Ki67), luminal BH- (ER + and/or PR +, HER2-, Ki67 high), luminal BH + (ER + and/or PR +, HER2 +), HER2 + (ER-, PR-, HER2 +), triple negative (ER-, PR-, HER2-) [10]. We also retrieved information on histologic grade, histotype, and pathological Tumor-Node-Metastasis (pTNM) stage, according to American Joint Committee on Cancer (AJCC) Cancer Staging Manual criteria [11].

Follow-up was obtained from the RTP. Out of 102 deaths, information on specific cause of death (BC vs other causes) was available for 90 patients.

Statistical analysis

We summarized the baseline characteristics of our sample using descriptive statistics, counts, and percentages. We stratified sample characteristics for MBD categories (BI-RADS 1, BI-RADS 2, and BI-RADS 3–4) and we evaluated differences across groups using the chi-square test (or Fisher's exact test as needed).

The overall survival (OS) was estimated using the Kaplan–Meier method. The log-rank test was applied to assess survival differences.

We estimated the effect of MBD by Cox proportional hazards models and expressed as hazard ratio (HR) with the corresponding 95% confidence interval (CI). We applied the cause-specific hazard regression model to consider death for causes other than BC as competing risk. The first model included terms for MBD (BI-RADS 1/BI-RADS 2–4) and age at diagnosis (modeled as < 40; 40–49; 50–59; 60–69; 70–79; ≥ 80 and as a continuous variable). The second model included all the previous covariates plus BMI (as a continuous variable) and pTNM stage (1/2/3). The third model included all the previous covariates plus education (low/high), smoking (never/ever), parity (no/yes), menopause (pre/post), breast cancer family history (no/yes), and diabetes (no/yes).

Results

Compared to women with BI-RADS 1, women with BI-RADS 2 and BI-RADS 3–4 were younger, more educated, and with a lower BMI. Parity is less frequent in BI-RADS 2 and BI-RADS 3–4, and these groups were more frequently in pre-menopause, no diabetes-affected, and smokers, as compared to BI-RADS 1. Compared to BI-RADS 1, BI-RADS 2 and BI-RADS 3–4 appeared less frequently with a higher grade and a triple-negative subtype and more frequently with a Luminal BH + subtype (Table 1).

Figure 1 shows Kaplan–Meier OS in strata of MBD (BI-RADS 1/BI-RADS 2–4), with the numbers at risk and the numbers of cumulative events by year of follow-up. After 3 years, the OS was 86% in subjects with BI-RADS 1 and 93% in those with BI-RADS 2–4; after 5 years, the OS was 69% in subjects with BI-RADS 1 and 88% in those with BI-RADS 2–4 ($p < 0.01$). The median follow-up was 1408 days (range 36–3682 days).

Table 2 shows mortality HRs by BI-RADS density, along with the corresponding 95% CIs. Compared to BI-RADS 2–4, the HRs of death for BI-RADS 1 were 1.65 (95% CI 1.06–2.58) in the crude model and 1.35 (95% CI 0.84–2.16) in the fully adjusted model. Compared to BI-RADS 2–4, the fully adjusted HRs for BI-RADS 1 were 1.52 (95% CI 0.74–3.13) for BC-related death and 1.83 (95% CI 0.84–4.00) for the other causes of death. In the fully adjusted model, compared to pTNM stage 1, the HRs of death from all causes were 2.38 (95% CI 1.38–4.13) for pTNM stage 2 and 5.41 (2.94–9.96) for pTNM stage 3. Grouping the BMI into four categories, compared to BMI < 18.5, the HRs were 0.74 (95% CI 0.27–1.99) for BMI 18.5–24.9, 0.95 (95% CI 0.35–2.59) for BMI 25–29.9, and 1.54 (95% CI 0.55–4.30) for BMI ≥ 30 (data not shown).

Discussion

Higher MBD, a strong risk factor for BC, does not appear to unfavorably affect survival. The role of MBD as prognostic factor has been addressed in a few studies with rather conflicting and inconclusive results.

A prospective analysis on the Breast Cancer Surveillance Consortium data of over 9000 women with invasive breast carcinoma showed that BI-RADS density (comparing BI-RADS 4 versus BI-RADS 2) was not related to the risk of death from BC (HR 0.92 95% CI 0.71–1.19) or any other cause (HR 0.83 95% CI 0.68–1.02), after accounting for some patient and tumor characteristics (site, age at and year of diagnosis, stage, BMI, mode of detection,

Table 1 Baseline characteristics of 693 women with invasive breast cancer**,** according to Breast Imaging-Reporting and Data System (BI-RADS) density

	BI-RADS 1		BI-RADS 2		BI-RADS 3–4		p (χ^2)
	No	%	No	%	No	%	
	185	26.7	308	44.4	200	28.9	
Patient characteristics							
Age							*< 0.001*
< 50	8	4.3	76	24.7	98	49.0	
50–64	44	23.8	117	38.0	72	36.0	
≥ 65	133	71.9	115	37.3	30	15.0	
Education*							*< 0.001*
Low	101	75.4	140	54.9	80	44.0	
High	33	24.6	115	45.1	102	56.0	
Body mass index (kg/m^2)*							*< 0.001*
< 18.5	3	1.8	20	6.8	34	17.5	
18.5–24.9	46	27.4	138	46.8	112	57.7	
25–29.9	69	41.1	97	32.9	36	18.6	
≥ 30	50	29.8	40	13.6	12	6.2	
Parity*							*0.002*
No	18	10.5	60	20.2	47	24.5	
Yes	153	89.5	237	79.8	145	75.5	
Menopause*							*< 0.001*
Pre	12	6.6	93	31.3	122	64.2	
Post	171	93.4	204	68.7	68	35.8	
Breast cancer family history*							*0.048*
No	109	74.7	174	62.8	124	66.0	
Yes	37	25.3	103	37.2	64	34.0	
Civil Status*							0.167
Unmarried	22	15.0	43	15.6	29	15.9	
Married	85	57.8	181	65.6	123	67.6	
Divorced	40	27.2	52	18.8	30	16.5	
Diabetes							*< 0.001*
No	162	87.6	285	92.5	198	99.0	
Yes	23	12.4	23	7.5	2	1.0	
Smoking*							*0.003*
Never	148	85.5	222	75.5	132	70.6	
Ever	25	14.5	72	24.5	55	29.4	
Tumor characteristics							
pTNM Stage*							0.573
1	67	41.1	128	45.2	83	45.6	
2	69	42.3	121	42.8	79	43.4	
3	27	16.6	34	12.0	20	11.0	
Grade*							0.073
1	49	27.7	84	27.9	74	38.7	
2	87	49.2	157	52.2	85	44.5	
3	41	23.2	60	19.9	32	16.8	
Histotype							0.362
CDI	124	67.0	190	61.7	130	65.0	
CLI	33	17.8	71	23.1	48	24.0	
Others	28	15.1	47	15.3	22	11.0	
Subtype							0.083
Luminal A	105	56.8	172	55.8	127	63.5	
Luminal BH-	44	23.8	62	20.1	38	19.0	
Luminal BH +	12	6.5	45	14.6	20	10.0	
HER2 +	6	3.2	11	3.6	4	2.0	
Triple negative	18	9.7	18	5.8	11	5.5	

Table 1 (continued)

Italics values denote statistical significance at the $p < 0.05$ level

pTNM pathological tumor-node-metastasis, *CDI* invasive ductal carcinoma, *CLI* invasive lobular carcinoma

*The sum does not add up to total because of missing values

Chi-squared test p (χ^2)

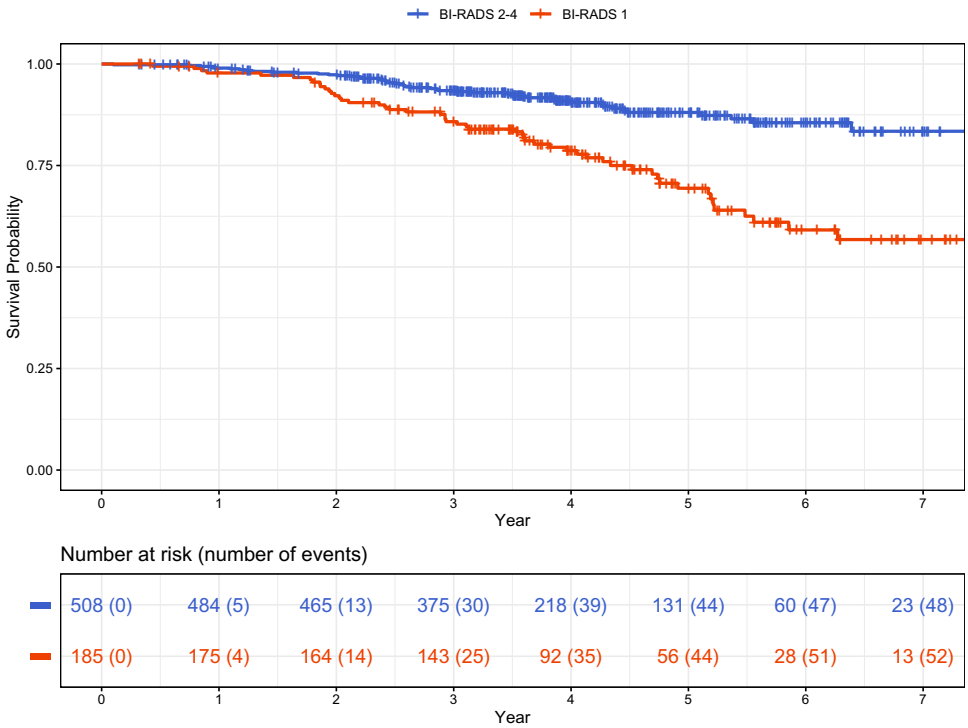

Fig. 1 Overall survival according to mammographic breast density, Breast Imaging-Reporting and Data System [BI-RADS] 2-4 vs BI-RADS 1

treatment, and income) [12]. In a German study on 2525 patients diagnosed with primary metastasis-free BCs, no association was found between semi-automated MBD and overall survival (adjustments included: age and year at diagnosis, BMI, tumor stage, grading, lymph node status, hormone receptor and HER2 status) [13]. Pre-diagnostic MBD, assessed using a computer-assisted method, among 607 BC cases within the Hawaii component of the Multiethnic Cohort was not associated with death from BC (HR 0.95 per 10% 95% CI 0.79–1.15) and from other causes (HR 1.08 per 10% 95% CI 0.98–1.20); the model was adjusted for age at diagnosis, ethnicity, overweight, stage at diagnosis, and radiation treatment [14]. Similarly, in a British hospital–based study of 759 women aged 50–69 with primary operable invasive BCs, BC-specific survival was unrelated to BI-RADS mammographic parenchymal pattern; a nonsignificant trend was observed for women with denser breasts who showed a better overall survival than women with fatty breasts [15]. Moreover, a Swedish study observed that high MBD, assessed according to Tabar's classification, was suggestively, but not significantly, associated with poorer long-term survival after adjustments for age, tumor size, node status, grade, and BMI (HR 1.75 95% CI 0.99–3.10) [16]. Focusing on BC-related deaths, a cohort study on 22,597 African American and White women with BC enrolled from the Carolina Mammography Registry showed no association with MBD (HR 0.91, p 0.124 dense [BI-RADS 3–4] versus fatty [BI-RADS 1–2] adjusted for age, ethnicity, and tumor stage) [17].

An analysis including 619 BC cases selected from a prospective cohort (i.e., The Malmö Diet and Cancer Study) showed that, after adjustment for age and other prognostic factors, women aged 50–69 with dense breast (BI-RADS 4), as compared to fatty one (BI-RADS 1), had an increased risk of BC-related death (HR 2.56 95% CI 1.07–6.11). In the same study, when deaths from causes other than BC were considered, the HR was 0.74 (95% CI 0.31–1.73) [18]. Moreover, including only women diagnosed with metastatic BC, a Saudi Arabian study observed that moderate/high MBD patients (> 25% of radio-dense fibroglandular tissue) had a worse median progression-free survival than low density ones (9.3 months, 95% CI 8.51–13.60 vs 18.4 months, 95% CI 14.88–22.15, respectively, $p = 0.002$) [19].

The association between lower MBD and poorer outcome has been observed in some studies worldwide. In a Finnish analysis assessed on 270 patients aged 32–86 with newly diagnosed BC, very low MBD at the time of diagnosis

Table 2 Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for all-causes death, breast cancer and other causes of death according to Breast Imaging-Reporting and Data System (BI-RADS) density among 693 women with invasive breast cancer

	Death		HR[a] (95% CI)	HR[b] (95% CI)	HR[c] (95% CI)
	No	%			
All-causes death					
Density					
BI-RADS 1	53	28.6	**1.65 (1.06–2.58)**	1.42 (0.91–2.23)	1.35 (0.84–2.16)
BI-RADS 2–4	49	9.6	*Ref*	*Ref*	*Ref*
Breast cancer death					
Density					
BI-RADS 1	21	11.4	1.85 (0.94–3.63)	1.40 (0.72–2.72)	1.52 (0.74–3.13)
BI-RADS 2–4	28	5.5	*Ref*	*Ref*	*Ref*
Other causes of death					
Density					
BI-RADS 1	28	15.1	1.94 (0.96–3.91)	1.95 (0.96–3.96)	1.83 (0.84–4.00)
BI-RADS 2–4	13	2.6	*Ref*	*Ref*	*Ref*

Bold values denote statistical significance at the $p < 0.05$ level

[a]Estimated through Cox model including terms for age at diagnosis (modelled as < 40; 40–49; 50–59; 60–69; 70–79; ≥ 80 and as a continuous variable)

[b]Estimated through Cox model including terms for age at diagnosis (modelled as < 40; 40–49; 50–59; 60–69; 70–79; ≥ 80 and as a continuous variable), body mass index (as continuous variable), Pathological Tumour-Node-Metastasis stage (1; 2; 3)

[c]Estimated through Cox model including terms for age at diagnosis (modelled as < 40; 40–49; 50–59; 60–69; 70–79; ≥ 80 and as a continuous variable), body mass index (as continuous variable), Pathological Tumor-Node-Metastasis stage (1; 2; 3), education (low; high), smoking (never; ever), parity (no; yes), menopause (pre; post), breast cancer family history (no; yes), diabetes (no; yes)

Ref Reference category

(percentage of glandular tissue < 10%) was an independent, poor prognostic factor even after correcting for possible confounders (HR 3.28 95% CI 1.75–6.13 compared to the remaining patients) [20]. In a Korean study on 969 patients with primary operable invasive BC, the high-density group (BI-RADS 3–4) had a higher overall survival compared to the lower one (BI-RADS 1–2) after adjustment for 14 factors including nine clinicopathologic factors and five treatment factors (HR 0.38 95% CI 0.21–0.71) [21]. A cohort study on 989 BC patients aged 50–69 identified within the Danish mammography screening program showed that patients with dense breast (BI-RADS 3–4), compared to those with fatty breast (BI-RADS 1–2), had a lower case fatality (case fatality rate ratio 0.60, 95% CI 0.43–0.84), as well as a reduced risk of BC death (age-adjusted RR 0.53, 95% CI 0.34–0.82) [22]. A case-only study including 2,233 women diagnosed with invasive BC aged from 38 to 97 showed, after adjustment for age and mode of detection, an association of borderline statistical significance between high MBD and BC-specific survival (HR 0.84 95% CI 0.68–1.03 for dense breast, Wolfe scale > 25%, versus fatty breasts, Wolfe scale ≤ 25%) [23].

Evidence that women with lower MBD are at increased risk of death may support the growing evidence that tumor microenvironment could be intertwined with the outcome. Until now, studies have widely explored characteristics of dense breast, while less attention has been given to the fat of breast tissue. Adipose tissue is an effective endocrine organ able to secrete a variety of bioactive molecules. The paracrine support of the tumors by cytokines and growth factors secreted by adipocytes, as well as the chronic low-grade inflammation sustained in surrounding tissue by the peritumoral fat, may, at least in part, enhance malignant progression mechanisms [24, 25]. However, we observed that the impact of MBD on prognosis declines after adjustments, highlighting that BMI and pTNM stage are possible confounders. Large-scale studies are needed in the near future to quantify the association between MBD and BC prognosis, including unexplored prognostic factors, as well as to elucidate the biological interconnections between MBD and BC aggressiveness.

Limitations of this study include MBD assessment that relied on BI-RADS classification, a visual and subjective method; held by a single reader, and hence, no formal assessment of intra or inter-observer variability was performed. Nevertheless, the BI-RADS reporting system allows to rank BC patients into interpretable descriptors without requiring special software. Further, due to known MBD changes with age, we assessed MBD at the time of diagnosis. We had no information on mode of detection (i.e., screening and interval cancers) and we were not able to establish treatment performed by enrolled women (e.g., chemotherapy, surgery,

hormonal, and radiation therapy). Disparities in diagnostic and therapeutic management could be, to a certain extent, controlled by BC subtypes adjustment. Moreover, all primary invasive BCs included were diagnosed and treated in the same hospital. We assessed a comprehensive spectrum of BC-related prognostic factors, including detailed tumor characteristics and several patient aspects (e.g., reproductive, sociodemographic, anthropometric, lifestyle factors). Although we assessed several potential confounding factors, we cannot exclude the possibility of unmeasured confounding in our study. Prior analyses showed remarkable differences in populations and methodologies, in MBD assessment method and classification, as well as in adjustment for confounding factors. These disparities limited comparison between studies and could partly explain a lack of concordance across them.

In conclusion, high MBD, a strong risk factor for BC, does not appear to unfavorably affect survival in women with primary invasive BC.

Acknowledgments None.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by GC, MP, and SR. The first draft of the manuscript was written by MP and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding Not applicable.

Data availability The Piedmont Cancer Registry (Registro Tumori Piemonte–RTP).

Code availability The data that support the findings of this study are available from the corresponding author, GC, upon reasonable request.

Declarations

Conflict of interest Not applicable.

Ethical approval Data were retrieved upon permission gathered from the local cancer registry that operates under national (22/3/2019 #29) and regional (11/3/2012 #4) laws. The investigation did not involve any human contact, but only record linkage analysis of administrative healthcare databases.

Informed Consent Not applicable.

Consent for publication Not applicable.

References

1. Spak DA, Plaxco JS, Santiago L, Dryden MJ, Dogan BE (2017) BI-RADS((R)) fifth edition: a summary of changes. Diagn Interv Imaging 98(3):179–190. https://doi.org/10.1016/j.diii.2017.01.001
2. Boyd NF, Rommens JM, Vogt K, Lee V, Hopper JL, Yaffe MJ, Paterson AD (2005) Mammographic breast density as an intermediate phenotype for breast cancer. Lancet Oncol 6(10):798–808. https://doi.org/10.1016/S1470-2045(05)70390-9
3. McCormack VA, dos Santos SI (2006) Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 15(6):1159–1169. https://doi.org/10.1158/1055-9965.EPI-06-0034
4. Kanbayti IH, Rae WID, McEntee MF, Ekpo EU (2019) Are mammographic density phenotypes associated with breast cancer treatment response and clinical outcomes? A systematic review and meta-analysis. Breast 47:62–76. https://doi.org/10.1016/j.breast.2019.07.002
5. Shawky MS, Huo CW, Henderson MA, Redfern A, Britt K, Thompson EW (2019) A review of the influence of mammographic density on breast cancer clinical and pathological phenotype. Breast Cancer Res Treat 177(2):251–276. https://doi.org/10.1007/s10549-019-05300-1
6. WHO International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). Available at: http://wwwwhoint/classifications/icd/adaptations/oncology/en/ (Last accessed Oct 2020)
7. Dowsett M, Nielsen TO, A'Hern R, Bartlett J, Coombes RC, Cuzick J, Ellis M, Henry NL, Hugh JC, Lively T, McShane L, Paik S, Penault-Llorca F, Prudkin L, Regan M, Salter J, Sotiriou C, Smith IE, Viale G, Zujewski JA, Hayes DF, International Ki-67 in Breast Cancer Working G (2011) Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in breast cancer working group. J Natl Cancer Inst 103(22):1656–1664. https://doi.org/10.1093/jnci/djr393
8. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, Francis G, Goldstein NS, Hayes M, Hicks DG, Lester S, Love R, Mangu PB, McShane L, Miller K, Osborne CK, Paik S, Perlmutter J, Rhodes A, Sasano H, Schwartz JN, Sweep FC, Taube S, Torlakovic EE, Valenstein P, Viale G, Visscher D, Wheeler T, Williams RB, Wittliff JL, Wolff AC (2010) American society of clinical oncology/College of American pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 28(16):2784–2795. https://doi.org/10.1200/JCO.2009.25.6529
9. Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, Bilous M, Ellis IO, Fitzgibbons P, Hanna W, Jenkins RB, Press MF, Spears PA, Vance GH, Viale G, McShane LM, Dowsett M (2018) Human epidermal growth factor receptor 2 testing in breast cancer: American Society of clinical oncology/College of American pathologists clinical practice guideline focused update. Arch Pathol Lab Med 142(11):1364–1382. https://doi.org/10.5858/arpa.2018-0902-SA
10. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thurlimann B, Senn HJ, Panel M (2013) Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International expert consensus on the primary therapy of early breast cancer 2013. Ann Oncol 24(9):2206–2223. https://doi.org/10.1093/annonc/mdt303
11. Giuliano AE, Connolly JL, Edge SB, Mittendorf EA, Rugo HS, Solin LJ, Weaver DL, Winchester DJ, Hortobagyi GN (2017) Breast cancer-major changes in the American joint committee on cancer eighth edition cancer staging manual. Cancer J Clin 67(4):290–303
12. Gierach GL, Ichikawa L, Kerlikowske K, Brinton LA, Farhat GN, Vacek PM, Weaver DL, Schairer C, Taplin SH, Sherman ME (2012) Relationship between mammographic density and breast cancer death in the breast cancer surveillance consortium.

J Natl Cancer Inst 104(16):1218–1227. https://doi.org/10.1093/jnci/djs327
13. Heindl F, Fasching PA, Hein A, Hack CC, Heusinger K, Gass P, Poschke P, Stubs FA, Schulz-Wendtland R, Hartmann A, Erber R, Beckmann MW, Meyer J, Haberle L, Jud SM, Emons J (2021) Mammographic density and prognosis in primary breast cancer patients. Breast 59:51–57. https://doi.org/10.1016/j.breast.2021.06.004
14. Maskarinec G, Pagano IS, Little MA, Conroy SM, Park SY, Kolonel LN (2013) Mammographic density as a predictor of breast cancer survival: the Multiethnic Cohort. Breast Cancer Res 15(1):R7. https://doi.org/10.1186/bcr3378
15. Porter GJ, Evans AJ, Cornford EJ, Burrell HC, James JJ, Lee AH, Chakrabarti J (2007) Influence of mammographic parenchymal pattern in screening-detected and interval invasive breast cancers on pathologic features, mammographic features, and patient survival. AJR Am J Roentgenol 188(3):676–683. https://doi.org/10.2214/AJR.05.1950
16. Chiu SY, Duffy S, Yen AM, Tabar L, Smith RA, Chen HH (2010) Effect of baseline breast density on breast cancer incidence, stage, mortality, and screening parameters: 25-year follow-up of a Swedish mammographic screening. Cancer Epidemiol Biomarkers Prev 19(5):1219–1228. https://doi.org/10.1158/1055-9965.EPI-09-1028
17. Zhang S, Ivy JS, Diehl KM, Yankaskas BC (2013) The association of breast density with breast cancer mortality in African American and white women screened in community practice. Breast Cancer Res Treat 137(1):273–283. https://doi.org/10.1007/s10549-012-2310-3
18. Olsson A, Sartor H, Borgquist S, Zackrisson S, Manjer J (2014) Breast density and mode of detection in relation to breast cancer specific survival: a cohort study. BMC Cancer 14:229. https://doi.org/10.1186/1471-2407-14-229
19. Elsamany S, Alzahrani A, Elkhalik SA, Elemam O, Rawah E, Farooq MU, HA M, KO F (2014) Prognostic value of mammographic breast density in patients with metastatic breast cancer. Med Oncol 31(8):96. https://doi.org/10.1007/s12032-014-0096-3
20. Masarwah A, Auvinen P, Sudah M, Rautiainen S, Sutela A, Pelkonen O, Oikari S, Kosma VM, Vanninen R (2015) Very low mammographic breast density predicts poorer outcome in patients with invasive breast cancer. Eur Radiol 25(7):1875–1882. https://doi.org/10.1007/s00330-015-3626-2
21. Hwang KT, Chu AJ, Kim J, Lee JY, Chang JH, Oh S, Kim YA, Jung J, Oh B (2018) Prognostic influence of preoperative mammographic breast density in operable invasive female breast cancer. Sci Rep 8(1):16075. https://doi.org/10.1038/s41598-018-34297-8
22. Olsen AH, Bihrmann K, Jensen MB, Vejborg I, Lynge E (2009) Breast density and outcome of mammography screening: a cohort study. Br J Cancer 100(7):1205–1208. https://doi.org/10.1038/sj.bjc.6604989
23. van der Waal D, Verbeek ALM, Broeders MJM (2018) Breast density and breast cancer-specific survival by detection mode. BMC Cancer 18(1):386. https://doi.org/10.1186/s12885-018-4316-7
24. Masarwah A, Tammi M, Sudah M, Sutela A, Oikari S, Kosma VM, Tammi R, Vanninen R, Auvinen P (2015) The reciprocal association between mammographic breast density, hyaluronan synthesis and patient outcome. Breast Cancer Res Treat 153(3):625–634. https://doi.org/10.1007/s10549-015-3567-0
25. Tiainen S, Masarwah A, Oikari S, Rilla K, Hamalainen K, Sudah M, Sutela A, Vanninen R, Ikonen J, Tammi R, Tammi M, Auvinen P (2020) Tumor microenvironment and breast cancer survival: combined effects of breast fat, M2 macrophages and hyaluronan create a dismal prognosis. Breast Cancer Res Treat 179(3):565–575. https://doi.org/10.1007/s10549-019-05491-7