Research Square

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Mammographic breast density and survival in women with invasive breast cancer

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Abstract

Purpose: Mammographic breast density (BD) is strongly associated to breast cancer (BC) risk; however, its association with survival is unclear.

Methods: Using data from the Piedmont Cancer Registry (Registro Tumori Piemonte), we identified 693 women diagnosed with primary invasive BC between 2009-2014. We applied the Kaplan-Meier method to estimate overall survival in strata of BD and the log-rank test to assess survival differences. We evaluated the hazard ratios (HRs) of death using Cox proportional hazards model and HRs of BC-related and other causes of death using the cause-specific hazards regression model. Models included terms for BD (assessed according to the Breast Imaging Reporting and Data System [BI-RADS] density classification) and were adjusted for selected patient and tumour characteristics.

Results: There were102 deaths, of which 49 were from BC. After 5 years, the overall survival was 70% in women with BI-RADS 1, 85% in those with BI-RADS 2, about 95% in those with BI-RADS 3-4 ($p < 0.01$). As compared to women with low BD (BI-RADS 1), the adjusted HRs of death was 0.71 (95% confidence interval (CI) 0.44–1.14) for BI-RADS 2 and 0.38 (95% CI 0.18–0.80) for BI-RADS 3-4 (p for trend = 0.010). As compared to BI-RADS 1, the adjusted HRs of BC-related death decreased with increasing BI-RADS BD from 0.90 (95% CI 0.43–1.87) for BI-RADS 2 to 0.32 (95% CI 0.12–0.91) for BI-RADS 3-4 (p for trend = 0.047).

Conclusion: In women with BC, low BD has a negative prognostic impact.

Introduction

Mammographic breast density (BD) reflects breast tissue composition as projected on a two-dimensional mammographic image. BD 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 BD on breast cancer (BC) risk has been widely assessed (with a 2- to 6-fold increase in risk between the highest and the lowest BD category [2,3]), the prognostic effect of BD on BC patients is still debated [4,5].

We therefore analysed the impact of BD 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 1332 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. Data on BD was available for 693 cases.

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 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.

BD 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. We re-categorized BD into BI-RADS 1, BI-RADS 2 and BI-RADS 3-4.

From pathology reports we extracted information on Estrogen (ER) and Progesterone (PR) receptors, HER2 and Ki67 status and classified it 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 retrieved also information on histologic grade, histotype and pathological Tumor-Node-Metastasis (pTNM) stage, categorised according to 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

The effect of BD was estimated 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 models included terms for BD (BI-RADS 1/ BI-RADS 2/BI-RADS 3-4), age at diagnosis ($\leq$50/51-64/$\geq$65), histotype (Ductal/Lobular/Others), grade (1/2/3), subtype (luminal A/luminal BH-/luminal BH+/HER2+/triple negative), pTNM stage (1/2/3), education (Low/High), BMI (<25/$\geq$25 kg/m^2), smoking (Never/Ever), parity (No/Yes), menopause (Pre/Post), family history of breast cancer (No/Yes), marital status (Unmarried/Married/Divorced), diabetes (No/Yes). Test for trend was performed by including BD as ordinal variable.

The overall survival (OS) was estimated using the Kaplan Meier method.

Results

Table 1 shows the main baseline characteristics of our dataset. Median age was 61. Out of 693 women, about 27% had BI-RADS 1 density, 44% BI-RADS 2 and 29% BI-RADS 3-4. As regards other tumour

characteristics, luminal A subtype was reported for 58% of patients, luminal BH- for 21%, luminal BH+ for 11%, HER2+ for 3% and triple negative for 7%. Over 64% had ductal histotype, 22% lobular and 14% others histotypes. About 44% had pTNM stage 1, 43% had pTNM 2 and 13% had pTNM 3. About 31% of women had grade 1, 49% had grade 2 and 20% grade 3. Considering other baseline characteristics, most women had low education, normal weight, had at least one child, were in post menopause, had no family history of BC, were married, not affected by diabetes, had never smoked. There were 102 deaths (15%) and 49 deaths from BC.

Figure 1 shows Kaplan-Meier OS in strata of BD (BI-RADS 1/BI-RADS 2/BI-RADS 3-4), with the numbers at risk and the numbers of cumulative events by year of follow-up. After 3 years, the OS was 85% in subjects with BI-RADS 1, 90% in those with BI-RADS 2, 95% in those with BI-RADS 3-4; after 5 years, the OS was 70% in subjects with BI-RADS 1, 85% in those with BI-RADS 2, 95% in those with BI-RADS 3-4 ($p < 0.01$).

Table 2 shows mortality HR by BI-RADS density, along with the corresponding 95% CI. Women with BI-RADS 2 and BI-RADS 3-4 had a better survival compared to those with BI-RADS 1. Compared to BI-RADS 1, the HRs of death were 0.71 (95% CI 0.44–1.14) for BI-RADS 2 and 0.38 (95% CI 0.18–0.80) for BI-RADS 3-4. Considering BC deaths, the HRs were 0.90 (95% CI 0.43-1.87) for BI-RADS 2 and 0.32 (95%CI 0.12-0.91) for BI-RADS 3-4, compared to BI-RADS 1. The HR for other causes of deaths was 0.43 (95% CI 0.20-0.93) for BI-RADS 2-3-4, compared to BI-RADS 1.

Discussion

This study showed that women with higher BD had a reduced risk of death from all causes and breast cancer.

The role of BD as prognostic factor has been addressed in several studies with, however, 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 tumour characteristics (site, age at and year of diagnosis, stage, BMI, mode of detection, treatment and income) [12]. Pre-diagnostic BD, 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 [13]. 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 [14]. Moreover, a Swedish study observed that high BD, assessed according to Tabar's classification, was suggestively, but not significantly, associated with poorer long-term survival after adjustments for age, tumour size, node status, grade, and BMI (HR 1.75 95% CI 0.99-3.10) [15]. 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 BD (HR 0.91, p= 0.124 dense [BI-RADS 3-4] versus fatty [BI-RADS 1-2] adjusted for age, ethnicity, and tumour stage) [16].

Partially in contrast with our results, an analysis including 619 BC cases selected from a prospective cohort (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) [17]. Moreover, including only women diagnosed with metastatic BC, a Saudi Arabian study observed that moderate/high BD 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) [18].

The association that we observed between lower BD and poorer outcome is consistent with several studies. In a Finnish analysis assessed on 270 patients aged 32 to 86 with newly diagnosed BC, very low BD at the time of diagnosis (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) [19]. In a Korean study on 969 patients with primary operable invasive BC, the high density group (BI-RADS 3-4) demonstrated a superior 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) [20]. 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) [21]. A case-only study including 2233 women diagnosed with invasive breast aged from 38 to 97 showed, after adjustment for age and mode of detection, an association of borderline statistical significance between high BD 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%) [22].

Evidence that women with lower BD are at increased risk of BC-related death, irrespective of several well-known risk factors, supports the growing evidence that tumour microenvironment is closely intertwined with the outcome of the disease. 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 tumours 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 [23,24].

Limitations of this study included BD assessment that relied on BI-RADS classification, a visual and subjective method; held by a single reader, 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 BD changes with age, we assessed BD at the time of diagnosis. We had no information on mode of detection (i.e., screening and interval cancers), treatment received and cancer recurrence. However, we assessed a comprehensive spectrum of BC related prognostic factors, including detailed tumour characteristics and several patient aspects (e.g., reproductive, sociodemographic, anthropometric, lifestyle factors). Prior studies showed remarkable differences in populations and methodologies, in BD 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, low BD appears to affect survival in women with invasive BC, even after adjusting for several known prognostic factors. Readily available data on BD at diagnosis may provide useful prognostic information.

Abbreviations

Mammographic breast density (BD), Breast Imaging Reporting and Data System (BI-RADS), breast cancer (BC), Piedmont Cancer Registry (Registro Tumori Piemonte – RTP), International Classification of Disease for Oncology 3rd edition (ICD-O-3), AOU (Azienda Ospedaliera Universitaria), Body mass index (BMI), estrogen receptor (ER), progesterone receptor (PR), pathological Tumor-Node-Metastasis (pTNM), hazard ratio (HR), confidence interval (CI), overall survival (OS),

Declarations

Funding: None

Conflict of interest statement: The authors declare that they have no potential conflict of interest.

Availability of data and material: The data that support the findings of this study are available from Piedmont Cancer Registry (Registro Tumori Piemonte – RTP) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of RTP.

Authors' contributions:

Margherita Pizzato: study concepts and design, data acquisition, data analysis and interpretation, manuscript writing, editing and review.

Greta Carioli: data analysis and interpretation, manuscript preparation, editing and review.

Stefano Rosso: study design, data acquisition, manuscript writing and review.

Roberto Zanetti: study design, manuscript writing and review

Carlo La Vecchia: study concepts and design, results interpretation, manuscript writing and review.

Ethics approval and consent to participate: The investigation did not involve any human contact, but only record linkage analysis of administrative healthcare databases

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. doi: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. doi:10.1016/S1470-2045(05)70390-9
3. McCormack VA, dos Santos Silva I (2006) Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 15 (6):1159-1169. doi: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. doi: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. doi: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. doi: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. doi: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. doi: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. doi: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. CA Cancer J Clin 67 (4):290-303. doi:10.3322/caac.21393
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. doi:10.1093/jnci/djs327
13. 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. doi:10.1186/bcr3378
14. 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. doi:10.2214/AJR.05.1950
15. 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. doi:10.1158/1055-9965.EPI-09-1028
16. 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. doi:10.1007/s10549-012-2310-3
17. 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. doi:10.1186/1471-2407-14-229
18. Elsamany S, Alzahrani A, Elkhalik SA, Elemam O, Rawah E, Farooq MU, M HA, F KO (2014) Prognostic value of mammographic breast density in patients with metastatic breast cancer. Med Oncol 31 (8):96. doi:10.1007/s12032-014-0096-3
19. 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. doi:10.1007/s00330-015-3626-2
20. 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. doi:10.1038/s41598-018-34297-8

21. 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. doi:10.1038/sj.bjc.6604989
22. van der Waal D, Verbeek ALM, Broeders MJM (2018) Breast density and breast cancer-specific survival by detection mode. BMC Cancer 18 (1):386. doi:10.1186/s12885-018-4316-7
23. 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. doi:10.1007/s10549-015-3567-0
24. 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. doi:10.1007/s10549-019-05491-7

Tables

Tables 1 and 2 are available in the Supplementary Files.

Figures

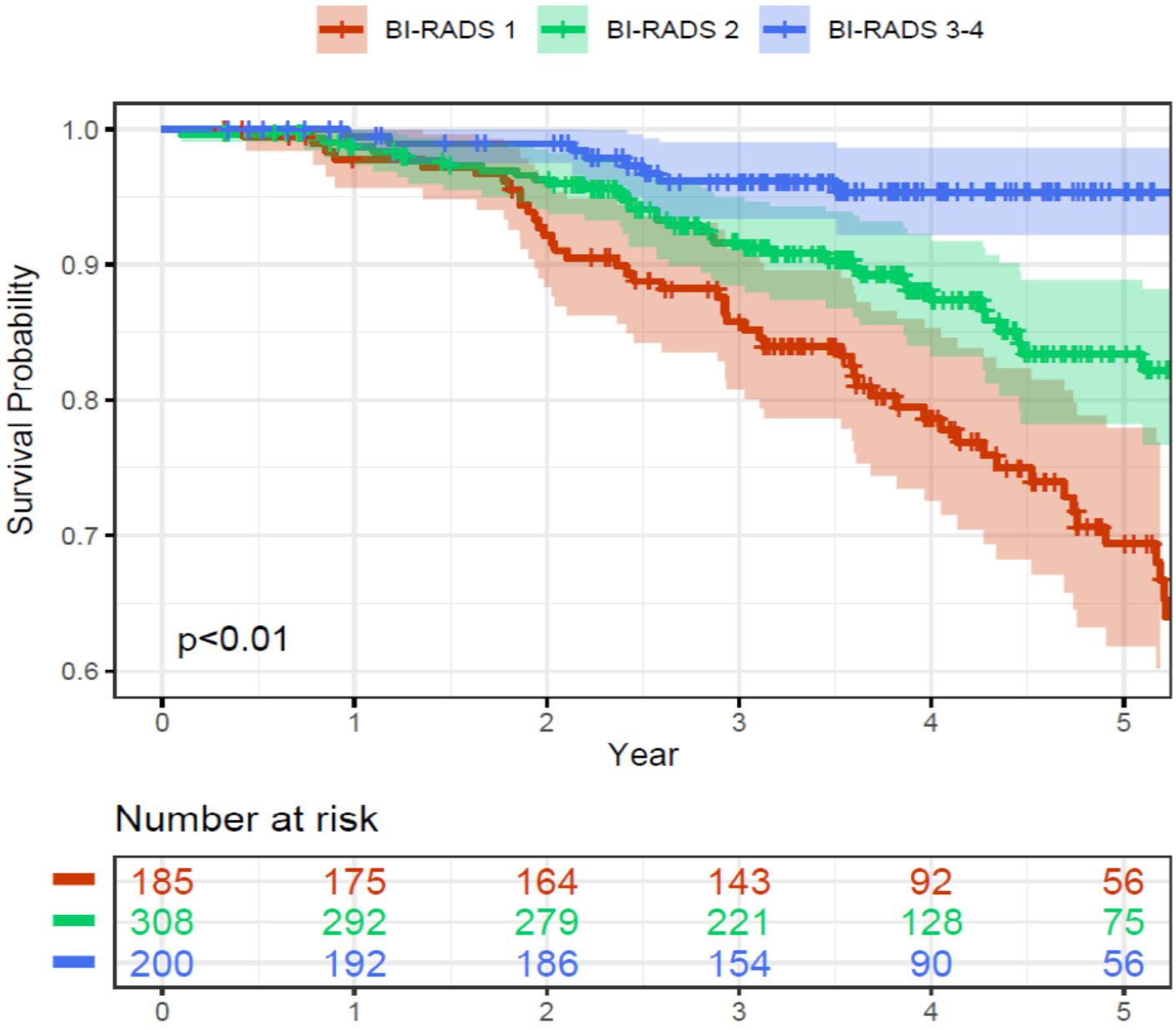

Figure 1

Kaplan-Meier estimates of survival stratified by BI-RADS (Breast Imaging- Reporting and Data System) breast density among 693 women with invasive breast cancer.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1ok.pdf
- Table2ok.pdf