The Breast 59 (2021) 51–57

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Mammographic density and prognosis in primary breast cancer patients

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ARTICLE INFO

Article history:
Received 16 March 2021
Received in revised form
11 June 2021
Accepted 12 June 2021
Available online 17 June 2021

Keywords:
Mammographic density
Mammographic breast density
Breast cancer
Breast cancer risk
Prognosis

ABSTRACT

Purpose: Mammographic density (MD) is one of the strongest risk factors for breast cancer (BC). However, the influence of MD on the BC prognosis is unclear. The objective of this study was therefore to investigate whether percentage MD (PMD) is associated with a difference in disease-free or overall survival in primary BC patients.

Methods: A total of 2525 patients with primary, metastasis-free BC were followed up retrospectively for this analysis. For all patients, PMD was evaluated by two readers using a semi-automated method. The association between PMD and prognosis was evaluated using Cox regression models with disease-free survival (DFS) and overall survival (OS) as the outcome, and the following adjustments: age at diagnosis, year of diagnosis, body mass index, tumor stage, grading, lymph node status, hormone receptor and HER2 status.

Results: After median observation periods of 9.5 and 10.0 years, no influence of PMD on DFS ($p = 0.46$, likelihood ratio test (LRT)) or OS ($p = 0.22$, LRT), respectively, was found. In the initial unadjusted analysis higher PMD was associated with longer DFS and OS. The effect of PMD on DFS and OS disappeared after adjustment for age and was caused by the underlying age effect.

Conclusions: Although MD is one of the strongest independent risk factors for BC, in our collective PMD is not associated with disease-free and overall survival in patients with BC.

1. Introduction

One of the major challenges in the treatment of breast cancer (BC) is to identify patients who are likely to have a poor prognosis. Well-known prognostic factors include tumor size, axillary lymph node status, grading, HER2 status, hormone receptor status, and Ki-67 [1–3]. MD is also one of the principal risk factors for BC [2,4].

The radiographic appearance of breasts varies due to differences in the tissue composition of epithelium, stroma, and fat. On mammograms, dense areas appear light, while nondense areas appear dark. Fat appears translucent, while epithelium and stroma attenuate x-rays, accounting for radiographically dense-looking regions. These dense areas are referred to as mammographic density (MD) [5,6].

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https://doi.org/10.1016/j.breast.2021.06.004

Abbreviations

ACR	American College of Radiology
BC	Breast cancer
BMI	Body mass index
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
ER	Estrogen receptor
HR	Hazard ratio
IQR	Interquartile range
LNS	Lymph node status
LRT	Likelihood ratio test
MD	Mammographic density
OS	Overall survival
PMD	Percent mammographic density
PR	Progesterone receptor

There are various established methods for radiological assessment of MD, including subjective methods such as Wolfe's grades, including four patterns [7]; Boyd's classification, containing six categories [8]; and subjective assessment of the percentage density [9]. In efforts to obtain a more objective method of assessing mammographic density, the proportion of dense breast tissue area relative to the area of the whole breast has been defined as percent mammographic density (PMD). Various computer-aided systems, such as Cumulus and Madena, have been developed to assess PMD [10–12].

Women with a high PMD (>75%) compared to women with a low PMD (<5%) have an up to fivefold increase in the risk of BC [4,13–15]. Although the impact of MD on the risk of BC is well known, its influence on the prognosis is still controversial. Some studies have reported that MD affects the prognosis of BC patients [16,17], and MD has been found to correlate with tumor proliferation in several subgroups [18,19]. However other studies did not show a correlation between MD and Prognosis [20–23] and further no association was found between MD and lymph node metastases [24].

Several studies have investigated the impact of tissue compositions on BC. Fibroblasts in breast stroma provide an environment that modifies tumor cell growth [25,26], cancer progression, and metastasis [27,28]. In addition, the mesenchymal stem cell environment derived from adipose tissue was found to reduce tumor cell viability and migration in another study [29].

Since the composition of fat, epithelium, and stroma differs in breasts with various PMD values, it may be hypothesized that PMD has an effect on tumor progression and prognosis of BC patients. The aim of the present study was therefore to assess the impact of percent mammographic density on the prognosis in primary BC patients.

2. Methods

2.1. Patients

The patients included in the study were selected from the BC database of the University Breast Center for Franconia, Germany. A total of 14,041 patients with BC are recorded in the database for the period 1967–2018. In this study, patients were excluded from the final analysis in the following hierarchical order: missing values for the variable of interest (PMD), 10,350 cases; male sex, nine cases; distant metastasis at initial diagnosis, 182 cases; survival time less than 1 day, 17 cases; second BC in the same woman, 240 cases; and missing values for HER2 status, 718 cases. This resulted in 2525 patients with unilateral invasive BC being included in the final study population (Fig. 1). This study was approved by the ethics committee of the Faculty of Medicine at Friedrich Alexander University of Erlangen-Nuremberg.

2.2. Data collection and follow-up

All of the characteristics of the BC patients and tumors had to be fully documented in the institution as part of the process required for official certification as a BC center in Germany. The data include histopathological information such as tumor stage, lymph node status, grading, estrogen receptor (ER) and progesterone receptor (PR) status, HER2 status, and follow-up data for overall survival and disease-free survival (DFS). This information has to be collected prospectively from the original pathology reports and is audited annually by the German Cancer Society (*Deutsche Krebsgesellschaft*) and the German Society for Breast Diseases (*Deutsche Gesellschaft für Senologie*) as part of a continuous quality-assurance process [30,31]. The patients' body mass index (BMI) was calculated at the time of initial diagnosis for treatment purposes (i.e., surgery or chemotherapy).

2.3. Assessment of percent mammographic density

Mammograms were eligible for this analysis, when they were taken one year prior or three months after BC diagnosis. PMD was assessed on the contralateral side (i.e., the breast not affected by BC and therefore an influence of tumor burden on PMD was minimized) in cranio-caudal (CC) images. Only in these cases where no image of the contralateral side was available the CC image of the BC affected side was analyzed.

Two separate readers with special training in the method carried out the breast area measurements and quantitative computer-based threshold density assessments. In this study full field digital mammograms and film based mammograms were analyzed. The mammographic films were digitized using a CadPro Advantage® film digitizer (VIDAR Systems Corporation, Herndon, Virginia, USA). The readers analyzed each mammogram independently in an arbitrary order. The mean PMD from the two readers was used for this analysis. The MD proportion was assessed using the Madena software program, version 3.26 (Eye Physics, LLC, Los Alamitos, California, USA). The evaluation method has been described and validated elsewhere [11,32].

2.4. Statistical analysis

Disease-free survival (DFS) was defined as the time from the date of primary diagnosis to the earliest date of disease progression (distant metastasis, local recurrence, death from any cause) or the date of censoring. Patients who were lost to follow-up before the maximum observation period of 10 years or were disease-free after the maximum observation time were censored at the last date on which they were known to be disease-free, or at the maximum observation time. Overall survival (OS) was defined as the time from primary diagnosis to death from any cause. The primary objective was to study whether percent mammographic density (PMD) was associated with DFS in BC patients, taking well-known predictors of DFS into account. For this purpose, Cox regression analyses were performed as described below.

A Cox regression model (the basic model) was fitted with DFS as the outcome and the following predictors: Age at diagnosis (dichotomous, < 55 and ≥ 55 years), year of diagnosis (dichotomous, < 2006 and ≥ 2006), body mass index (BMI; categorical, $<$ 25, 25–30, and ≥ 30 kg/m^2), tumor stage (ordinal, pT1 to pT4),

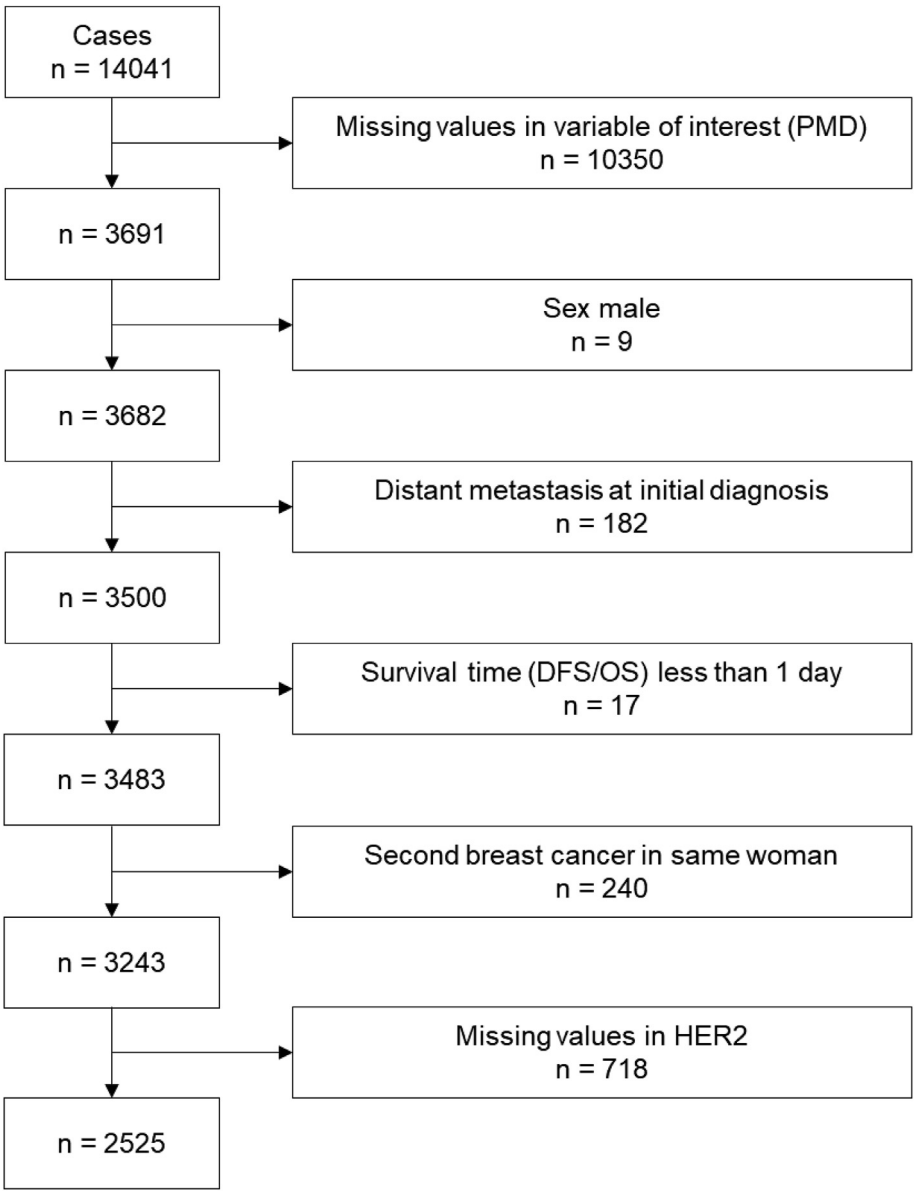

Fig. 1. Flowchart of patient selection.

grading (dichotomous, grade 1 and 2 versus grade 3), lymph node status (LNS; dichotomous, pN0 and pN+), estrogen receptor status (ER, positive and negative), progesterone receptor status (PR, positive and negative), and HER2 status (positive and negative). The proportional hazards assumption was checked using the Grambsch and Therneau method [33]. Missing predictor values were imputed as described in Salmen et al. [34]. Patients with missing information on PMD or HER2 status were excluded from the analysis. Patients with missing HER2 information were excluded due to a large proportion of missing values (n = 718). Patients (n = 17) with non-positive survival times were also excluded (Fig. 1).

Next, an extended Cox model (the full interaction model) was fitted, containing the predictors from the basic model, PMD, and the interactions of PMD with all predictor variables with the exception of the year of diagnosis, which was included in the models to address the introduction of trastuzumab in 2005. PMD was used as a natural cubic spline function with two degrees of freedom to describe nonlinear effects [35]. The basic and full interaction models were compared using the likelihood ratio test (LRT). A significant test result indicates that PMD influences DFS in addition to the well-known predictors, either across all patients or at least within one of the subgroups defined by the interaction terms considered. In case of a non-significant result, no further subgroup-specific analyses were conducted, in order to avoid false-positive results. Instead, a reduced Cox model (the reduced model) containing the basic predictors and PMD, but not the interaction terms, was fitted in order to obtain hazard ratios (HRs) for PMD and survival rates relative to PMD values. However, if the p value was significant, subgroup-specific HRs and survival rates were estimated using the interaction model.

A similar analysis was performed for the secondary outcome, OS. Unadjusted DFS and OS rates for patients grouped by PMD categories were estimated using the Kaplan–Meier product limit method.

All of the tests were two-sided, and $p < 0.05$ was regarded as statistically significant. Calculations were carried out using the R

system for statistical computing (version 3.4.0; R Development Core Team, Vienna, Austria, 2017).

3. Results

3.1. Patient characteristics

PMD data were available for 2525 patients, with a median value of 0.35 (Table 1, Fig. 2). The patients' mean age at diagnosis was 59.0 years and their median BMI was 25.4 kg/m^2. The postoperative lymph node status was negative in 1653 patients (65.5%) and most of the tumors were pT1 tumors (1455 patients, 57.6%) and had a grading of 1 or 2 (1967 patients, 77.9%). ER positivity, PR positivity, and HER2 positivity were found in 2035 (80.6%), 1844 (73.0%), and 399 (15.8%) patients, respectively. The baseline characteristics of the study population are presented in Table 1.

3.2. Disease-free survival

The median observation time was 9.5 years. In this time 716 events occurred. It was not found that PMD influenced DFS (LRT, $p = 0.46$). Adjusted hazard ratios and 5-year and 10-year disease-free survival rates from the reduced model relative to PMD are shown in Table 2. Kaplan-Meier curves from the unadjusted Cox model for three PMD categories are presented in Fig. 3. In the initial analysis using the unadjusted Cox model, higher PMD was associated with better prognosis. The apparent effect of PMD on DFS was induced by the underlying age effect and disappeared after adjustment for age.

3.3. Overall survival

The median observation time was 10.0 years, during which 554 deaths of any cause occurred. It was not found that PMD influenced OS (LRT, $p = 0.22$). Hazard ratios for PMD and the 5-year and 10-year overall survival rates relative to PMD from the reduced model are shown in Table 2. The survival rates from the unadjusted Cox model are presented in Fig. 4 for three PMD categories. In the unadjusted model higher PMD seemed to be associated with better OS. Again, the apparent effect of PMD on OS was induced by the underlying age effect.

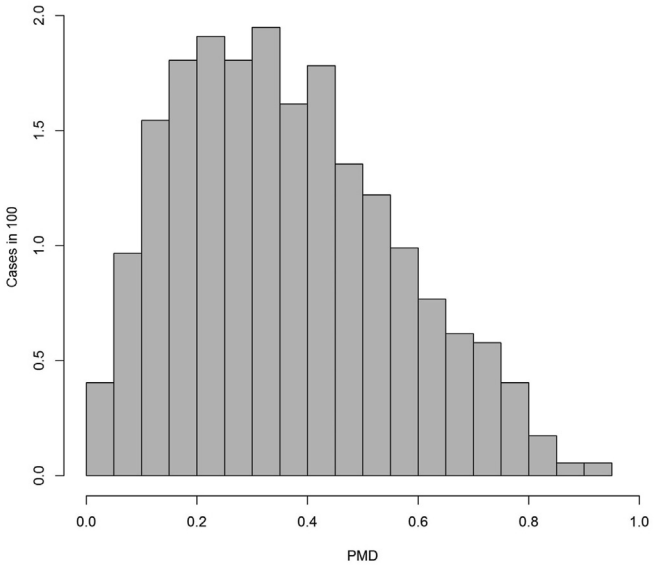

Fig. 2. Distribution of percent mammographic density (PMD).

4. Discussion

Since the beginning of the systematic use of mammography for screening and diagnosis of BC there were efforts to use mammographic patterns such as MD for risk stratification of the individual BC patient. This study of 2525 patients investigated the influence of

Table 1
Baseline characteristics of the study population (n = 2525), overall and by percentage mammographic density (PMD) categories (first quartile, second and third quartile, forth quartile).

	All patients (n = 2525)	PMD < 0.21 (n = 596)	0.21 ≤ PMD < 0.50 (n = 1285)	PMD ≥ 0.50 (n = 644)
Age (y) at diagnosis (mean, SD)	59.0 (12.6)	65.4 (10.4)	60.2 (11.6)	50.6 (12.0)
Year of diagnosis				
1968–2005	1651 (65.4)	395 (66.3)	830 (64.6)	426 (66.1)
2006–2016	874 (34.6)	201 (33.7)	455 (35.4)	218 (33.9)
BMI (median, IQR)	25.4 (22.9, 28.8)	28.4 (25.5, 32)	25.4 (23.2, 28.6)	22.8 (20.6, 25.3)
Lymph node status				
pN0	1653 (65.5)	394 (66.1)	840 (65.4)	419 (65.1)
pN+	872 (34.5)	202 (33.9)	445 (34.6)	225 (34.9)
Tumor stage				
pT1	1455 (57.6)	338 (56.7)	741 (57.7)	376 (58.4)
pT2	870 (34.5)	210 (35.2)	445 (34.6)	215 (33.4)
pT3	115 (4.6)	24 (4.0)	54 (4.2)	37 (5.7)
pT4	85 (3.4)	24 (4.0)	45 (3.5)	16 (2.5)
Grading				
1 + 2	1967 (77.9)	458 (76.8)	1014 (78.9)	495 (76.9)
3	558 (22.1)	138 (23.2)	271 (21.1)	149 (23.1)
ER				
Negative	490 (19.4)	101 (16.9)	248 (19.3)	141 (21.9)
Positive	2035 (80.6)	495 (83.1)	1037 (80.7)	503 (78.1)
PR				
Negative	681 (27.0)	153 (25.7)	354 (27.5)	174 (27.0)
Positive	1844 (73.0)	443 (74.3)	931 (72.5)	470 (73.0)
HER2				
Negative	2126 (84.2)	509 (85.4)	1076 (83.7)	541 (84.0)
Positive	399 (15.8)	87 (14.6)	209 (16.3)	103 (16.0)

Values are frequencies (percent) for categorical variables and mean (SD) or median (IQR) where appropriate for continuous variables.
BMI, body mass index; ER, estrogen receptor; IQR, interquartile range; PMD, percent mammographic density; PR, progesterone receptor; SD, standard deviation.

Table 2
Main survival analysis, showing adjusted hazard ratios and survival rates relative to percent mammographic density (PMD), with the corresponding 95% confidence intervals (in brackets) resulting from the reduced model.

Outcome	PMD[a]	Hazard ratio[b] (95% CI)	5-year survival rate[c] (95% CI)	10-year survival rate[c] (95% CI)
DFS	Low (13%)	1 (reference)	0.87 (0.85,0.90)	0.76 (0.71,0.81)
	Intermediate (35%)	0.90 (0.59,1.21)	0.89 (0.86,0.91)	0.78 (0.75,0.82)
	High (65%)	0.84 (0.51,1.17)	0.89 (0.87,0.92)	0.79 (0.75,0.83)
OS	Low (13%)	1 (reference)	0.91 (0.89,0.93)	0.81 (0.77,0.85)
	Intermediate (35%)	0.89 (0.54,1.23)	0.92 (0.90,0.94)	0.83 (0.80,0.86)
	High (65%)	0.80 (0.43,1.17)	0.93 (0.91,0.95)	0.84 (0.81,0.88)

CI, confidence interval; DFS, disease-free survival; OS, overall survival.

[a] PMD was regarded as a continuous predictor and used as a natural spline with two degrees of freedom. It was evaluated at the 10th percentile ("low"), median ("intermediate"), and 90th percentile ("high"). The percentiles were chosen arbitrarily for the purpose of describing results. The underlying statistical model is not affected of that choice.

[b] Hazard ratios and survival rates were estimated using the reduced Cox regression model, with the following predictors: age at diagnosis (<55 and ≥ 55 years), year of diagnosis (before and after 2006), body mass index (<25, 25–30, and ≥30 kg/m^2), tumor stage (pT1 to pT4), grading (grade 1 and 2 versus grade 3), lymph node status (pN0 and pN+), estrogen receptor status (ER, positive and negative), progesterone receptor status (PR, positive and negative) and HER2 status (positive and negative).

[c] Survival rates were estimated for an "average" patient — i.e., a patient belonging to the most frequent categories (age ≥ 55 years, year of diagnosis before 2006, BMI < 25 kg/m^2, pT1, grading 1 or 2, pN0, ER-positive, PR-positive, HER2-negative).

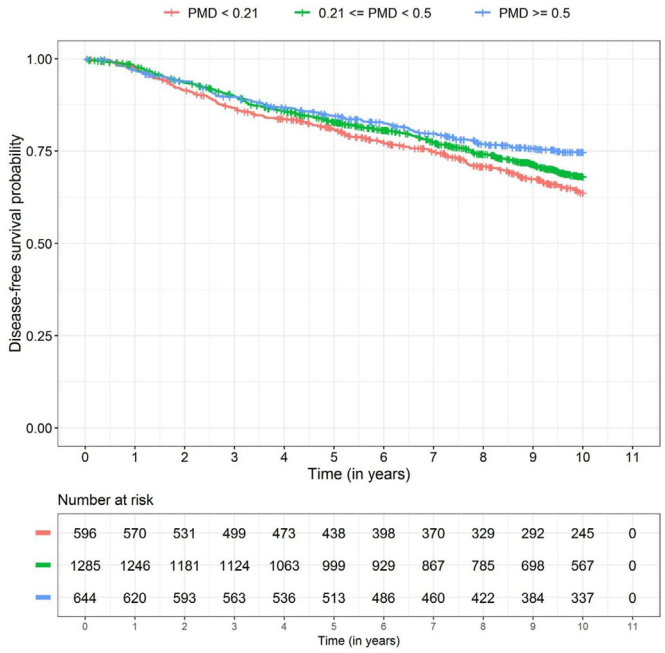

Fig. 3. Kaplan-Meier curves for disease-free survival in patients with low (<0.21, 25th percentile), intermediate (0.21–0.50, interquartile range) and high (≥0.50, 75th percentile) percent mammographic density (PMD).

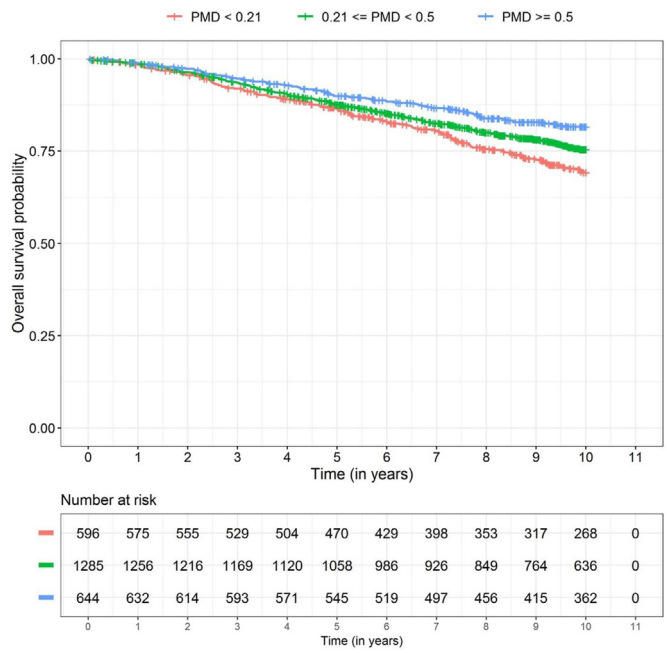

Fig. 4. Kaplan-Meier curves for overall survival in patients with low (<0.21, 25th percentile), intermediate (0.21–0.50, interquartile range) and high (≥0.50, 75th percentile) percent mammographic density (PMD).

MD on BC prognosis in a German population. After a median observation period of 9.5 years, no differences in disease-free survival were observed in relation to PMD. Nor were any differences seen with regard to overall survival (OS) for various PMD values after a median observation period of 10.0 years. Survival rates from the unadjusted Cox model suggested an effect of different PMD values on OS. However, the effect of PMD on OS disappeared after adjustment for age.

Earlier results published by our research group showed a negative association between MD and ER expression and a statistical trend toward a positive relation between MD and PR expression [19,36]. Since Estrogen receptor (ER) and Progesterone receptor (PR) expression is associated with BC prognosis one of the assumptions in this study was therefore an effect of the combination of MD and hormone receptor status on the prognosis.

In addition to the above results, PMD showed no significant effect in subgroups (i.e. HER2 groups). An impact of hormone receptor status in subgroups with different PMD values on DFS or OS is thus quite unlikely.

Several studies reported on this topic, however their findings are not consistent. There is an ongoing debate whether MD influences BC prognosis in different clinical settings, e.g. screening or incident BC population.

Previous cohort studies have examined the effect of MD on prognosis in patients with BC. In line with the presented results, these studies found no influence of MD on the prognosis of BC [21,37]. In a large study, analyzing a screening population a significant correlation between MD and survival was not observed, but showed an increased mortality in patients with high MD. One of the weaknesses of this study is the rather small number of 873 BC cases [37]. It remains unclear whether the observed non-significant impact on mortality is a direct effect of MD or just an effect confounded by a higher BC incidence in dense breasts.

Mammographic screening is limited to patients in predefined

age groups. A smaller study using the subjective BI-RADS® classification of MD did not find a significant difference in relation to BC-specific survival. In this age-restricted approach (50–64 years) with median follow-up of 9.0 years, grade 3 tumors were more frequent than in our study. However, even in this screening scenario with younger patients and a more aggressive tumor biology no impact on survival was observed [21]. In contrast, the presented study included women without age restriction in a case only population. Therefore representing a more comprehensive patient collective and minimization of bias based on selective patient exclusion was achieved.

Values for MD can be acquired in a qualitative or a quantitative fashion. Subjective MD measurement using the BI-RADS® classification from two case only studies [20,22] did not report any association between high MD values and risk of death from BC. In order to minimize the risk of bias we performed MD assessment with an objective computer-based threshold method. While the BI-RADS® classification is used during routine diagnosis and treatment of BC, there are several pitfalls for the use in research. Especially for the intermediate density categories, MD classification is not always consistent between different observers [38]. Because these intermediate dense categories are most common, an accurate differentiation between these categories is essential. By using a semi-automated MD assessment method one can avoid this pitfall and obtain reproducible intra- and interobserver results.

The rather short follow-up period of 6.6 years [22] and 30 months [20] of the last two mentioned studies contains the risk to underestimate existing effects. Nevertheless, longer follow-up times in our and other studies of ten, nine [21] and up to 25 years [37] respectively, also could not find a significant effect of MD on prognosis.

Concerning the effect of age adjustment and other confounders (e.g. BMI, tumor stage) on the impact of MD on BC prognosis, not all studies are consistent with our findings. None of these studies reported a significant impact of MD on prognosis, regardless of adjustment of age [22,37]. While in another study no adjustment for age was performed [21]. In our collective we observed a correlation between MD and prognosis in the unadjusted Cox model. This effect vanished after adjustment for age, highlighting age as a strong confounder in BC prognosis. None of the studies mentioned above presented adjusted and unadjusted data.

By contrast, other studies have observed an effect of MD on the risk of recurrence or prognosis [17,39]. Patients with high MD especially had an unfavorable prognosis if adjuvant radiotherapy was omitted. Interestingly, patients with high MD values had a better prognosis after radiotherapy [17]. The underlying effect is unclear. Since the data for adjuvant radiotherapy is not included in our analysis a direct comparison between these two studies is somewhat difficult. Consistent with our results, in the overall model, no association between mammographic density and breast cancer-specific survival was observed (HR = 0.95 per 10%; 95% CI: 0.79–1.15) [17].

There are several studies examining the influence of MD on BC recurrence and disease progression depending on type of surgery, recurrence site and tumor biology [23,40–42]. For patients after breast surgery with high MD values a high risk of locoregional recurrence, but no influence on distant recurrence or survival was observed [23,40]. Similar results in BC patients treated with radical mastectomy were reported [40]. With regard to tumor biology patients with primary unilateral ductal carcinoma in situ (DCIS) and high MD were found to be at increased risk for invasive BC or DCIS in the ipsilateral or contralateral breast [41]. BC patients omitting adjuvant radiotherapy with high MD have an increased risk for recurrence after breast conserving surgery [42]. With regard to our work we did not analyze, whether adjuvant radiotherapy has an impact on prognosis. In this presented study both types of breast surgery (breast conserving surgery and mastectomy) were included for invasive BC cases only, therefore we do not report DCIS cases. Because of missing data for adjuvant radiotherapy and exclusion of DCIS cases we did not analyze these subgroups. This should be addressed in further studies.

One additional limitation of our study is the retrospective study design with the potential of missing data. The highest level of study design to answer questions about prognostic factors would be a prospective cohort study with collection of more data overcoming the disadvantage of retrospective studies with potentially incomplete data. Furthermore, it is possible that we did not find an effect although an effect existed. The reasons for this could be variability in MD measurement and lack of information on systematic status at diagnosis.

As with all large studies, without initial exclusion criteria and a long patient recruitment over more than four decades several cases had to be excluded due to missing values in the variable of interest (i.e. PMD). The exclusion of cases occurred in a random manner, minimizing the risk of bias on our results. In comparison to other studies listed above our study includes the second largest number of BC cases.

The presented data is not obtained from a screening facility. It originates from a tertiary referral center in a university hospital. Screening mammography generally detects earlier tumor stages than diagnostic mammography. We did not differentiate between screening or diagnostic mammography. Nonetheless, as shown in the patient and tumor characteristics we represent the whole range of BC patients.

In brief, the advantage of this study is the use of an objective MD assessment method in contrast to most of the other above-mentioned studies. The case only study design with the absence of specific inclusion criteria (e.g. age-restriction, type of surgery or adjuvant radiotherapy), the large study population of 2525 BC cases, and the lengthy follow-up of the BC patients for 9.5 and 10.0 years for PFS and OS, respectively, separates this study from others.

5. Conclusion

In conclusion, this study investigated the association between mammographic density and disease-free and overall survival in 2525 BC patients. We could not find a direct influence of PMD on DFS or OS. Therefore, a risk stratification in clinical routine based on PMD assessment seems not feasible.

Ethical approval

This study was approved by the ethics committee of the Faculty of Medicine at Friedrich Alexander University of Erlangen-Nuremberg. All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Written informed consent was obtained from each participant included in this study.

Declaration of competing interest

Peter A. Fasching reports research grants from Novartis and BioNTech and personal fees from Novartis, Roche, Pfizer, Celgene, Daiichi-Sankyo, TEVA, AstraZeneca, Puma, Eisai, Merck Sharp & Dohme, and Myelo Therapeutics. Carolin C. Hack reports personal

fees from Roche and Novartis. Julius Emons reports personal fees from Novartis, Pfizer and Eisai. Arndt Hartmann has received honoraria from BMS, MSD, Roche, AstraZeneca, Boehringer Ingelheim, Abbvie, Jansen-Cilag, Diaceutics, Cepheid, Lilly, Agilent, and Ipsen. Ramona Erber has received honoraria from Roche, Eisai, Pfizer, and Novartis and travel grants from BioNTech. The institution of Arndt Hartmann and Ramona Erber conducts research for AstraZeneca, Roche, Janssen-Cilag, NanoString Technologies, Novartis, Cepheid, and BioNTech.

All the other authors declare that they have no conflicts of interest.

Acknowledgments

Katharina Heusinger was funded by the ELAN Program at Erlangen University Hospital, Friedrich Alexander University of Erlangen–Nuremberg, Germany. We are grateful to Michael Robertson for professional medical editing services.

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