European Journal of Radiology 110 (2019) 81–87

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Research article

Mammographic breast density: How it affects performance indicators in screening programmes?

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ARTICLE INFO

Keywords:
Breast neoplasms
Early detection of cancer
Mammography
Breast density

ABSTRACT

Objectives: To investigate how breast density affects screening performance indicators in a digital mammography context.

Methods: We assessed the effect of breast density over the screen-detected and interval cancers rates, false-positives, specificity, sensitivity, recall rate, positive predictive value of recall (PPV-1), and PPV of invasive tests (PPV-2). Radiologists classified breast density using the BIRADS System. We used generalized estimating equations to account for within-woman correlation by means of the robust Huber-White variance estimator.

Results: We included 177,164 women aged 50–69 years who underwent 499,251 digital mammograms from 2004 to 2015 in Spain. According to the fibroglandular tissue percentage, 24.7% of mammograms were classified as BI-RADS 1 (< 25% glandular), 54.7% as BI-RADS 2 (25–50% glandular), 14.0% as BI-RADS 3 (51–75% glandular) and 6.6% as BI-RADS 4 (> 75% glandular). Overall, women with BI-RADS 3 had the highest screen-detected cancer rate (5.9 per 1000) and BI-RADS 4 the highest interval cancer rate (2.4 per 1000). Sensitivity decreased from 89.2% in women with BI-RADS 1 to 67.9% in BI-RADS 4. Both PPV-1 and PPV-2 decreased from 10.4% to 5.7% and from 49.8% to 32.4% in women with BI-RADS 1 and BI-RADS 4, respectively. Women aged 60–69 years with BI-RADS 4 had the lowest sensitivity (54.9%) and the highest interval cancer rate (3.8 per 1000).

Conclusions: Performance screening measures are negatively affected by breast density falling to a lower sensitivity and PPV, and higher interval cancer rate as breast density increases. Particularly women aged 60–69 years with > 75% glandular breasts had the worst results and therefore may be candidates for screening using other technologies.

1. Introduction

Radiologists determine breast density based on the amount of radiopaque breast parenchyma that is visualized on the mammogram. Radiopaque areas correspond to regions in the breast that are rich in epithelial and stromal tissue while the non-dense, darker grey areas, correspond to regions that are predominantly fat [1].

The assessment of breast density in mammography screening has become relevant because it can limit the screening accuracy [2,3]. Several authors have reported that small breast cancers are likely to be easily diagnosed in a breast containing substantial fatty tissue. Conversely, it would be difficult to detect if the lesions are superimposed on dense tissue [4,5]. The role of breast density as a contributor to interval cancers has also been reported [3,6]. Thus, evaluating breast density as

Abbreviations: BI-RADS, American College of Radiology Breast Imaging Reporting and Data System; DCIS, ductal carcinoma in situ; GEE, generalised estimating equations; PPV-1, positive predictive value of recall; PPV-2, positive predictive value of invasive tests

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https://doi.org/10.1016/j.ejrad.2018.11.012
Received 27 June 2018; Received in revised form 9 November 2018; Accepted 12 November 2018

an influence on accuracy of detection is essential in screening programs.

Compared to film-screen, digital mammography can mitigate the breast density masking effect and improve cancer detection, especially in women with extremely dense breasts [7]. However, challenges when reading digital mammograms of women with dense breasts still exists, and whether this impact on the performance measures in screening needs further assessment in the light of modern digital technology.

Breast cancer screening in Spain started using digital mammography early in the 2000 decade, and spread rapidly afterwards [8]. Evaluating performance measures across breast dense categories provides valuable information for mammographic screening that can be used to guide clinical practice and screening policies. Our purpose was to assess the effect of breast density on the screening performance measures in a population-based program that uses digital mammography.

2. Materials and methods

2.1. Setting and study population

The Spanish, government funded, Breast Cancer Screening Program started in 1990 and became nationwide in 2006. All women aged 50–69 years biennially receive an invitation letter to participate in the program. The standard procedure for radiological performance is two-view mammography and double reading with consensus arbitration in case of disagreement. Mammograms were read by highly experienced radiologists who interpreted at least 1500 screening mammograms per year. Certified screening radiologists routinely evaluate mammograms. The BI-RADS® scale or equivalent is used to rate the probability of cancer. Women with positive mammographic findings, scored as 3; probably benign finding, 4; suspicious abnormality, 5; highly suspicious of malignancy, or 0; incomplete, are recalled for further assessments to confirm or rule out malignancy at the reference hospital of their screening geographic area.

We assessed information of digital screening exams performed in three Centres of the Spanish Breast Cancer Screening Program from July 2004 to December 2015 (Vallès Occidental, Barcelona- Àrea Metropolitana Sud, and Cantabria). From a total of 522,741 screening exams, we excluded 23,490 due to lack of information with regards to mammographic density. Hence, we included 499,251 digital exams performed on 177,164 women.

We included both screen-detected and interval cancers. Screen-detected cancers were diagnosed at routine screening. An interval breast cancer was defined as a breast carcinoma diagnosed after a negative screening test, or after a positive screening test where malignancy is finally ruled out, either before the next biennial invitation to screening, or within two years for women who had reached the upper age limit for screening. Invasive as well as in situ carcinomas (DCIS) were pathologically confirmed. Data on screening mammogram results, additional diagnostic tests, and pathological confirmation was obtained from the Breast Screening Centers database whereas we identified interval cancers by merging data from population-based cancer registries and hospital records. Each Ethics Committee at the participating institutions approved the study and informed consent was waived since we used anonymised retrospective data.

2.2. Breast density measurement

Breast density was determined per each mammogram by one or two radiologists using the Fourth Edition of the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS®) [9] and therefore all mammograms were categorized according to the percentage value of fibroglandular breast tissue as 1) < 25% glandular; 2) 25–50% glandular; 3) 51–75% glandular; or 4) > 75% glandular.

2.3. Accuracy measures

We assessed the cancer detection rate (screen-detected and interval cancers), false-positive rate, specificity, sensitivity, recall rate (frequency and type of additional tests), positive predictive value of recall (PPV-1), and PPV of invasive tests (PPV-2) according to breast density classification.

Breast cancer detection rates were defined as the number of cases per 1000 screening exams. False-positives were cases recalled for additional tests without an ultimate diagnosis of cancer. Sensitivity was defined as the number of screen-detected cancers divided by the number of screen-detected cancers plus interval cancers. Specificity was defined as the number of true-negative screening exams divided by the number of true-negatives tests plus false positives. PPV-1 was defined as the number of screen detected breast cancers divided by the number of recalls due to positive mammographic findings regardless of the additional test invasiveness. PPV-2 was defined as the number of screen detected breast cancers divided by the number of recalled exams including only invasive procedures (fine needle aspiration biopsy, core needle biopsy, open biopsy). The number of women needed to be recalled and to undergo an invasive procedure to detect one breast cancer was estimated by taking the inverse of PPV-1 (1/PPV-1) and PPV-2 (1/PPV-2), respectively.

2.4. Statistical analysis

The screening mammogram was the unit of analyses. Because women could have multiple screens during the study period, we used generalized estimating equations (GEE) to account for within-woman correlation in the performance indicators by means of the robust Huber-White (sandwich) variance estimator [10].

Screening accuracy measures were evaluated separately for the four breast density categories. Estimates of sensitivity and specificity, cancer detection rates, false-positive rates, PPV-1, and PPV-2 were stratified by type of screening (first or subsequent), and age at screening (50–59 or 60–69 years of age). Proportions across breast density categories were compared using the z-test for column proportions. The 95% confidence intervals (95% CIs) were calculated based on the standard errors obtained from the GEE models. P-values < 0.05 were considered statistically significant.

3. Results

The study included 499,251 digital mammograms from 177,164 women who underwent screening at age 50 to 69 years between 2004 and 2015. Among the mammograms analyzed, and according to its breast density, 123,292 (24.7%) were classified as BI-RADS 1, 272,964 (54.7%) as BI-RADS 2, 70,066 (14.0%) as BI-RADS 3, and 32,929 (6.6%) as BI-RADS 4. In terms of age, 280,312 (56.1%) mammograms were performed to women aged 50–59 years and 218,939 (43.9%) to woman aged 60–69 years. When classifying by type of screen, 103,308 (20.6%) were first screening examinations and 396.213 (79.4%) were subsequent screens. Overall, 2047 cancers were screen-detected and 550 were interval cancers.

The screen-detected invasive cancer rate increased from 2.23 per 1000 screening exams in the BI-RADS 1 group to 2.69 in the BI-RADS 2 group and to 3.95 in the BI-RADS 3 group. However, this rate decreased in the BI-RADS 4 group with a rate of 2.28. The rate of screen-detected DCIS increased with increasing density, ranging from 0.58 in women with BI-RADS 1 to 2.76 in those with BI-RADS 4. Regarding interval cancers, the rate of all malignancies (invasive cancer and DCIS) also increased with increasing density, from 0.34 to 2.40 per 1000 screening exams in BI-RADS 1 and BI-RADS 4, respectively. The false positive rate increased with increasing breast density for both additional imaging and invasive procedures. The overall proportion was 2.44%, 5.46%, 7.58% and 8.46% in women with BI-RADS 1, 2, 3 and 4, respectively

Table 1
Number and rate of screen-detected, interval cancer and false-positive results in mammographic screening according to breast density.

	BI-RADS 1 (< 25% glandular) (n = 123,292)	BI-RADS 2 (25-50% glandular) (n = 272,694)	BI-RADS 3 (50-75% glandular) (n = 70,066)	BI-RADS 4 (> 75% glandular) (n = 32,929)	Total (n = 499,251)
Screen detected cancers					
All malignant lesions, n (per 1000)	348 (2.82) [a,b]	1,116 (4.09) [a]	416 (5.94) [a]	167 (5.07) [b]	2,047 (4.10)
Invasive, n (per 1000)	275 (2.23) [a,b]	733 (2.69) [a]	277 (3.95) [b]	75 (2.28) [a,b]	1,360 (2.72)
DCIS, n (per 1000)	71 (0.58) [a,b]	379 (1.39) [a]	139 (1.98) [b]	91 (2.76) [a,b]	680 (1.36)
Unknown, n (per 1000)	2 (0.02)	4 (0.01)	0 (0.00)	1 (0.03)	7 (0.01)
Interval cancers					
All malignant lesions, n (per 1000)	42 (0.34) [c,d]	290 (1.06) [c,d]	139 (1.98) c	79 (2.40) [d]	550 (1.10)
Invasive, n (per 1000)	31 (0.25) [c]	239 (0.88) [c,d]	111 (1.58) [c,d]	73 (2.22) [d]	454 (0.91)
DCIS, n (per 1000)	6 (0.05)	31 (0.11)	13 (0.19)	2 (0.06)	52 (0.10)
Unknown, n (per 1000)	5 (0.04)	17 (0.06)	9 (0.13)	3 (0.09)	34 (0.07)
False positives					
All, n (per 1000)	3,012 (2.44) [e]	14,899 (5.46) [e]	5,314 (7.58) [e]	2,785 (8.46) [e]	26,010 (5.21)
Additional imaging, n (per 1000)	2,661 (2.16) [e]	13,422 (4.92) [e]	4,807 (6.86) [e]	2,436 (7.40) [e]	23,326 (4.67)
Invasive procedures, n (per 1000)	351 (0.28) [e]	1477 (0.54) [e]	507 (0.72) [e]	349 (1.06) [e]	2,684 (0.54)

DCIS: Ductal carcinoma in situ.
[a,b,c,d,e] Those values of the same row that share a same superscript are significantly different at $p < 0.05$ in a two-sided test for column proportions (z-test). Tests are adjusted using the Bonferroni correction for multiple comparison.

(Table 1).

Sensitivity decreased while increasing breast density ranging between a sensitivity of 89.2% in women with BI-RADS 1 and 67.9% in those with BI-RADS 4. This decrease was statistically significant except when comparing BI-RADS groups 2 versus 3 and BI-RADS 3 versus 4. Specificity significantly decreased with increasing breast density ranging from 97.5% to 91.5% in women with BI-RADS 1 and BI-RADS 4, respectively. Similarly to sensitivity and specificity, both PPV-1 (positive predictive value for all recall tests) and PPV-2 (positive predictive value for invasive procedures) decreased with increasing breast density but showing differences between the extreme groups. PPV-1 significantly decreased from 10.4% in women with BI-RADS 1, to 5.7% in those with BI-RADS 4. The decrease translates to 9.7 recalls needed for further workup to detect one breast cancer in women with BI-RADS 1, and 17.7 in women with BI-RADS 4. Regarding invasive procedures, 2.0 biopsies were required to detect one cancer in women with BI-RADS 1 whereas 3.1 biopsies were needed in those with BI-RADS 4 (Table 2).

Sensitivity decreased with increasing breast density in both women aged 50–59 and 60–69 years. A significant lower sensitivity in women aged 60–69 years was found in the extremely dense group compared with women aged 50–59 years (54.9% vs 73.1%) (Fig. 1). The lower sensitivity is explained by the high interval cancer rate amongst women with BI-RADS 4 aged 60 to 69 years (4 per 1000). Without considering the BI-RADS 4 group, the screen-detected cancer rate increased with increasing density in women aged 50 to 59 years as well as in those aged 60 to 69 years. In the younger age group it ranged from 2.1 to 6.0 and in the older age group from 3.5 to 5.8 per 1000 screening exams in women with BI-RADS 1 and BI-RADS 3, respectively (Fig. 1).

The analyses stratified by type of screening confirmed the lowest sensitivity in women with BI-RADS 4 (75.7% at first screen and 62.9% in subsequent screen). Sensitivity was significantly higher in women with BI-RADS 3 at first screen compared with subsequent screen (83.7% and 70.8%, respectively). Women with BI-RADS 4 also showed higher screen-detected cancer rate at first screen compared with subsequent screen (7.1 and 4.2, respectively)). We did not find differences when comparing interval cancer rates by type of screening in the different density groups (Fig. 2).

4. Discussion

Our results showed that the high breast density has a negative effect on the screening performance measures in a population-based program that uses digital mammography. We found that both sensitivity and positive predictive value were remarkably lower in women with BI-RADS 4. Compared to women with BI-RADS 1, the group with BI-RADS 4 had over a three-fold increased rate of interval cancer and false positives. Notably, women aged 60–69 years with BI-RADS 4 had the lowest sensitivity, which implied that one out of two breast cancers in

Table 2
Sensitivity, specificity, positive predictive value of recalls (PPV-1) and invasive procedures (PPV-2) in mammographic screening according to breast density with the 95% confidence intervals.

	BI-RADS 1 (< 25% glandular) % (95% CI)	BI-RADS 2 (25-50% glandular) % (95% CI)	BI-RADS 3 (50-75% glandular) % (95% CI)	BI-RADS 4 (> 75% glandular) % (95% CI)	Total % (95% CI)
Sensitivity	89.2 (85.7-91.9)	79.4 (77.2-81.4)	75.0 (71.2-78.4)	67.9 (61.8-73.4)	78.8 (77.2-80.4)
Specificity	97.5 (97.5-97.6)	94.5 (94.4-94.6)	92.4 (92.2-92.6)	91.5 (91.2-91.8)	94.8 (94.7-94.8)
PPV-1	10.4 (9.4-11.4)	7.0 (6.6-7.4)	7.3 (6.6-8.0)	5.7 (4.9-6.6)	7.3 (7.0-7.6)
1/PPV-1	9.7 (8.7-10.7)	14.4 (13.6-15.2)	13.8 (12.6-15.1)	17.7 (15.3-20.5)	13.7 (13.1-14.3)
PPV-2	49.8 (46.1-53.5)	43.0 (41.1-45.0)	45.1 (41.9-48.3)	32.4 (28.5-36.5)	43.3 (41.9-44.7)
1/PPV-2	2.0 (1.9-2.2)	2.3 (2.2-2.4)	2.2 (2.1-2.4)	3.1 (2.7-3.5)	2.3 (2.2-2.4)

CI: Confidence Intervals, PPV-1: Positive predictive value of recall, PPV-2: Positive predictive value of invasive tests, 1/PPV-1: Inverse of the positive predictive value of recall, 1/PPV-2: Inverse of the positive predictive value of invasive test.

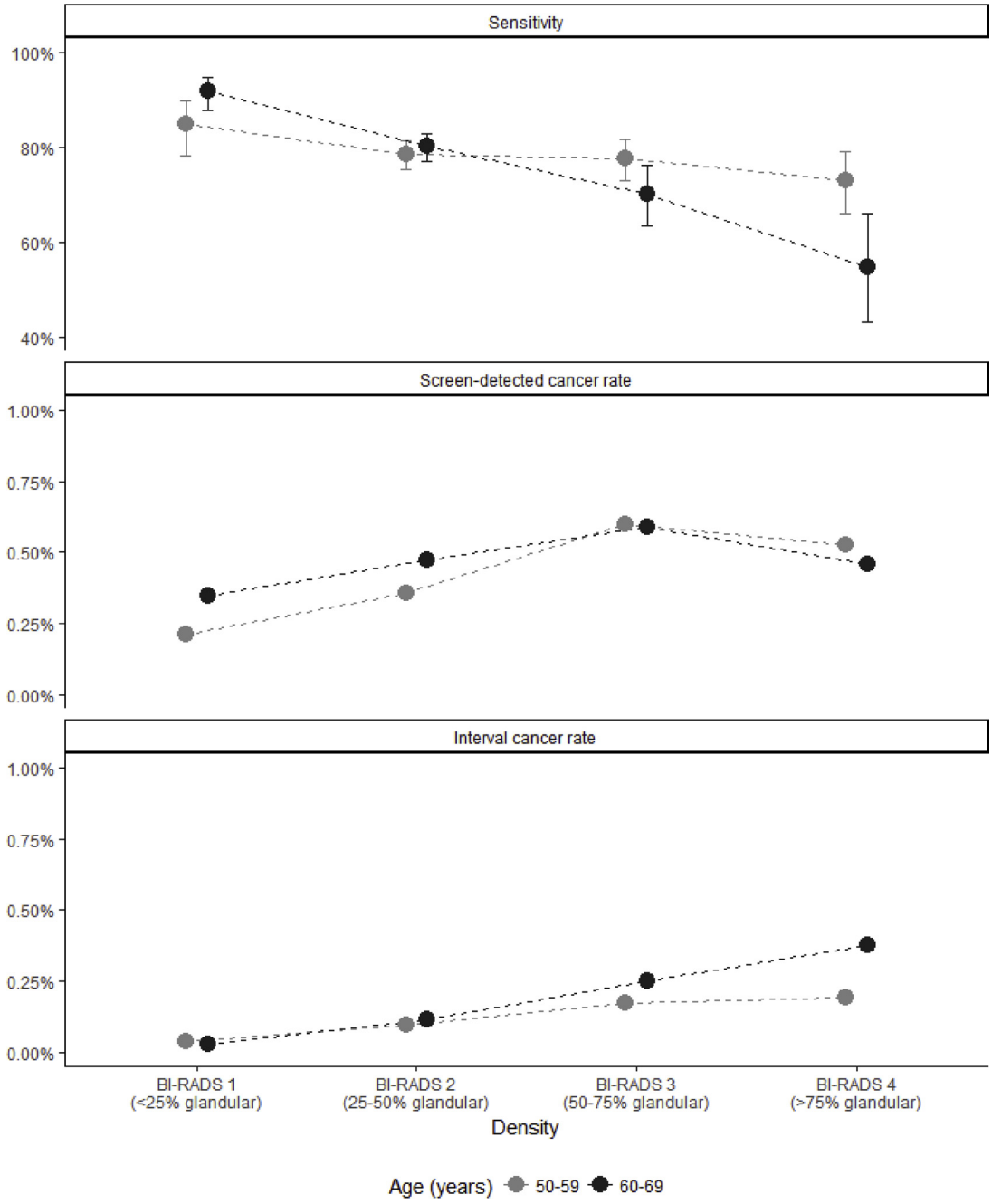

Fig. 1. Sensitivity, screen-detected cancer rate and interval cancer rate stratified by age group.

this group were diagnosed as an interval cancer.

Although sensitivity decreased with increasing breast density, the cancer detection rate shows an opposite trend. Two main factors can explain this finding. First, the masking effect of breast density reduces the likelihood of several tumours to be detected and therefore reduces the sensitivity. A plausible consequence is the higher interval cancer rate in women with dense breasts compared to fatty breasts, which is consistent with our results. Several studies have reported high interval cancer rates in women with BI-RADS 4, exceeding in some cases the amount of screen detected cancers [11,12]. Second, breast density acts as an independent risk factor for breast cancer [13,14] as it was observed in our study where both women with BI-RADS 3 and BI-RADS 4 had a higher rate of screen detected cancer than women with fatty breasts.

It also should be noticed that in our cohort the rate of DCIS constantly increased with increasing density whereas for invasive cancers this tendency was not conclusive. This can be explained by the fact that the observed density does not necessary imply histologic abnormality at the time of mammography screening. Several studies have demonstrated a strong relationship between mammographic density and histological precursors of breast cancer and also with DCIS [15,16]. Whether breast density is related or not to a biological phenotype promoting faster tumour growth or to a specific histological cancer type remains to be elucidated. However, our findings could be explained by the fact that in very dense breasts it is hard to spot small masses, asymmetries or distortions that are often the mammographic finding of invasive cancers, thereby leading to a lower incidence of screen-detected invasive cancers in women with BI-RADS 4. DCIS are on the other hand often associated with calcifications, and calcifications are almost as easy to spot in a dense breast as in a fatty breast. Thus, one

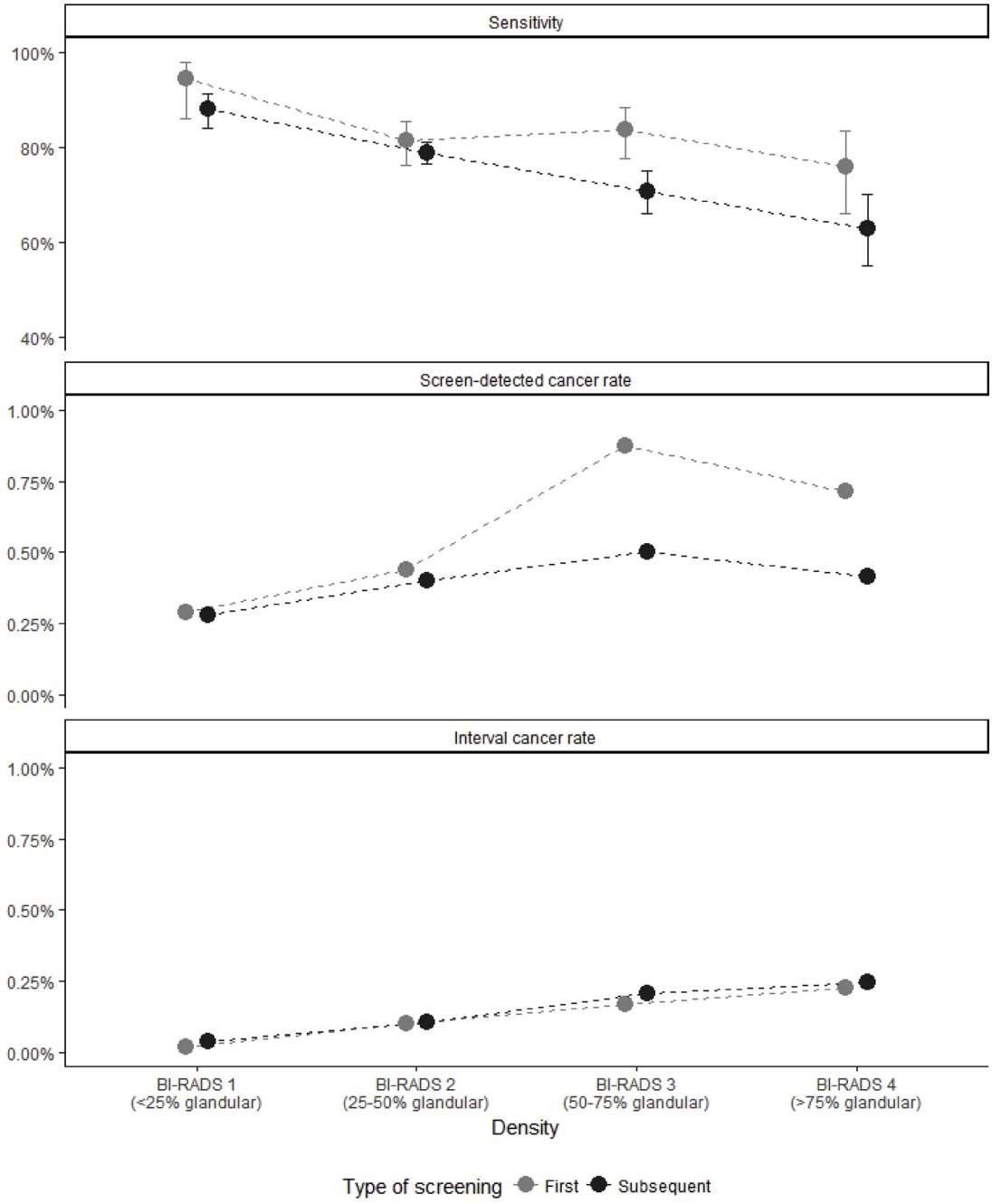

Fig. 2. Sensitivity, screen-detected cancer rate and interval cancer rate stratified by first and subsequent screening.

could expect the incidence of DCIS to be higher in women with BI-RADS 4 than in women with more fatty breasts because the extremely dense women have the highest risk of breast malignancy. This would also lead to a higher incidence of DCIS relative to invasive cancer in these women compared to women with less dense breasts. Overall, the increased risk can be even higher in women with dense breasts and therefore, as well as other factors [17], it should be considered when offering their follow-up strategies.

Previous studies conducted with screen-film mammography showed that sensitivity decreased from approximately 80% in women with BI-RADS 1 to 50% in women with BI-RADS 4 [18–20]. Digital mammography was expected to perform better in women with dense breasts, with several trials showing between 70% to 80% sensitivity in women with BI-RADS 3 and BI-RADS 4 in non-organized screening [7,21]. More recently, studies conducted in population-based European screening programs confirmed a sensitivity of about 70% in these groups [12,22], which is in agreement with our results. Overall, although the diagnostic accuracy of digital mammography outperforms conventional screen-film mammography, other techniques such as digital breast tomosynthesis, may improve screening performance measures among women with dense breasts [14].

Interestingly, we found that women aged 60 to 69 years with BI-RADS 4 showed the lowest sensitivity (54.9%) and the highest interval cancer rate (4 per 1000 screening exams). Breast density is expected to gradually decrease with increasing age after menopause [20,23]. However, there is a small proportion of women who remain at a high breast density ages 60 to 69 years. The explanation for why the sensitivity is lower in 60–69 years old women with BI-RADS 4 than in 50–59 year old women with BI-RADS 4 has not been established. However, it could be related to a higher incidence of cancer in older

women with dense breasts than in younger women with dense breasts. From our results, it seems that routine biennial screening in these group of women may not be as effective as in the average target population. These women may benefit from personalized screening strategies that combine new diagnostic tests.

In our study, women with dense breasts were more likely to be recalled for additional tests, including invasive procedures. Most additional tests were associated with an increased false positive rate and a decrease in the predictive value. In agreement with our findings, a previous study showed that women with dense breasts were more likely to undergo additional imaging tests [24]. However, they found that breast density was not significantly associated with biopsy and/or surgical consultation in women without additional imaging tests. The authors suggested that having imaging tests, especially ultrasound, was the factor associated with unnecessary biopsies in women with dense breasts. The distribution of diagnostic tests performed should be further evaluated, particularly in women aged 60–69 years and BI-RADS 4 because they showed low positive predictive values.

Almost 21% of mammograms in our cohort and up to 40% in other cohorts [13,25] were classified as BI-RADS 3 or BI-RADS 4, which represent a large proportion of screened women. Thus, to study breast density is helpful to better planning the screening process and resources needed, especially for women with dense breasts. Breast density is particularly relevant in the screening context, since it contributes more to the population risk than other much stronger but less common risk factors, such as BRCA mutations. In fact, some authors have proposed that breast density is the risk factor that increases far more the accuracy of a breast cancer risk prediction model [26]. Therefore, offering more accurate diagnostic tests to these women can positively affect the overall performance of screening programs by increasing sensitivity and/or decreasing interval cancers.

This study is based on a large cohort of screened women, involving more than 150,000 women followed for at least 10 years that allowed us to obtain robust conclusions. However, several limitations should be considered. First, variability between radiologists can affect the results since breast density measurements are inherently inaccurate depending on the subjective observation [25,27,28]. Despite this limitation, our results are consistent with those published by other European screening programs. Furthermore, highly trained radiologists performed breast density classification. Second, the BI-RADS edition that is referred to in this manuscript is the fourth edition published in 2003 [9] and differs from the current edition in how breast density is categorized [29], which focuses more on the qualitative description of breast density. We do not have data regarding the Fifth edition since it has been implemented since 2015. Although BI-RADS 1 to 4 is similar to BI-RADS a to d, it should be noticed that some women who, for example, had mostly fatty breast but with focal dense areas might now be classified as BI-RADS c, while they were previously classified as BI-RADS 2 [30]. Third, due to lack of information, we could not differentiate true interval cancers from false negatives and therefore we combined both of them in one category as interval cancers. This fact could lead us to a slight bias when estimating sensitivity.

5. Conclusions

Performance measures in screening mammography are negatively affected by breast density, falling to a lower sensitivity, positive predictive value and higher interval cancer rates. Although digital mammography is expected to have better results in women with dense breast, it seems that the performance improvements of this technique is less effective for screening women with BI-RADS 3 or BI-RADS 4. Women with dense breast may not obtain benefit from screening to the same extent as women with lower breast density. Particularly, women aged 60 to 69 years with BI-RADS 4 showed the lower sensitivity and higher interval cancer rate and therefore they may be more likely to have benefits from other screening technologies such as digital breast tomosynthesis.

Funding

This work was supported by Grants from Instituto de Salud Carlos III FEDER, [PI15/00098 and PI17/00047] and by the Network for Research into Healthcare in Chronic Diseases, REDISEC [RD12/0001/0015].

Role of the funding source

This funding source had no role in the design of this study and did not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Acknowledgements

The authors acknowledge the Benign Lesion (BELE) Study Group, listed here in alphabetical order and grouped by institution: (a) IMIM (Hospital Del Mar Medical Research Institute), Barcelona, Spain: Andrea Burón, Xavier Castells, Laia Domingo, Javier Louro, Margarita Posso, Ana Rodríguez-Arana, Marta Román, Maria Sala, Sònia Servitja, Mar Vernet; (b) Parc Taulí University Hospital, Sabadell, Spain: Marisa Baré; (c) Catalan Institute of Oncology, Cancer Prevention and Monitoring Program, Barcelona, Spain: Llucia Benito, Carmen Vidal; (d) Hospital de la Santa Creu i Sant Pau, Epidemiology Department, Barcelona, Spain: María Jesús Quintana, Judit Solà-Roca; (e) General Directorate of Public Health, Government of Cantabria, Santander, Spain: Mar Sánchez; (f) Principality of Astúrias Health Service, Spain: Miguel Prieto; (g) Fundació Lliga per a La Investigació i Prevenció Del Càncer, Universitat Rovira i Virgili, Tarragona, Spain: Jaume Galceran, Francina Saladié; (h) Hospital Santa Caterina, Girona, Spain: Joana Ferrer; (i) Catalan Cancer Plan, Department of Health, Barcelona, Spain: Josep Alfons Espinàs; (*j*) Private Foundation Asil Hospital, Granollers, Spain: Lupe Peñalva; and (k) Hospital Clinic, Preventive Medicine and Epidemiology Department, Barcelona, Spain: Isabel Torá-Rocamora, Xavier Bargalló. Javier Louro is a Ph.D. candidate at the Methodology of Biomedical Research and Public Health program, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain.

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