Mammographic and clinical characteristics of different phenotypes of screen-detected and interval breast cancers in a nationwide screening program

Marisa Baré^{1,2,3}, Núria Torà^{1,3}, Dolores Salas⁴, Melchor Sentís⁵, Joana Ferrer⁶, Josefa Ibáñez⁴, Raquel Zubizarreta⁷, Garbiñe Sarriugarte⁸, Teresa Barata⁹, Laia Domingo¹⁰, Xavier Castells^{2,3,10}, Maria Sala^{2,3,10} on behalf of the INCA STUDY GROUP

1. Clinical Epidemiology and Cancer Screening. UDIAT-DC. Parc Taulí Sabadell, Sabadell, Spain
2. Department of Pediatrics, Obstetrics and Gynecology, and Preventive Medicine and Public Health. Faculty of Medicine, Autonomous University of Barcelona (UAB), Bellaterra, Spain
3. Research network on health services in chronic diseases (REDISSEC), Barcelona, Spain
4. General Directorate Public Health and Centre for Public Health Research (CSISP), FISABIO, Valencia, Spain
5. Breast Imaging. Department of Radiology. UDIAT-DC. Parc Taulí Sabadell, Sabadell, Spain
6. Department of Radiology, Hospital de Santa Caterina, Salt, Girona, Spain
7. Galician Breast Cancer Screening Programme, Directorate for innovation and management of public health, Santiago de Compostela, Spain
8. Osakidetza Breast Cancer Screening Programme, Basque Country Health Service, Bilbao, Spain
9. General Directorate of Health Care Programmes, Canary Islands Health Service, Las Palmas de Gran Canaria, Spain.
10. Department of Epidemiology and Evaluation, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain

Corresponding author: Marisa Baré, MD, MPH, PhD
Clinical Epidemiology and Cancer Screening
UDIAT-DC. Parc Taulí Sabadell-University Hospital
Autonomous University of Barcelona (UAB)
Health Services Research on Chronic Patients Network (REDISSEC)
Parc Taulí 1, 08208 Sabadell, SPAIN
e-mail: mbare@tauli.cat

Word count (excluding abstract): 3234

Abstract

Purpose: In the context of a population-based screening program, we aimed to evaluate the major mammographic features and clinicopathological characteristics of breast tumors at diagnosis and the associations between them, focusing on tumors with the worst prognosis.

Methods: We analyzed cancers diagnosed in a cohort of 645,764 women aged 45 to 69 years participating in seven population-based screening programs in Spain, between January 1, 2000 and December 31, 2006 and followed up until June 2009. We included all interval cancers and a sample of screen-detected cancers, whether invasive or *in situ*. We compared tumor-related information and breast density for different phenotypes (Triple-negative (TN), HER2+, Luminal B and Luminal A) in screen-detected and interval cancers. We used chi-square or Fisher's exact test to compare major mammographic features of invasive vs. *in situ* tumors, of screen-detected vs. interval cancers, and of different types of interval cancers.

Results: We included 2582 tumors (1570 screen-detected and 1012 interval cancers). There were significant differences in the distribution of most clinicopathological variables between screen-detected and interval cancers. Invasive TN interval tumors were more common than other phenotypes in breasts with low mammographic density; three-quarters of these tumors presented as masses without associated calcifications. HER2+ tumors were more common in denser breasts and were associated with calcifications and multifocality. Architectural distortion was more common in Luminal A and Luminal B tumors.

Conclusions: Certain radiologic findings are associated with pre-invasive lesions; these differ among invasive tumor phenotypes. We corroborate that TN and HER2+ cancers have distinctive appearances also in the context of population-based screening programs. This information can be useful for establishing protocols for diagnostic strategies in screening units.

Keywords: breast cancer; HER2+; Triple-negative; mammographic features; screening; interval cancer

Introduction

Breast cancer can present and progress in various ways. Early detection and characterization are essential to ensure optimal treatment. On mammography, the best technique for screening, certain findings (e.g., certain types of calcifications, spiculated masses, or architectural distortion) suggest malignancy and can even be considered markers of poor prognosis [1, 2]. However, findings among tumors vary, and few findings are specific for malignant or premalignant lesions.

On the other hand, breast tumors have different biological profiles called phenotypes. Tumor phenotypes define subgroups of tumors associated with the expression of particular immunohistochemical markers [3]. Recognized phenotypes include the triple-negative subtype (negative for ER, PR, and HER2+), which is associated with aggressive histological features, poor prognosis, unresponsiveness to usual endocrine therapies, and shorter survival. Another phenotype, HER2+, is also associated with poor prognosis. Tumor phenotypes can be identified after immunohistochemical analysis; however, in some cases the mammographic findings could be markers of phenotype and even of the likelihood of regional or distant spread. Recent studies analyzing the mammographic findings in the phenotypes that have the worst prognosis (e.g., triple-negative) appear to show that certain findings are common in these tumors; however, contrary to what would be expected, the findings that are most suspicious for malignancy, such as architectural distortion or spiculated lesions, are uncommon in this group [4-10]. Most of these studies considered small series at a single center and analyzed mammographic findings together with those of other imaging techniques used in the clinical context. Our group recently reported differences in mammographic density associated with tumor phenotype and presentation in screening or in the interval between planned screenings [11]. To date, the relationship between the most representative mammographic findings and tumor phenotype has not been analyzed in the context of population-based mammography screening programs. For these reasons, this study aimed to evaluate the major mammographic features and clinicopathological characteristics of tumors at diagnosis and the associations between them in a screening program, focusing on the phenotypes with the worst prognosis.

Methods

We analyzed breast cancers diagnosed in a cohort of 645,764 women aged 45 to 69 years participating in one of seven population-based screening programs carried out in 32 imaging centers in five regions in Spain; women were screened between January 1, 2000 and December 31, 2006 and were followed up until June 2009. In accordance with the European guidelines for Quality Assurance in Mammographic Screening Recommendations [12], every two years women in the target population are sent a letter inviting them to participate in the population-based screening program. This nationwide program achieves the required standards.

The ethics committee of Parc de Salut Mar (CEIC Parc de Salut MAR) approved the protocol for data collection and waived the requirement for specific patient consent because we used retrospective data from screening participants who had previously signed information release documents.

During the study period, 5309 cancers were detected in routine screening mammograms and 1669 emerged as interval cancers (primary tumors diagnosed in the interval between an unremarkable screening mammogram and the next planned screening mammogram). We included both invasive and *in situ* carcinomas. The analysis included all interval cancers and a sample of cancers detected at screening, as specified in Domingo et al. [11]; cancers for which the diagnostic mammogram was unavailable were excluded. The final analysis focused on the clinical information and mammographic features of 2582 tumors, 1570 diagnosed at screening and 1012 diagnosed in the interval between screenings.

Three panels consisting of three experienced radiologists classified interval cancers; two radiologists independently reviewed both screening and diagnostic mammograms, and the third decided in cases of discrepant findings. Radiologists blinded to the diagnostic mammogram and histological findings first reviewed screening mammograms. Interval cancers were definitively classified into: true interval cancers (the screening mammogram showed normal or benign results), false negatives (the screening mammogram showed an

1 abnormality suspicious for malignancy), minimal-signs (the screening mammogram had
2 detectable but non-specific signs), or occult tumors (the diagnostic mammogram had no
3 abnormalities despite clinical signs). More details of the classification process were
4 reported in a previous study [11].
5
6

7 We ensured that the site where the minimal signs were identified correlated with the site
8 of the interval cancer. When there was no correlation, the case was considered a true
9 interval cancer.
10
11

12 *Mammographic features and clinical variables*

13
14

15 Age at diagnosis was calculated from the patient's date of birth and date of the
16 mammogram.
17
18

19 Mediolateral-oblique and craniocaudal views were obtained in both the initial and
20 successive rounds, except in one program. All film mammograms were read by two
21 radiologists, except in two programs. For both interval and screening-detected cancers,
22 one radiologist from each panel evaluated the density of the cancer-free breast using a
23 semiquantitative score and aggregated in four categories using percentages of density,
24 similar to the BI-RADS classification: A: Up to 25%; B: 25% to 50%; C: 50% to 75%; D: 75%
25 to 100% [13]. The same radiologist classified mammographic features at diagnosis into
26 the following mutually exclusive categories: mass only, distortions only, calcifications
27 only, asymmetries, concomitant mass and calcifications, concomitant distortion and
28 calcifications, and others. The radiologist also recorded whether the tumor was multifocal
29 and/or multicentric (focality).
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45

46 Tumor-related information (histology, grade, size, lymph node involvement, estrogen
47 receptor expression (ER), progesterone receptor expression (PR), HER2 overexpression,
48 and Ki67 status) was obtained from the cancer registries, hospital-based registers, and
49 clinical records. Biomarkers were assessed during the diagnostic process in the hospitals.
50 The criteria for positivity used by each hospital followed international recommendations
51 and their updates throughout the study period [14,15]. For the purposes of this study,
52 tumors were considered positive for Ki67 when more than 20% of cells stained positive.
53
54
55
56
57
58
59
60
61
62
63
64
65

For the histological classification, we used the International Classification of Diseases for Oncology, 3rd edition. Histological grade was defined according to the Scarff-Bloom-Richardson criteria, as modified by Elston [16].

As in the earlier study published by our group [11], tumors were classified into four immunophenotypes on the basis of the expression of ER, PR, and HER2: 1) Luminal A: ER+/HER2- or PR+/HER2-; 2) Luminal B: ER+/HER2+ or PR+/HER2+; 3) HER2+: ER-/PR-/HER2+; and 4) triple negative (TN): ER-, PR-, HER2- [17].

Statistical analysis

First, we compared the clinical and radiological characteristics of screen-detected vs. interval cancers. Clinical characteristics were tabulated by immunophenotype. We compared the main prognostic factors (tumor size, histological grade, ki67, lymph node involvement), metastases at diagnosis, and breast density between invasive TN, HER2+, Luminal A, and Luminal B tumors. We also analyzed the radiological findings and focality by comparing invasive vs. *in situ* tumors and screen-detected vs. interval cancers; furthermore, we compared the radiologic findings in the four types of interval cancers. Finally, we compared the degree of regional invasion in function of tumor size and focality. We used SPSS v.20.0 for all statistical analyses. P-values <0.05 on two-sided chi-square or Fisher's exact test for categorical variables were considered significant.

Results

A total of 2582 tumors were included; of these, 1570 were detected during routine screening and 1012 were interval cancers. Figure 1 shows the tumors included, broken down by detection mode and availability of information about phenotype. Tumor phenotype was available for 1701 invasive tumors (921 screen-detected and 780 interval) and for 133 *in situ* tumors (108 screen-detected and 25 interval). Table 1 reports the clinical and pathological characteristics of all tumors. There were significant differences in the distribution of most variables between screen-detected and interval tumors. Interval tumors included a smaller proportion of *in situ* tumors and greater proportions of tumors

measuring more than 20 mm, of tumors classified as histological grade III, of Ki67-positive tumors, and of tumors with lymph node involvement and remote metastases at the time of diagnosis.

In the entire sample, the phenotype expressed was Luminal A in 63% of the tumors, Luminal B in 15.5%, HER2+ in 9.4%, and TN in 12.3%. These percentages differed significantly between screen-detected and interval tumors: more interval tumors were TN (15.3% vs. 9.9% in screen-detected tumors) and fewer were Luminal A (58.9% vs 66%).

Table 2 shows the main prognostic factors and mammographic density for the 1701 invasive tumors in function of mode of detection and phenotype. In general, interval tumors were larger than screen-detected tumors. Whereas about one-third of screen-detected tumors measured ≤ 10 mm, nearly two-thirds of interval tumors measured ≥ 20 mm. Among screen-detected tumors, 12.1% of HER2+ tumors measured > 50 mm at detection and among interval cancers, the percentage of tumors measuring >50 mm at detection was higher for TN (12.3%), HER2+ (14.1%), and Luminal B(18.7%). Histological grade III and positivity to Ki67 were more frequent in interval cancers. Among both screening-detected and interval cancers, TN and HER2+ tumors had higher histological grade and greater Ki67 positivity, whereas Luminal A tumors had the highest percentages of histological grade I and negativity to Ki67. Lymph node involvement at the time of diagnosis was more common in interval (58.6%) than screen-detected tumors (32.5%). However, in screen-detected tumors, lymph node involvement was present in nearly 50% of tumors with HER2+ phenotype. Among interval cancers, lymph node involvement at diagnosis was most common (62.8%) in Luminal B tumors, followed by HER2+ (56.1%). Finally, breast density at mammography was associated with tumor phenotype, but the association was only significant in interval cancers. In this sense, compared to other phenotypes, a greater proportion of TN tumors were found in less dense breasts in interval cancers (45.8%); only 8.3% of interval TN and 6.6% of screen-detected TN tumors were found in extremely dense breasts ($>75\%$). By contrast, Luminal B or even Luminal A interval tumors were more common in extremely dense breasts.

Table 3 reports the mammographic findings for all the invasive and *in situ* tumors classified by phenotype and detection. In general, the distribution of mammographic features was similar among screen-detected and interval invasive cancers. However,

some differences between phenotypes, especially in screen-detected tumors but also in interval cancers, merit comment. Invasive TN tumors presented as masses with similar frequency between screen-detected and interval tumors (75% vs. 74.1%, respectively). Among invasive HER2+ screen-detected tumors, 41.7% showed calcifications alone and 15% calcifications associated with a mass, whereas the findings for *in situ* HER2+ tumors were calcifications alone in 100%. In invasive HER2+ interval tumors, calcifications alone were less common (13.2%). In both screen-detected and interval invasive Luminal A and Luminal B tumors, apart from masses, architectural distortion was also relatively common (10.4%-14.5%). On the other hand, the percentage of multifocality and/or multicentricity (MM) was similar in screen-detected and interval cancers, and more common in *in situ* tumors than in invasive ones. Thus, about 18% to 20% of invasive tumors were multifocal while over 30% of the *in situ* were multifocal. There were some differences in MM between different phenotypes, but this association reached statistical significance only in screen-detected invasive cancers: TN and HER2+ tumors had significantly more MM (27% and 27.9%), whereas Luminal A tumors were the type that presented MM less often (15.2%)..

When we compared the mammographic features and MM for each subtype of invasive interval tumor (true interval vs. false-negative vs. minimal signs, but not occult tumors) according to phenotype (Table 4), significant differences between phenotypes in the mammographic features were observed only for the true interval tumors, where the pattern was similar to the invasive interval tumors shown in Table 3. Nevertheless, calcifications alone or associated with masses were present in more than 46% of HER2+ false negatives. On the other hand, in false-negatives we also found significant differences in MM among phenotypes: 30.8% of HER2+ and 39.3% of Luminal B had MM, whereas only 6.7% of the TN and 16.4% Luminal A had MM. In true interval tumors and those that presented with minimal signs, no significant differences in MM were observed between phenotypes, although MM seemed to be more frequent in HER2+ interval tumors with minimal-signs.

Figure 2 shows lymph node involvement in invasive tumors according to tumor size and MM. In screen-detected tumors, larger size was associated with greater lymph node involvement, and the percentage of lymph node involvement was significantly greater in both screen-detected and interval MM tumors measuring more than 20 mm. Lymph node

invasion was found in 72.1% of screen-detected tumors with MM and measuring between 21 mm and 50 mm.

Discussion

This original nationwide study is one of the first to compare the main mammographic findings in different tumor phenotypes within the context of a population-based breast cancer screening program. The most noteworthy findings were that invasive TN interval tumors are more common than other phenotypes in breasts with low mammographic density (<25%); three-quarters of these tumors presented as masses without associated calcifications. By contrast, invasive HER2+ interval tumors were more common in denser breasts and were associated with calcifications and MM; this was true of both interval and screen-detected tumors, but especially of the latter. Architectural distortion was more common in Luminal A and Luminal B tumors.

In the attempt to find useful clues to guide treatment decisions, many studies have analyzed different radiologic findings as possible markers for biologic or clinical traits of tumors; however, few studies have compared these findings among tumor phenotypes. In a recent series of invasive carcinomas, Sun et al. [5] found an association between mammographic findings at the time of diagnosis and the molecular phenotype or other clinical characteristics. They reported that malignant calcifications were more common in HER2+ and Luminal B tumors, whereas architectural distortion was more common in TN tumors; our findings in TN tumors differ. Ildefonso et al. [18] analyzed the mammographic findings and prognoses in a series of invasive tumors, finding the worst prognosis in tumors that presented mammographically as distortion or asymmetries in density and in those that had suspicious microcalcifications, without taking the immunophenotype into account. In our study, distortion was more common in Luminal A and Luminal B tumors.

In fact, TN and HER2+ tumors represent an important challenge in the management of breast cancer, given their worse prognosis compared to others such as Luminal A and even Luminal B. Our study corroborates that TN and HER2+ tumors have certain radiologic characteristics that differentiate them from other tumor phenotypes. In 2013,

1 Brouckaert et al. [19] analyzed a large series of screen-detected tumors and compared
2 their long-term prognosis according to phenotype and other clinical aspects of the tumor,
3 with the aim of identifying tumors that might represent overdiagnosis given their
4 excellent prognosis. Tumor palpability was an independent predictor of poor prognosis,
5 regardless of phenotype and lymph node invasion; the authors surmised that palpability
6 might be related to a high cellular concentration or density and/or fibrosis. This might
7 explain why three-quarters of the invasive TN tumors in our study presented on
8 mammography as a mass without calcifications, being larger than 20 mm in nearly 56% of
9 cases. A remarkable finding was the TN distribution regarding mammographic density.
10 Recently, Holm et al. [20] reported similar results, noting the significant relationship
11 between TN interval cancer and low mammographic density. In our study, this
12 relationship also appears to exist for screen-detected cancers. Another noteworthy
13 aspect is the frequency of radiologic multifocality and/or multicentricity in screen-
14 detected TN tumors, which in turn was associated with greater lymph node invasion for
15 the same tumor size. These observations make sense in the context of the greater
16 aggressiveness and faster progression of TN tumors [21]. In a recent systematic review,
17 Vera-Badillo et al. [22] found that multifocal and/or multicentric lesions probably have a
18 worse prognosis, although the authors insist that the results of the studies analyzed were
19 heterogeneous and further studies are necessary to settle this question.
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35

36 Our results regarding HER2+ tumors corroborate those reported in Elias et al.'s [4]
37 systematic review of the mammographic findings in 2559 HER2+ tumors, in which
38 microcalcifications with or without an associated mass were the finding with the
39 strongest association with HER2+ overexpression. Although this review also reported a
40 weak association with very high breast density (BI-RADS 4), the authors did not compare
41 breast density between HER2+ tumors and other phenotypes. In our study, invasive
42 HER2+ tumors were the least commonly diagnosed tumors in less dense breasts.
43 Although we were able to analyze only a small sample of *in situ* tumors with an
44 identifiable phenotype, and although calcifications were the most common finding in this
45 type of tumor, it is nevertheless noteworthy that in 100% of the screen-diagnosed *in situ*
46 HER2+ tumors the only findings were calcifications; this frequency is much higher than in
47 the other phenotypes, even in *in situ* tumors. Our findings and those of other studies such
48 as the Nurses' Health Study [23] that the HER2+ phenotype is more common in *in situ*
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

tumors than in invasive tumors lend strength to the hypothesis that most HER2+ tumors go through a pre-invasive stage and that some of them do not evolve into invasive tumors. Furthermore, in true interval HER2+ tumors, more aggressive lesions with shorter lead-time, calcifications were less common.

One of the strengths of this study is that it analyzed a nationwide cohort. This made it possible to compare the radiologic appearances of different tumor phenotypes in the context of population-based breast cancer screening programs and to distinguish between tumors diagnosed in routine screening and those diagnosed before the next planned screening. Thus, it includes a large series of TN and HER2+ tumors. This study continues in the line of research about different aspects of mammographic screening for breast cancer and goes one step further in the characterization of screen-detected and interval tumors, despite the difficulty of obtaining exhaustive retrospective data. Moreover, the protocolization and centralization of the method of reviewing the images and collecting the data adds robustness to the study. Although patients' age range was defined by the norm in European screening programs, there is no reason to think that the results would have differed in many aspects if the study had included patients outside this range. In fact, some of the studies cited above did not incorporate the entire range of possible ages, either.

Other findings reported elsewhere, such as the appearance of the masses or of the calcifications, or even whether an intraductal component was associated to an invasive tumor and its characteristics [24], have not been analyzed in the present study because these aspects were outside the scope of our objectives. Finally, the findings might have varied slightly if phenotypes had been classified using another system, such as the most recent markers proposed at the St. Gallen conference [25], in which some phenotypes are subdivided in function of Ki67 or the percentage of positivity of the other receptors. Nevertheless, this marker was not routinely determined in the years covered by our study, and a broad consensus about these classification systems is still lacking. Moreover, the classification used in the present study is the same one used in earlier publications, and this makes our results easy to compare.

The analysis of this large series of tumors diagnosed in the context of population-based screening programs has enabled us to corroborate relations between radiologic findings and clinical and pathological findings. In particular, it has enabled us to confirm the distinctive appearances of the tumors with the worst prognosis, TN and HER2+, which we will now be able to evaluate prospectively. In conclusion, certain radiologic findings are associated with pre-invasive lesions; these differ among invasive tumor phenotypes. In the context of population-based screening programs for breast cancer, this information can be useful for establishing protocols for diagnostic strategies in screening units. Further studies should seek more information about the signs that point to the risk of poor prognosis.

This work was supported by Instituto de Salud Carlos III-FEDER (PI 09/01153, PI09/02385, PI09/01340).

INCA STUDY GROUP

The authors acknowledge the dedication and support of the entire Interval Cancer (INCA) Study Group. The members of the Interval Cancer (INCA) Study Group are (alphabetical order): IMIM (Hospital del Mar Medical Research Institute), Barcelona: Jordi Blanch, Xavier Castells, Mercè Comas, Laia Domingo, Francesc Macià, Juan Martínez, Ana Rodríguez-Arana, Marta Román, Anabel Romero, Maria Sala. General Directorate Public Health and Centre for Public Health Research (CSISP), FISABIO, Valencia: Carmen Alberich, María Casals, Josefa Ibáñez, Amparo Lluch, Inmaculada Martínez, Josefa Miranda, Javier Morales, Dolores Salas, Ana Torrella. Galician Breast Cancer Screening Programme, Xunta de Galicia: Raquel Almazán, Miguel Conde, Montserrat Corujo, Ana Belén Fernández, Joaquín Mosquera, Alicia Sarandeses, Manuel Vázquez, Raquel Zubizarreta. General Directorate of Health Care Programmes. Canary Islands Health Service: Teresa Barata, Isabel Díez de la Lastra, Juana María Reyes. Basque Country Breast Cancer Screening Programme, Osakidetza: Arantza Otegi, Garbiñe Sarriugarte. Parc Taulí Sabadell, Sabadell: Marisa Baré, Núria Torà. Hospital Santa Caterina, Girona: Joana Ferrer, Francesc Castanyer, Gemma Renart. Epidemiology Unit and Girona Cancer Registry; and University of Girona: Rafael Marcos-Gragera, Montserrat Puig-Vives. Biomedical Research Institut of Lleida (IRBLLEIDA): Carles Forné, Montserrat Martínez-Alonso, Albert Roso, Montse Rué, Ester Vilaprinçó. Universitat Rovira i Virgili, Tarragona: Misericordia Carles, Aleix Gregori, María José Pérez, Roger Pla.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Tabar L, Tony Chen HH, Amy Yen MF, Tot T, Tung TH, Chen LS, Chiu YH, Duffy SW, Smith RA (2004) Mammographic tumor features can predict long-term outcomes reliably in women with 1-14-mm invasive breast carcinoma. *Cancer* 101(8):1745-1759
2. Sartor H, Borgquist S, Hartman L, Olsson A, Jawdat F, Zackrisson S (2015) Do mammographic tumor features in breast cancer relate to breast density and invasiveness, tumor size, and axillary lymph node involvement? *Acta Radiol* 56(5):536-544
3. Eroles P, Bosch A, Pérez-Fidalgo JA, Lluch A (2012) Molecular biology in breast cancer: intrinsic subtypes and signaling pathways. *Cancer Treat Rev* 38(6):698-707
4. Elias SG, Adams A, Wisner DJ, Esserman LJ, van't Veer LJ, Mali WP, Gilhuijs KG, Hylton NM (2014) Imaging features of HER2 overexpression in breast cancer: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 23(8):1464-1483
5. Sun SS, Zhang B, Zhao HM, Cao XC (2014) Association between mammographic features and clinicopathological characteristics in invasive ductal carcinoma of breast cancer. *Mol Clin Oncol* 2(4):623-629
6. Gao B, Zhang H, Zhang SD, Cheng XY, Zheng SM, Sun YH, Zhang DW, Jiang Y, Tian JW (2014) Mammographic and clinicopathological features of triple-negative breast cancer. *Br J Radiol* 87(1039):20130496
7. Krizmanich-Conniff KM, Paramagul C, Patterson SK, Helvie MA, Roubidoux MA, Myles JD, Jiang K, Sabel M (2012) Triple receptor-negative breast cancer: imaging and clinical characteristics. *AJR Am J Roentgenol* 199(2):458-464
8. Ko ES, Lee BH, Kim HA, Noh WC, Kim MS, Lee SA (2010) Triple-negative breast cancer: correlation between imaging and pathological findings. *Eur Radiol* 20(5):1111-1117

9. Wang Y, Ikeda DM, Narasimhan B, Longacre TA, Bleicher RJ, Pal S, Jackman RJ, Jeffrey SS (2008) Estrogen receptor-negative invasive breast cancer: imaging features of tumors with and without human epidermal growth factor receptor type 2 overexpression. *Radiology* 246(2):367-375
10. Yang WT, Dryden M, Broglio K, Gilcrease M, Dawood S, Dempsey PJ, Valero V, Hortobagyi G, Atchley D, Arun B (2008) Mammographic features of triple receptor-negative primary breast cancers in young premenopausal women. *Breast Cancer Res Treat* 111(3):405-410
11. Domingo L, Salas D, Zubizarreta R, Baré M, Sarriugarte G, Barata T, Ibáñez J, Blanch J, Puig-Vives M, Fernández A, Castells X, Sala M; INCA Study Group (2014) Tumor phenotype and breast density in distinct categories of interval cancer: results of population-based mammography screening in Spain. *Breast Cancer Res* 16(1):R3
12. Perry N, Broeders M, de Wolf C, Törnberg C, Holland R, von Karsa L (2006) European guidelines for quality assurance in breast cancer screening and diagnosis. 4th edition. Office for Official Publications of the European Communities, Luxembourg
13. Boyd NF, Byng JW, Jong RA, Fishell EK, Little LE, Miller AB, Lockwood GA, Tritchler DL, Yaffe MJ (1995) Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. *J Natl Cancer Inst* 87(9):670–675
14. 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; American Society of Clinical Oncology; College of American Pathologists (2010) American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). *Arch Pathol Lab Med* 134(7):e48–e72

15. Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, Dowsett M, Fitzgibbons PL, Hanna WM, Langer A, McShane LM, Paik S, Pegram MD, Perez EA, Press MF, Rhodes A, Sturgeon C, Taube SE, Tubbs R, Vance GH, van de Vijver M, Wheeler TM, Hayes DF; American Society of Clinical Oncology/College of American Pathologists (2007) American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *Arch Pathol Lab Med* 131(1):18–43
16. Elston CW, Ellis IO (1991) Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology* 19(5):403–410
17. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ; Panel members (2011) Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol* 22(8):1736–1747
18. Ildefonso C, Vazquez J, Guinea O, Perez A, Fernandez A, Corte MD, Junquera S, Gonzalez LO, Pravia P, Garcia-Moran M, Vizoso FJ (2008) The mammographic appearance of breast carcinomas of invasive ductal type: relationship with clinicopathological parameters, biological features and prognosis. *Eur J Obstet Gynecol Reprod Biol* 136(2):224–231
19. Brouckaert O, Schoneveld A, Truyers C, Kellen E, Van Ongeval C, Vergote I, Moerman P, Floris G, Wildiers H, Christiaens MR, Van Limbergen E, Neven P; MBC Leuven, Belgium (2013) Breast cancer phenotype, nodal status and palpability may be useful in the detection of overdiagnosed screening-detected breast cancers. *Ann Oncol* 24(7):1847–1852
20. Holm J, Humphreys K, Li J, Ploner A, Cheddad A, Eriksson M, Törnberg S, Hall P, Czene K (2015) Risk factors and tumor characteristics of interval cancers by mammographic density. *J Clin Oncol* 33(9):1030–1037

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
21. Kurbel S (2013) In search of triple-negative DCIS: tumor-type dependent model of breast cancer progression from DCIS to the invasive cancer. *Tumour Biol* 34(1):1-7
22. Vera-Badillo FE, Napoleone M, Ocana A, Templeton AJ, Seruga B, Al-Mubarak M, AlHashem H, Tannock IF, Amir E (2014) Effect of multifocality and multicentricity on outcome in early stage breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat* 146(2):235-244
23. Tamimi RM, Baer HJ, Marotti J, Galan M, Galaburda L, Fu Y, Deitz AC, Connolly JL, Schnitt SJ, Colditz GA, Collins LC (2008) Comparison of molecular phenotypes of ductal carcinoma in situ and invasive breast cancer. *Breast Cancer Res* 10(4):R67
24. Gajdos C, Tartter PI, Bleiweiss IJ, Hermann G, de Csepe J, Estabrook A, Rademaker AW (2002) Mammographic appearance of nonpalpable breast cancer reflects pathologic characteristics. *Ann Surg* 235(2):246-251
25. Esposito A, Criscitiello C, Curigliano G (2015) Highlights from the 14(th) St Gallen International Breast Cancer Conference 2015 in Vienna: Dealing with classification, prognostication, and prediction refinement to personalize the treatment of patients with early breast cancer. *Ecanermedicalscience* 9:518

Table 1. Clinicopathological characteristics of screen-detected vs. interval breast cancers

		Mode of detection n (col%)				P-value
		Total (n=2582)	Screen- detected cancer (n=1570)	Interval cancer (n=1012)		
Age						<0.001
	44-49	194 (7.5)	109 (6.9)	85 (8.4)		
	50-54	721 (27.9)	393 (25)	328 (32.4)		
	55-59	709 (27.5)	438 (27.9)	271 (26.8)		
	60-64	684 (26.5)	460 (29.3)	224 (22.1)		
	>=65	274 (10.6)	170 (10.8)	104 (10.3)		
Histological type						<0.001
	<i>In situ</i>	314 (12.3)	259 (16.6)	55 (5.5)		
	Invasive	2245 (87.7)	1297 (83.4)	948 (94.5)		
	Unknown	23	14	9		
Interval cancer						
	True interval			489 (48.3)		
	False negative			235 (23.2)		
	Minimal-signs			174 (17.2)		
	Occult tumor			114 (11.3)		
Tumor size						<0.001
	<=10 mm	633 (27.2)	532 (38.1)	101 (10.8)		
	11 to 20 mm	915 (39.3)	567 (40.6)	348 (37.4)		
	21 to 50 mm	672 (28.9)	271 (19.4)	401 (43.1)		
	>50 mm	109 (4.7)	28 (2)	81 (8.7)		
	Unknown	253	172	81		
Histological grade						<0.001
	I	544 (28.5)	393 (35.2)	151 (19)		
	II	818 (42.8)	476 (42.6)	342 (43.1)		
	III	549 (28.7)	249 (22.3)	300 (37.8)		
	Unknown	671	452	219		
Ki67						0.001
	Negative	1002 (56.9)	638 (60.2)	364 (51.9)		
	Positive	758 (43.1)	421 (39.8)	337 (48.1)		
	Unknown	822	511	311		
Lymph node involvement						<0.001
	Negative	1642 (65.6)	1139 (74.6)	503 (51.5)		
	Positive	861 (34.4)	388 (25.4)	473 (48.5)		
	Unknown	79	43	36		
Metastasis at diagnosis						<0.001
	Yes	47 (1.9)	12 (0.8)	35 (3.5)		
	No	2457 (98.1)	1505 (99.2)	952 (96.5)		
	Unknown	78	53	25		
Tumor phenotype						<0.001
	TN	225 (12.3)	102 (9.9)	123 (15.3)		
	HER2	172 (9.4)	83 (8.1)	89 (11)		
	Luminal B	284 (15.5)	165 (16)	119 (14.8)		
	Luminal A	1155 (62.9)	680 (66)	475 (58.9)		
	Unknown	746	540	206		

TN = Triple-negative

Table 2. Clinicopathological characteristics and mammographic density of 1701 invasive cancers according to mode of detection and phenotype

	Tumor phenotype n (col%)											
	Screen-detected cancer						Interval cancer					
	Total (n=921)	TN (n=91)	HER2 (n=62)	Luminal B (n=139)	Luminal A (n=629)	P-value	Total (n=780)	TN (n=120)	HER2 (n=83)	Luminal B (n=115)	Luminal A (n=462)	P-value
Age						0.517						0.179
44-49	56 (6.1)	4 (4.4)	4 (6.5)	5 (3.6)	43 (6.8)		66 (8.5)	6 (5)	8 (9.6)	13 (11.3)	39 (8.4)	
50-54	226 (24.5)	24 (26.4)	18 (29)	34 (24.5)	150 (23.8)		266 (34.1)	39 (32.5)	35 (42.2)	40 (34.8)	152 (32.9)	
55-59	253 (27.5)	21 (23.1)	19 (30.6)	49 (35.3)	164 (26.1)		205 (26.3)	36 (30)	18 (21.7)	37 (32.2)	114 (24.7)	
60-64	279 (30.3)	33 (36.3)	15 (24.2)	37 (26.6)	194 (30.8)		166 (21.3)	23 (19.2)	16 (19.3)	15 (13)	112 (24.2)	
>=65	107 (11.6)	9 (9.9)	6 (9.7)	14 (10.1)	78 (12.4)		77 (9.9)	16 (13.3)	6 (7.2)	10 (8.7)	45 (9.7)	
Tumor size						<0.001						<0.001
<=10 mm	305 (33.1)	20 (22.7)	22 (37.9)	49 (36)	214 (34.7)		69 (8.8)	7 (6.1)	4 (5.1)	3 (2.8)	55 (12.4)	
11 to 20 mm	385 (41.8)	37 (42)	16 (27.6)	52 (38.2)	280 (45.5)		287 (36.8)	31 (27.2)	23 (29.5)	29 (27.1)	204 (45.9)	
21 to 50 mm	187 (20.3)	25 (28.4)	13 (22.4)	33 (24.3)	116 (18.8)		317 (40.6)	62 (54.4)	40 (51.3)	55 (51.4)	160 (36)	
>50 mm	21 (2.3)	6 (6.8)	7 (12.1)	2 (1.5)	6 (1)		70 (9)	14 (12.3)	11 (14.1)	20 (18.7)	25 (5.6)	
Unknown	23	3	4	3	13		37	6	5	8	18	
Histological grade						<0.001						<0.001
I	281 (34.4)	12 (14.6)	2 (4.3)	32 (25)	235 (41.9)		133 (19.9)	7 (7)	3 (4.1)	12 (12.4)	111 (28)	
II	344 (42.1)	20 (24.4)	17 (36.2)	62 (48.4)	245 (43.7)		282 (42.3)	18 (18)	17 (23)	41 (42.3)	206 (52)	
III	193 (23.6)	50 (61)	28 (59.6)	34 (26.6)	81 (14.4)		252 (37.8)	75 (75)	54 (73)	44 (45.4)	79 (19.9)	
Unknown	103	9	15	11	68		113	20	9	18	66	
Ki67						<0.001						<0.001
Negative	444 (59.3)	21 (27.6)	20 (42.6)	52 (44.1)	351 (69.1)		306 (51)	17 (18.3)	18 (30.5)	31 (34.1)	240 (67.2)	
Positive	305 (40.7)	55 (72.4)	27 (57.4)	66 (55.9)	157 (30.9)		294 (49)	76 (81.7)	41 (69.5)	60 (65.9)	117 (32.8)	
Unknown	172	15	15	21	121		180	27	24	24	105	
Lymph node involvement						0.005						0.031
Negative	623 (69.8)	60 (65.9)	32 (51.6)	86 (62.8)	445 (71.4)		370 (54.9)	64 (54.7)	36 (43.9)	42 (37.2)	228 (50.3)	
Positive	290 (32.5)	31 (34.1)	30 (48.4)	51 (37.2)	178 (28.6)		395 (58.6)	53 (45.3)	46 (56.1)	71 (62.8)	225 (49.7)	
Unknown	8	0	0	2	6		15	3	1	2	9	
Metastasis at diagnosis						0.418						0.119
Yes	10 (1.1)	1 (1.1)	2 (3.2)	1 (0.7)	6 (1)		25 (3.3)	1 (0.9)	5 (6)	6 (5.3)	13 (2.9)	
No	896 (98.9)	90 (98.9)	60 (96.8)	137 (99.3)	609 (99)		744 (96.7)	116 (99.1)	78 (94)	108 (94.7)	442 (97.1)	
Unknown	15	0	0	1	14		11	3	0	1	7	
Breast density						0.306						<0.001
<25%	360 (39.1)	42 (46.2)	20 (32.3)	51 (36.7)	247 (39.3)		239 (30.6)	55 (45.8)	17 (20.5)	29 (25.2)	138 (29.9)	
25 to 50%	254 (27.6)	24 (26.4)	16 (25.8)	49 (35.3)	165 (26.2)		218 (27.9)	34 (28.3)	30 (36.1)	26 (22.6)	128 (27.7)	
51 to 75%	202 (21.9)	19 (20.9)	17 (27.4)	24 (17.3)	142 (22.6)		193 (24.7)	21 (17.5)	26 (31.3)	33 (28.7)	113 (24.5)	
>75%	105 (11.4)	6 (6.6)	9 (14.5)	15 (10.8)	75 (11.9)		130 (16.7)	10 (8.3)	10 (12)	27 (23.5)	83 (18)	

TN = Triple-negative

Table 3. Mammographic findings for both invasive and *in situ* tumors, according to mode of detection and phenotype

		Tumor phenotype n (col%)																																									
		Screen-detected cancer						Interval cancer																																			
		Total	TN		HER2		Luminal B		Luminal A		P-value	Total	TN		HER2		Luminal B		Luminal A		P-value																						
Invasive																																											
Mammographic features																						<0.001																					0.001
Mass	567 (63.3)	66 (75)	20 (33.3)	76 (56.3)	405 (66.1)																		409 (60.5)	80 (74.1)	43 (56.6)	56 (52.8)	230 (59.6)																
Distortion	105 (11.7)	8 (9.1)	1 (1.7)	14 (10.4)	82 (13.4)																		75 (11.1)	3 (2.8)	3 (3.9)	13 (12.3)	56 (14.5)																
Calcification	114 (12.7)	9 (10.2)	25 (41.7)	18 (13.3)	62 (10.1)																		31 (4.6)	4 (3.7)	10 (13.2)	6 (5.7)	11 (2.8)																
Asymmetries	33 (3.7)	1 (1.1)	5 (8.3)	8 (5.9)	19 (3.1)																		60 (8.9)	8 (7.4)	5 (6.6)	12 (11.3)	35 (9.1)																
Mass with calcifications	57 (6.4)	3 (3.4)	9 (15)	13 (9.6)	32 (5.2)																		57 (8.4)	7 (6.5)	10 (13.2)	12 (11.3)	28 (7.3)																
Distortion with calcifications	17 (1.9)	0 (0)	0 (0)	5 (3.7)	12 (2)																		15 (2.2)	1 (0.9)	1 (1.3)	2 (1.9)	11 (2.8)																
Other	3 (0.3)	1 (1.1)	0 (0)	1 (0.7)	1 (0.2)																		29 (4.3)	5 (4.6)	4 (5.3)	5 (4.7)	15 (3.9)																
Unknown	25	3	2	4	16																		104	12	7	9	76																
Total	921	91	62	139	629																		780	120	83	115	462																
Focalty																						0.005																					0.131
Unifocal	741 (81.9)	65 (73)	44 (72.1)	108 (78.8)	524 (84.8)																		597 (79.5)	98 (86.7)	59 (74.7)	85 (75.9)	355 (79.4)																
Multifocal and/or multicentric	164 (18.1)	24 (27)	17 (27.9)	29 (21.2)	94 (15.2)																		154 (20.5)	15 (13.3)	20 (25.3)	27 (24.1)	92 (20.6)																
Unknown	16	2	1	2	11																		29	7	4	3	15																
Total	921	91	62	139	629																		780	120	83	115	462																
In situ																																											
Mammographic features																						0.006																					0.564
Mass	13 (12.9)	1 (10)	0 (0)	3 (12.5)	9 (19.6)																		9 (40.9)	1 (50)	1 (16.7)	2 (50)	5 (50)																
Distortion	7 (6.9)	1 (10)	0 (0)	2 (8.3)	4 (8.7)																		1 (4.5)	0 (0)	0 (0)	1 (25)	0 (0)																
Calcification	72 (71.3)	5 (50)	21 (100)	17 (70.8)	29 (63)																		10 (45.5)	1 (50)	4 (66.7)	1 (25)	4 (40)																
Asymmetries	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)																		1 (4.5)	0 (0)	0 (0)	0 (0)	1 (10)																
Mass with calcifications	5 (5)	0 (0)	0 (0)	2 (8.3)	3 (6.5)																		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)																
Distortion with calcifications	3 (3)	2 (20)	0 (0)	0 (0)	1 (2.2)																		1 (4.5)	0 (0)	1 (16.7)	0 (0)	0 (0)																
Other	1 (1)	1 (10)	0 (0)	0 (0)	0 (0)																		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)																
Unknown	7	1	0	2	4																		3	1	0	0	2																
Total	108	11	21	26	50																		25	3	6	4	12																
Focalty																						0.795																					0.405
Unifocal	73 (68.2)	8 (72.7)	13 (61.9)	16 (64)	36 (72)																		16 (69.6)	2 (66.7)	2 (40)	3 (75)	9 (81.8)																
Multifocal and/or multicentric	34 (31.8)	3 (27.3)	8 (38.1)	9 (36)	14 (28)																		7 (30.4)	1 (33.3)	3 (60)	1 (25)	2 (18.2)																
Unknown	1	0	0	1	0																		2	0	1	0	1																
Total	108	11	21	26	50																		25	3	6	4	12																

TN = Triple-negative

Table 4. Mammographic findings according to phenotype, for different types of invasive interval cancers.

	True interval n (col%)						False negative n (col%)						Minimal-signs n (col%)					
	Total	TN	HER2	Luminal B	Luminal A	P-value	Total	TN	HER2	Luminal B	Luminal A	P-value	Total	TN	HER2	Luminal B	Luminal A	P-value
Mammographic features						0,004						0,626						0,350
Mass	230 (61,8)	55 (76,4)	30 (58,8)	30 (50,8)	115 (60,5)		97 (55,7)	8 (61,5)	6 (46,2)	18 (62,1)	65 (54,6)		81 (62,8)	17 (73,9)	7 (58,3)	8 (44,4)	49 (64,5)	
Distortion	43 (11,6)	1 (1,4)	3 (5,9)	7 (11,9)	32 (16,8)		23 (13,2)	2 (15,4)	0 (0)	4 (13,8)	17 (14,3)		9 (7)	0 (0)	0 (0)	2 (11,1)	7 (9,2)	
Calcification	21 (5,6)	3 (4,2)	8 (15,7)	6 (10,2)	4 (2,1)		6 (3,4)	0 (0)	1 (7,7)	0 (0)	5 (4,2)		4 (3,1)	1 (4,3)	1 (8,3)	0 (0)	2 (2,6)	
Asymmetries	37 (9,9)	6 (8,3)	5 (9,8)	8 (13,6)	18 (9,5)		10 (5,7)	0 (0)	0 (0)	1 (3,4)	9 (7,6)		13 (10,1)	2 (8,7)	0 (0)	3 (16,7)	8 (10,5)	
Masses with calcifications	19 (5,1)	4 (5,6)	2 (3,9)	4 (6,8)	9 (4,7)		28 (16,1)	2 (15,4)	5 (38,5)	5 (17,2)	16 (13,4)		10 (7,8)	1 (4,3)	3 (25)	3 (16,7)	3 (3,9)	
Distortion with calcifications	4 (1,1)	0 (0)	0 (0)	0 (0)	4 (2,1)		6 (3,4)	1 (7,7)	0 (0)	1 (3,4)	4 (3,4)		5 (3,9)	0 (0)	1 (8,3)	1 (5,6)	3 (3,9)	
Other	18 (4,8)	3 (4,2)	3 (5,9)	4 (6,8)	8 (4,2)		4 (2,3)	0 (0)	1 (7,7)	0 (0)	3 (2,5)		7 (5,4)	2 (8,7)	0 (0)	1 (5,6)	4 (5,3)	
Unknown	15	5	2	1	7		8	2	1	0	5		4	0	1	0	3	
Total	387	77	53	60	197		182	15	14	29	124		133	23	13	18	79	
Focality						0,335						0,018						0,452
Unifocal	295 (79,7)	61 (85,9)	41 (80,4)	48 (82,8)	145 (76,3)		142 (79,8)	14 (93,3)	9 (69,2)	17 (60,7)	102 (83,6)		96 (75,6)	18 (81,8)	7 (58,3)	13 (72,2)	58 (77,3)	
Multifocal and/or multicentric	75 (20,3)	10 (14,1)	10 (19,6)	10 (17,2)	45 (23,7)		36 (20,2)	1 (6,7)	4 (30,8)	11 (39,3)	20 (16,4)		31 (24,4)	4 (18,2)	5 (41,7)	5 (27,8)	17 (22,7)	
Unknown	17	6	2	2	7		4	0	1	1	2		6	1	1	0	4	
Total	387	77	53	60	197		182	15	14	29	124		133	23	13	18	79	

Occult tumors are not described because, by definition, there are no radiological features in mammogram

TN = Triple-negative

Figure 1. Tumors included and analyzed according to mode of detection and invasiveness.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Figure 2. Lymph node involvement according to tumor size and focality, for invasive (a) screen-detected and (b) interval cancers.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

P<0.001
P=0.899 p=0.070 p=0.014 p=0.603

■ Unifocal ■ Multifocal and/or multicentric

p=0.160
p=0.802 p=0.469 p=0.036 p=0.715

BREAST CANCER RESEARCH AND TREATMENT

Authorship/Disclosure Form

All necessary documentation must be submitted with the manuscript to avoid delays in publication. Manuscripts will not be accepted without the signed forms received.

MANUSCRIPT ID NUMBER IF AVAILABLE.

Mammographic and clinicopathological characteristics of screen-detected and interval

Article title (first few words)

First/Corresponding Author: ...Marisa Baré, MD, MPH, PhD.....

E-mail: mbare@tauli.cat.....

1. AUTHORSHIP

I, the undersigned author(s), certify that:

- I have seen and approved the final version of the manuscript, and all subsequent versions.
- I have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;
- I have drafted the article or revised it critically for important intellectual content.

I accept public responsibility for it, and believe it represents valid work. As an author of this article, I certify that none of the material in the manuscript has been previously published, nor is included in any other manuscript. I certify that this manuscript is not under consideration for publication elsewhere, nor has it been submitted or accepted in another publication in any form. The rights or interest in the manuscript have not been assigned to any third party.

Moreover, should the editors request the data upon which the manuscript is based, I shall produce it. I also certify that I have read and complied with the copyright information, as found on the *BREAST CANCER RESEARCH AND TREATMENT* home page website.

After submission of this agreement signed by all authors, changes of authorship or in the order of the authors listed will not be accepted.

2. FINANCIAL DISCLOSURE/CONFLICT OF INTEREST

It is the policy of *Breast Cancer Research and Treatment* to ensure balance, independence, objectivity, and scientific rigor in the Journal. All authors are expected to disclose to the readers any real or apparent conflict(s) of interest that may have a direct bearing on the subject matter of the article.

This pertains to relationships with pharmaceutical companies, biomedical device manufacturers or other corporation whose products or services may be related to the subject matter of the article or who have sponsored the study.

The intent of the policy is not to prevent authors with a potential conflict of interest from publication. It is merely intended that any potential conflict should be identified openly so that the readers may form their own judgments about the article with the full disclosure of the facts.

Please ensure that all and any disclosures/conflicts, are listed below and included within the manuscript. If no conflicts exist, please state: "Disclosures: None". Disclosures should be added in a separate section before the Reference list.

By checking the box next to my signature, I certify that:

- all financial support or benefits received by me, by any member of my immediate family, or any individual or entity with whom or with which I have a significant relationship from any commercial source related directly or indirectly to the scientific work reported in the article have been disclosed and have been included in the submitted manuscript.
- neither I, nor any member of my immediate family, nor any individual or entity with whom or with which I have a significant relationship has a financial interest in the subject matter discussed in the manuscript, except as disclosed. (I understand an example of such a financial interest would be a stock interest in any business entity which is included in the subject matter of the manuscript or which sells a product relating to the subject matter of the manuscript.)
- all funding sources supporting the work and all institutional or corporate affiliations are acknowledged in a footnote.
- I have had full access to all the data in the study (if applicable) and thereby accept full responsibility for the integrity of the data and the accuracy of the data analysis.

MANUSCRIPT ID NUMBER _____

Completed forms must be scanned and included as a PDF file as part of the online submission process.

Author 1 (printed name): Marisa Baré

☐ Remuneration	Entity: _____
☐ Consultant/advisory role:	Entity: _____
☐ Stock ownership	Entity: _____
☐ Funding	Entity: _____

☐ Signature: _____ Date: June 19th 2015

Author 2 (printed name): Núria Torà

☐ Remuneration	Entity: _____
☐ Consultant/advisory role:	Entity: _____
☐ Stock ownership	Entity: _____
☐ Funding	Entity: _____

☐ Signature: _____ Date: June 19th 2015

Author 3 (printed name): Dolores Salas

☐ Remuneration	Entity: _____
☐ Consultant/advisory role:	Entity: _____
☐ Stock ownership	Entity: _____
☐ Funding	Entity: _____

☐ Signature: _____ Date: June 19th 2015

Author 4 (printed name): Melchor Sentis

☐ Remuneration	Entity: _____
☐ Consultant/advisory role:	Entity: _____
☐ Stock ownership	Entity: _____
☐ Funding	Entity: _____

☐ Signature: _____ Date: June 19th 2015

Author 5 (printed name): Joana Ferrer

☐ Remuneration	Entity: _____
☐ Consultant/advisory role:	Entity: _____
☐ Stock ownership	Entity: _____
☐ Funding	Entity: _____

☐ Signature: _____ Date: June 19th 2015

Author 6 (printed name): Josefa Ibáñez

☐ Remuneration	Entity: _____
☐ Consultant/advisory role:	Entity: _____
☐ Stock ownership	Entity: _____
☐ Funding	Entity: _____

☐ Signature: _____ Date: June 19th 2015

Author 7 (printed name): Raquel Zubizarreta

☐ Remuneration	Entity: _____
☐ Consultant/advisory role:	Entity: _____
☐ Stock ownership	Entity: _____
☐ Funding	Entity: _____

☐ Signature: Date: June 19th 2015

Author 8 (printed name): Garbiñe Sarriugarte

☐ Remuneration	Entity: _____
☐ Consultant/advisory role:	Entity: _____
☐ Stock ownership	Entity: _____
☐ Funding	Entity: _____

☐ Signature: Date: June 19th 2015

Author 9 (printed name): Teresa Barata

☐ Remuneration	Entity: _____
☐ Consultant/advisory role:	Entity: _____
☐ Stock ownership	Entity: _____
☐ Funding	Entity: _____

☐ Signature: Date: June 19th 2015

Author 10 (printed name): Laila Domingo

☐ Remuneration	Entity: _____
☐ Consultant/advisory role:	Entity: _____
☐ Stock ownership	Entity: _____
☐ Funding	Entity: _____

☐ Signature: Date: June 19th 2015

Author 11 (printed name): Xavier Castellis

☐ Remuneration	Entity: _____
☐ Consultant/advisory role:	Entity: _____
☐ Stock ownership	Entity: _____
☐ Funding	Entity: _____

☐ Signature: Date: June 19th 2015

Author 12 (printed name): Maria Sala

☐ Remuneration	Entity: _____
☐ Consultant/advisory role:	Entity: _____
☐ Stock ownership	Entity: _____
☐ Funding	Entity: _____

☐ Signature: Date: June 19th 2015