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The association of breast density with clinicopathological characteristics and survival in patients with early stage ER+ HER2- lobular breast cancer

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Introduction

Breast density (BD) is typically identified and measured via radiological imaging**.** There are different classifications of breast density based on their appearance on mammogram. Fibroglandular tissue is radiographically dense and fat tissue is radiolucent. **BI-RADS** lexicon is the most reproducible visual assessment method. It is a dynamic marker impacted by factors such as - but not limited to - age, parity, hormone therapy, nutrition, family history and obesity. Higher BD is a known breast cancer risk factor, not only due to reduced screening sensitivity but also because of biological processes. Dense breast tissue contains higher density of stroma and epithelium. A dense breast is characterized by higher deposition of dense collagen fibers by fibroblast in association or not with proliferative epithelial changes in the breast parenchyma. Breast cancer reaserch is mainly histo-type agnostic and receptor-status centered, neglecting the pivotal underlying biological differences between invasive breast cancer of no special type (IBC-NST) and invasive lobular carcinoma (ILC). Given that interactions with the tumor microenvironment (TME) are particularly pronounced in ILC, further investigation into the role of breast density in this specific subtype is needed.

Objective

To investigate the association between breast density (BD) and clinicopathological characteristics as well as survival outcomes in patients with early-stage ER+/HER2− invasive lobular carcinoma (ILC).

Methods

- Retrospective analysis
- Patients diagnosed with pure early ILC at University Hospitals of Leuven between 01/2000-12/2020
- BI-RADS 5th edition scoring was used:
  - A) the breast is almost entirely fatty
  - B) there are scattered areas of fibroglandular density
  - C) the breasts are heterogeneously dense
  - D) the breasts are extremely dense

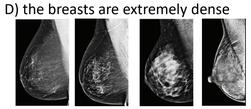


Figure 1. Breast density by BIRADS 5th edition, from A to D .

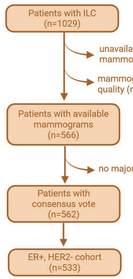
- All mammograms were independently re-evaluated by 5 different radiologists from Belgium and France. Final score was based on the majority vote. Cases lacking a majority vote were excluded.
- Survival data were collected until 10/2025
- Concordance analysis for density scoring between the different radiologists was performed using Krippendorff's α and Weighted Cohen's κ
- Multinomial logistic regression and Cox regression were employed to evaluate the associations of BD scoring (B/C vs. A, and D vs. A) with clinic-pathological characteristics and survival in the ER+/HER2- cohort. The characteristics include age, parity, BMI, tumor grade, tumor size, focality, nodal status and radio- and chemotherapy.

Results

- Our database included 1029 patients
- Of 566 patients mammograms were available
- For 562 patients consensus votes were assigned
- Of which 533 patients had ER+/HER2- ILC

- Concordance analysis between 5 radiologists:
  - Krippendorff's α = 0.71
  - Weighted Cohen's κ = 0.71

- ER+, HER2- cohort:
  - BI-RADS A 6.4%
  - BI-RADS B 37.1%
  - BI-RADS C 47.7 %
  - BI-RADS D 8.8%



- Patient and tumor characteristics are summarized in Table 1.

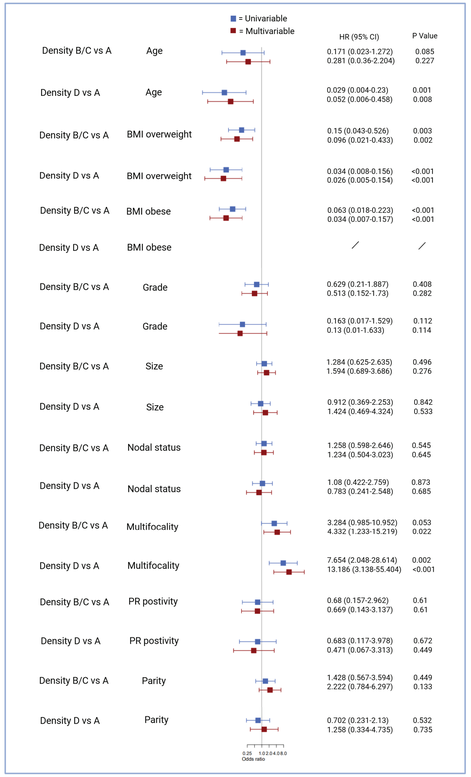
	ER+,HER2- cohort (n= 533)
Menopausal status at diagnosis – n (%)	
-Pre/perimenopausal	115 (22)
-Postmenopausal	396 (74)
-Unknown	22 (4)
BMI (kg/m²)	
-Underweight	12 (2)
-Lean	252 (47)
-Overweight	181 (34)
-Obesity	86 (17)
Age – median (years)	61
Size – n (%)	
-T1a/b	48 (9)
-T1c	131 (25)
-T2	229 (43)
-T3	122 (23)
-T4b	3 (2)
Nodal status – n (%)	
-N0	333 (63)
-N1-3	151 (28)
-N≥4	47 (9)
-Unknown	2 (0.4)
Grade	
-G I	6 (1)
-G II	503 (90)
-G III	52 (9)
-Unknown	1(0.1)
PR status – n (%)	
-Negative	45 (8.4)
-Positive	470 (88.2)
-Unknown	18 (3.4)
Multifocality – n (%)	132 (25)
Adjuvant Radiotherapy - n (%)	450 (84)
Adjuvant Chemotherapy - n (%)	115 (22)
Adjuvant Endocrine Treatment - n (%)	527 (99)
Parity – n (%)	
-Nulliparous	76 (14)
-Parous	457 (86)

Table 1. Patient and tumor characteristics of ER+, HER2- cohort . *Underweight (BMI ≤18,5 kg/m2). Lean (BMI > 18.5 kg/m2 and < 25 kg/m2). Overweight (BMI ≥ 25 kg/m2 and < 30 kg/m2). Obesity (BMI ≥30kg/m2)*

Associations with Clinicopathological characteristics

- We observe a significant association between higher breast density and (*= significant):
  - Lower age (*D vs A)
  - Less overweight and obese patients (*D vs A and *B/C vs A)
  - Lower grade (trend, not significant)
  - More multifocality (*D vs A and *B/C vs A)

Figure 1. Uni- and multivariable logistic regression for the association of density with clinicopathological characteristics



Survival Analysis

- Median followup in the ER+/HER2- cohort is 9.57 years.
- Higher breast density is associated with a better **DFS** in the univariable analysis D vs A and B/C vs A
- Higher breast density is associated with a better **OS** in the uni- and multivariable model when comparing B/C vs A and in the univariable model when comparing D vs A

Figure 3. Kaplan Meier curves of OS by density category

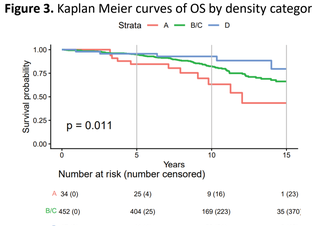
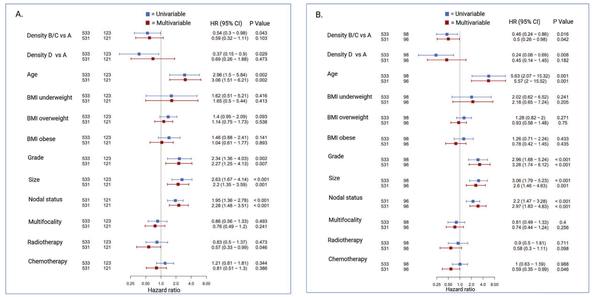


Figure 2. Uni- and multivariable logistic regression for the association of density with DFS (A) and OS (B)



Discussion

To our knowledge, this is the first cohort studying the association of breast density with clinicopathological characteristics, and survival specifically within a cohort of patients with invasive lobular carcinoma. Previous histo-type agnostic studies showed inconsistent and conflicting results. Some observed a better overall survival[1,2], whereas others found either no significant association between density and survival or a worse survival in dense breasts[3,4]. Importantly, none of these studies conducted subgroup analysis based on histological subtype. Gierach *et al* adjusted for histological subtype and reported that lower breast density was associated with improved survival only in cases where the tumor measured at least 2 cm or the patient was obese[5].

Conclusions

In ER+ HER2- ILC, higher breast density is associated with younger age, lower BMI and more multifocality, and our data suggests a potential link with lower tumor grade. Higher density was associated with better OS and DFS. These results highlight the need for further research into the biological mechanisms underlying these associations.

References

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