Obesity and menopausal status impact the features and molecular phenotype of invasive lobular breast cancer

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Abstract
Purpose We investigated the relationship between obesity, menopausal status, and invasive lobular carcinoma (ILC), the second most common histological subtype of breast cancer. Specifically, we evaluated the association between body mass index (BMI), metabolic syndrome, the 21-gene Oncotype Recurrence Score (Oncotype RS), and pathological features in patients with hormone receptor (HR)-positive, human epidermal growth factor receptor-2-negative ILC.

Methods The study cohort included 491 patients from a prospectively maintained institutional database consisting of patients with stage I-III, HR-positive ILC who underwent surgical treatment between 1996 and 2019.

Results Contrary to our expectations, we found that lower BMI was significantly associated with having higher Oncotype RS (18.9% versus 4.8%, p = 0.028) in post-menopausal patients, but was not related to tumor characteristics in pre-menopausal patients. Multivariate network analyses suggested a strong relationship between post-menopausal status itself and tumor characteristics, with lesser influence of BMI.

Conclusion These findings provide further insight into the recently appreciated heterogeneity within ILC and support the need for further investigation into the drivers of this disease and tailored treatment strategies.

Keywords Invasive lobular carcinoma · Metabolic syndrome · Oncotype RS · Menopausal status · BMI

Abbreviations
BMI Body Mass Index
ER Estrogen Receptor
HER2 Human Epidermal Growth Factor Receptor-2
HR Hormone Receptor
IDC Invasive Ductal Carcinoma
ILC Invasive Lobular Carcinoma
LASSO Least Absolute Shrinkage and Selection Operator
PR Progesterone Receptor
RS Recurrence Score

Introduction
Invasive lobular carcinoma (ILC) is the second most common histological subtype of breast cancer, accounting for 10%–15% of all invasive breast tumors [1]. ILC, of which the majority are estrogen receptor (ER) positive, appears to be particularly hormonally driven, as it is more strongly associated with early menarche, late menopause, and hormone replacement therapy use compared to invasive ductal carcinoma (IDC) [2–5]. Interestingly, as the rate of obesity has increased, the incidence of ILC among post-menopausal women has also increased, while that of invasive ductal carcinoma has remained stable [6].

While the complex relationship between obesity and breast cancer has been well studied, it remains incompletely understood. Obesity at breast cancer diagnosis has been shown to confer worse disease-free survival and overall survival in all breast cancer subtypes [7]. More specifically,
increased adiposity has been implicated in breast cancer development in post-menopausal women and is associated with increased recurrence risk and mortality among patients with ER positive breast cancer [8–12]. These effects may be related to the production of estrogen and other mitogens by adipocytes, along with inflammation, vascularity, and fibrosis that stimulate breast tumor growth [13, 14]. Additionally, insulin resistance and systemic inflammation associated with obesity are thought to create a pro-tumoral environment, and indeed those with metabolic dysregulation described as the metabolic syndrome have been shown to have higher risk of breast cancer development [15]. Conversely, some studies find a protective effect of obesity on the risk of breast cancer development in pre-menopausal women, suggesting that the relationship between obesity and breast cancer differs by menopausal status [16]. In addition to impacting the risk of breast cancer development or recurrence, one study showed that obesity may be associated with different biological characteristics of ILC. Robinson et al. found that among 76 women with ILC, those with metabolic syndrome were significantly more likely to have high risk tumors as determined by the 70-gene signature MammaPrint score compared to those without metabolic syndrome [17]. Given that the development of ILC may be particularly tied to hormonal exposure, we aimed to evaluate associations between body mass index (BMI), metabolic syndrome, and ILC histopathological features in pre- versus post-menopausal women with early stage ILC. Additionally, we explored whether BMI and metabolic syndrome were associated with the 21-gene recurrence score (Oncotype RS) in a subset of patients with available scores.

Methods

Following Institutional Review Board approval (17-23655, January 16, 2020), we retrospectively evaluated a prospectively maintained ILC database containing treatment and outcomes data for patients undergoing surgery at the University of California, San Francisco between January 1996 and September 2019. We included patients with stage I-III disease, and hormone receptor (HR) positive tumors. HR positivity was defined as having ≥1% either estrogen receptor (ER) or progesterone receptor (PR) staining on immunohistochemistry. ER and PR gene expression levels were also analyzed as continuous variables when data were available. We excluded cases with mixed ILC/IDC histology, human epidermal growth factor receptor-2 (HER2) overexpressing disease, and cases with missing BMI or menopausal status at the time of diagnosis. Histologic subtype was determined from review of surgical pathology reports, with ductal versus lobular histology determined with standard hematoxylin–eosin staining and selective use of E-cadherin staining. BMI was calculated as (weight kg)/((height m)^2) and categorized according to the World Health Organization classification (normal: < 25 kg/m^2; overweight: 25–30 kg/m^2; obese: ≥ 30 kg/m^2). Metabolic syndrome was defined as having any 3 of the following 5 factors: obesity, hypertension, hypercholesterolemia, hypertriglyceridemia, and/or diabetes mellitus, as determined by recorded diagnosis or abnormal lab values in the electronic medical record [17]. Menopausal status at the time of breast cancer diagnosis was ascertained from review of surgical pathology reports, with ductal versus lobular histology determined with standard hematoxylin–eosin staining and selective use of E-cadherin staining.
105 (21.9%) having hypercholesterolemia, 56 (11.7%) having high triglycerides, 181 (37.1%) having hypertension and 46 (9.6%) having diabetes mellitus. As expected, post-menopausal patients were significantly older (mean age 64.9 years versus 48 years, \( p < 0.0001 \)), were more likely to have a BMI above 25 (53.4% versus 40.0%, \( p = 0.017 \)), and had higher rates of metabolic syndrome (21.7% versus 6.7%, \( p < 0.001 \)) compared to pre-menopausal patients.

Most cases were stage I (\( n = 315, 65.1\% \)), with 105 (21.7%) being stage II and 64 (13.2%) being stage III. Most tumors were grade 2 (\( n = 316, 65.7\% \)), with 30.1% of patients having grade 1 and 4.2% having grade 3 disease. Tumor receptor subtype was ER positive/PR positive in 79.7%, with the remaining being ER positive/PR negative.

Of the 143 patients who had tumor profiling with Oncotype RS, 100 tumors (69.9%) were intermediate risk, 31 (21.7%) were low risk, and 12 (8.4%) were high risk (Table 2).

### Tumor characteristics

There was no significant difference in tumor grade or stage by menopausal status; however, there was a significant difference in tumor receptor subtype. Post-menopausal women were significantly more likely to have ER positive/PR negative ILC versus ER positive/PR positive ILC compared to pre-menopausal women (25.1% versus 9.7%, \( p < 0.001 \)).

Overall, we found no significant association between BMI and tumor receptor subtype. However, among the non-obese group (BMI < 25 kg/m²), post-menopausal patients were significantly more likely to have ER positive/PR negative tumors compared to pre-menopausal patients (27.6% versus

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**Table 1** Patient characteristics

| Characteristics                  | Overall (\( n = 491 \)) | Pre-menopausal (\( n = 150 \)) | Post-menopausal (\( n = 341 \)) | \( P \) Value |
|----------------------------------|--------------------------|---------------------------------|---------------------------------|--------------|
| Age, mean (SD)                   | 59.8 (11.6)              | 48 (5.5)                        | 64.9 (9.7)                      | <0.0001      |
| Body mass index (BMI)            |                          |                                 |                                 | 0.016        |
| Normal weight                    | 249 (50.7)               | 90 (60.0)                       | 159 (46.6)                      |              |
| Overweight                       | 145 (29.5)               | 39 (26.0)                       | 106 (31.1)                      |              |
| Obese                            | 97 (19.8)                | 21 (14.0)                       | 76 (22.3)                       |              |
| Metabolic syndrome present       | 84 (17.1)                | 10 (6.7)                        | 74 (21.7)                       | <0.001       |
| ILC grade \(^a\)                 |                          |                                 |                                 | 0.315        |
| 1                                | 145 (30.1)               | 51 (34.9)                       | 94 (28.1)                       |              |
| 2                                | 316 (65.7)               | 89 (61.0)                       | 227 (67.8)                      |              |
| 3                                | 20 (4.2)                 | 6 (4.1)                         | 14 (4.2)                        |              |
| Hormone receptor subtype \(^b\)  |                          |                                 |                                 | <0.001       |
| ER+/PR+                          | 373 (79.7)               | 131 (90.3)                      | 242 (74.9)                      |              |
| ER+/PR-                          | 95 (20.3)                | 14 (9.7)                        | 81 (25.1)                       |              |
| ILC stage \(^c\)                 |                          |                                 |                                 | 0.059        |
| I                                | 315 (65.1)               | 87 (58.4)                       | 228 (68.1)                      |              |
| II                               | 105 (21.7)               | 42 (28.2)                       | 63 (18.8)                       |              |
| III                              | 64 (13.2)                | 20 (13.4)                       | 43 (13.1)                       |              |

Data are expressed as n (%) unless otherwise specified. Total \( n = 491 \) unless otherwise specified. ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor.

\(^a\)Data available for 481

\(^b\)Data available for 468

\(^c\)Data available for 484
10.4%, $p < 0.001$). Among those with obesity, menopausal status was not associated with tumor receptor subtype.

There was no association between metabolic syndrome and tumor receptor subtype. However, those with metabolic syndrome were significantly more likely to have grade 3 tumors than those without metabolic syndrome, although grade 3 disease was uncommon overall (9.5% versus 3% grade 3, respectively, $p = 0.005$).

### Oncotype recurrence score

Of the 491 patients in the cohort, 143 (29%) had Oncotype RS available for analysis. Mean RS was significantly higher in post-menopausal women than pre-menopausal women (RS of 16.7 versus 13.8, $p = 0.006$). Overall, BMI was not associated with Oncotype RS category. However, the distribution of Oncotype RS varied significantly when both BMI and menopausal status were considered (Fig. 2). Among those with normal weight, post-menopausal patients were significantly more likely to have high RS tumors than pre-menopausal patients (18.9% versus 4.8%, $p = 0.028$). Among those with overweight/obesity, there was no significant association between menopausal status and RS category.

Similarly, the relationship between Oncotype RS and metabolic status was seen among post-menopausal patients only. In the post-menopausal cohort, mean RS was significantly lower in those with metabolic syndrome compared to those without metabolic syndrome (mean RS 13.6 versus 17.6, $p = 0.0297$). There was no significant association

#### Table 2  Census of patients with Oncotype Recurrence Score (RS) by BMI and menopausal status

| Categories                          | Overall | Pre-menopausal | Post-menopausal | $P$ Value |
|-------------------------------------|---------|----------------|-----------------|-----------|
| Mean RS (SD) ($n = 143$)            | 15.4 (6.5) | 13.8 (5.9)     | 16.7 (6.7)      | 0.006     |
| Patients with BMI < 25 ($n = 79$)   | 14 (17.7) | 11 (26.2)      | 3 (8.1)         | 0.028     |
| Low risk RS                         | 56 (70.9) | 29 (69.1)      | 27 (73.0)       |           |
| Intermediate risk RS                | 9 (11.4)  | 2 (4.7)        | 7 (18.9)        |           |
| High risk RS                        | 17 (26.6) | 6 (27.3)       | 11 (26.2)       | 0.714     |
| Patients with BMI > 25 ($n = 64$)   | 44 (68.8) | 16 (72.7)      | 28 (66.7)       |           |
| Low risk RS                         | 4 (6.6)   | 0 (0.0)        | 3 (7.1)         |           |
| Intermediate risk RS                | 3 (4.6)   |                |                |           |

Oncotype RS risk categories defined as: low < 11; intermediate 11–25; high > 25. Data are expressed as $n$ (%) unless otherwise specified.

![Network analysis with solid lines indicating a positive relationship and dashed lines indicating a negative relationship. Thicker lines and darker gradient designate stronger relationships. ER estrogen receptor, PR progesterone receptor, RS recurrence score](./Network_analysis.png)
between metabolic syndrome and RS among pre-menopausal patients in this cohort.

**Multivariate network analysis**

To understand the relationships between these multiple co-occurring variables, we utilized multivariate network analysis including continuous ER score, continuous PR score, Oncotype RS (high versus intermediate/low), BMI (< 25 versus ≥ 25), and menopausal status. In this network (Fig. 3), the strongest relationships were noted between Oncotype RS and both ER score and PR score, and between ER score, Oncotype RS, and menopausal status. Higher ER score and higher PR score were strongly related to intermediate/low Oncotype RS. Being post-menopausal was related to having a high Oncotype RS. Additionally, being post-menopausal was strongly related to having BMI ≥ 25 and with having higher ER score, while it was weakly related to having lower PR score. Those with normal BMI were strongly correlated with having pre-menopausal status. Normal BMI was weakly related to both lower PR score and high Oncotype scores. Overall in this network, menopausal status and ER score had the greatest impact on relationships between variables, while BMI category and PR score had the least impact.

**Discussion**

In this study of women with ER positive, HER2 negative, pure ILC, we found that BMI and metabolic syndrome impact ILC tumor biology as determined by histological grade, tumor receptor subtype, and Oncotype RS. These relationships, however, differ by menopausal status. Among non-obese patients, ER positive/PR negative tumors were significantly more common in post-menopausal versus pre-menopausal patients. However, among those with obesity, tumor receptor subtypes were similar by menopausal status. Interestingly, we found that post-menopausal patients had a significantly higher proportion of ER positive/PR negative tumors than pre-menopausal women, particularly among non-obese patients. Similarly, those with metabolic syndrome had a higher proportion of higher-grade tumors in post-menopausal women.

Our findings highlight the complex relationships between obesity/metabolic syndrome and breast cancer tumor biology by menopausal status in ILC, a particularly hormonally driven tumor type. The multivariate network analysis we performed illustrates the complex interplay that these variables have on ILC tumor biology.

Prior studies have found that high BMI is associated with less aggressive tumor types in the post-menopausal setting, and more aggressive tumor types in the pre-menopausal setting [19, 20]. Consistent with this, we found that overweight/obese post-menopausal patients in our study had lower RS compared to post-menopausal patients with normal BMI. Others have suggested that post-menopausal women with breast cancer are more likely to develop PR negative tumors and that circulating levels of estrogen are protective against breast cancer development in obese post-menopausal patients [21, 22]. Our findings raise the possibility that the hormonal pathogenesis and estrogenic drive behind ILC differs by menopausal status, possibly due to more local production of estrogen from higher breast adiposity in post-menopausal women relative to the greater systemic ovarian production of estrogen in pre-menopausal women.

Others have shown that obesity and metabolic syndrome result in worse outcomes, potentially suggesting that these are associated with more aggressive tumor types. Additionally, metabolic syndrome has been shown to be associated with more aggressive ILC as determined by MammaPrint scores. While we did not find a significant association between metabolic syndrome and tumor type overall, surprisingly we found a significant association between metabolic syndrome and lower RS in the post-menopausal group. This finding is contradictory to prior work and could be related to differences in Oncotype versus MammaPrint, with PR expression being

**Fig. 3** Box plot of Oncotype RS by menopausal status and BMI. In pre-menopausal women, mean RS did not differ significantly by BMI category (13.6 in normal weight versus 14.1 in overweight/obese, p=0.76). However, in post-menopausal women, those with normal BMI had significantly higher RS than those with overweight/obesity (18.9 versus 14.8, p=0.0072). Normal weight is defined as BMI < 25 kg/m², while overweight/obese is BMI ≥ 25 kg/m².
between BMI and RS in ILC. The differential impact of genetics potentially supports the finding of a relationship being involved in endocrine resistance in ILC [25–27].

Although ER-negative ILC was uncommon, we found that patients with lower RS were more likely to express PR. While some prior commentary has suggested that ER-negative ILC is associated with lower RS, our finding that higher BMI was associated with higher RS is consistent with the recent evidence that the pathogenesis of ILC may differ by menopausal status. These findings support the recently appreciated heterogeneity within ILC and suggest that further investigation into the drivers of this disease and more tailored prevention and treatment strategies are needed.

Conclusions

Overall, our findings suggest that BMI and menopausal status impact tumor characteristics in ILC, raising the possibility that the pathogenesis of ILC may differ by menopausal status. These findings support the recently appreciated heterogeneity within ILC and suggest that further investigation into the drivers of this disease and more tailored prevention and treatment strategies are needed.

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Author contributions Conceptualization: HR, CB, and RM; Methodology: HR and RM; Formal analysis and investigation: AS and RM; Data curation: HR and AP; Writing—original draft preparation: HR; Writing—review and editing: HR, AS, MKA, KB, CD, CB, and RM; Visualization: KG, HR, and AS. All authors have read and agreed to the published version of the manuscript.

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Data availability The data supporting all tables in this published article are not publicly available to protect patient privacy, but can be accessed from the corresponding author on request. Data will be made available to authorized researchers who have obtained Institutional Review Board (IRB) approval from their own institution and from the University of California, San Francisco IRB.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the IRB of the University of California, San Francisco (17-23655, January 16, 2020).
Consent to participate  Informed consent requirement was waived by the IRB, as no subjects were contacted for this study.

Consent to publication  Consent for publication was waived by the IRB, as no subjects were contacted for this study.

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