Menopausal status impacts the relationship between body mass index and tumor characteristics in invasive lobular carcinoma of the breast

Harriet Rothschild¹, Kent Goodman², Christopher Benz¹,²,³, Rita A Mukhtar²
¹UCSF School of Medicine, ²UCSF Department of General Surgery, ³Buck Institute for Research on Aging

Background
- ILC is the second most common type of breast cancer and is primarily ER positive.
- ILC is more strongly associated with risk factors that modulate sex steroid hormones, including obesity and use of hormone replacement therapy.
- BMI and metabolic syndrome may impact the molecular characteristics of ILC.
- Metabolic syndrome (3 of 5): Obesity, Hypertension, Hypercholesterolemia, Hypertriglyceridemia, or Diabetes mellitus.

We evaluated the relationship between BMI, metabolic syndrome, and tumor characteristics by menopausal status in a single institution cohort of women with newly diagnosed ILC between 1996-2020.

Methods
- 734 Patients with ILC
- 544 patients left for analysis
- 143 patients with OncotypeDx RS

Excluded patients with mixed ILC/IDC histology (n=59), triple negative or Her2 positive (n=48), patients with missing data (n=83)

Results

Main Finding 1: Post-menopausal patients had different metabolic phenotypes and hormonal subtypes of ILC.

Overall post-menopausal patients had:
- BMI over 25 (53.4% versus 40.0%, p = 0.017)
- Higher rate of metabolic syndrome (21.7% versus 6.7%, p<0.001)
- More ER+/PR- (11.1% versus 14.9%, p<0.001), especially with normal BMI
- Higher Oncotype RS (16.7 versus 13.8, p=0.006)

Main Finding 2: Within the post-menopausal group, normal weight patient had more aggressive tumors.
- Post-menopausal normal weight patients had greater proportion of aggressive RS compared to post-menopausal overweight/obese patients (18.9% versus 4.6%, p=0.028).

Conclusions
- These post-menopausal RS and ER+/PR- findings are unexpected since obesity is associated with worse outcomes for breast cancer.
- Raises the possibility that the hormonal pathogenesis/estrogenic drive behind ILC differs in pre- vs post-menopausal women consistent with their different PR positivity rates.
- Could be due to the 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.

Table 1. Tumor receptor subtype stratified by menopausal status and BMI.

<table>
<thead>
<tr>
<th></th>
<th>Pre-menopausal</th>
<th>Post-menopausal</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER+/PR+</td>
<td>107 (70.9)</td>
<td>44 (29.1)</td>
<td>0.001*</td>
</tr>
<tr>
<td>ER+/PR-</td>
<td>79 (89.8)</td>
<td>9 (10.2)</td>
<td></td>
</tr>
<tr>
<td>Normal weight</td>
<td>33 (89.2)</td>
<td>4 (10.8)</td>
<td>0.067*</td>
</tr>
<tr>
<td>Overweight</td>
<td>19 (95)</td>
<td>1 (5)</td>
<td>0.191</td>
</tr>
<tr>
<td>Obese</td>
<td>61 (83.6)</td>
<td>12 (16.4)</td>
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Figure 1. Consort diagram of case selection.

Figure 2. Oncotype score by menopausal status and BMI.

Figure 3. Simplified schematic of ILC development by BMI.

Contact: Harriet Rothschild (harriet.rothschild@ucsf.edu)