The Obesity-Inflammation Connection: Implications for Breast Cancer

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Obesity Trends* Among U.S. Adults in 1990, 2000 and 2010

*BMI ≥ 30
Summary of Mortality from Cancer According to BMI for U.S. Women in the Cancer Prevention Study II

Adapted from Calle EE et al. N Engl J Med 2003;348:1625-38

Obesity and Breast Cancer

- Risk factor for development of hormone receptor-positive breast cancer in postmenopausal women.

- Poor prognostic factor for breast cancer patients.

- Altered levels of hormones (estrogen, insulin, IGF-1), adipokines (leptin, adiponectin) and pro-inflammatory mediators (TNFα, IL-1β, PGE₂) contribute to obesity-related breast carcinogenesis.
Obesity, Estrogen and Increased Risk of Postmenopausal Breast Cancer

- After menopause, peripheral aromatization of androgen precursors in adipose tissue is largely responsible for estrogen synthesis.

- Obesity causes inflammation in visceral and subcutaneous fat.

- Inflammatory mediators (PGE$_2$, TNF-α, IL-1β, IL-6) induce aromatase, the rate-limiting enzyme for estrogen biosynthesis.

- Direct link between obesity→breast inflammation→aromatase expression was previously unknown.
Obesity Causes An Inflammatory State

Adapted from Olefsky J & Glass C. Annu Rev Physiol 2010;72:219-246

Hypothesis

Obesity induced inflammation will be accompanied with increased levels of pro-inflammatory mediators (PGE$_2$, TNF-$\alpha$, IL-1$\beta$) leading, in turn, to elevated aromatase expression in breast tissue and visceral fat.
Preclinical Study To Investigate the Obesity → Inflammation → Aromatase Axis

Female C57BL/6J Mice (n=40)

4 weeks of age Ovariectomy (n=20)

10 weeks of low fat (10kcal%) or high fat (60kcal%) diet

Low Fat n=10
Low Fat Ovariectomy n=10
High Fat n=10
High Fat Ovariectomy n=10

Diet Induced Obesity Causes Inflammation in the Mammary Gland and Visceral Fat

Obesity is Associated with Increased Levels of Pro-inflammatory Mediators and Aromatase

Obesity Causes Inflammation and Increased Aromatase Levels in the MG and VF of *ob/ob* Mice

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>MG</th>
<th>Wild-type</th>
<th>ob/ob</th>
<th>P</th>
<th>VF</th>
<th>Wild-type</th>
<th>ob/ob</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory foci</td>
<td></td>
<td>0.8 (0.9, 2.6)</td>
<td>13.8 (8.5, 20.4)</td>
<td>&lt;0.001</td>
<td></td>
<td>0 (0.0, 10.9)</td>
<td>54.5 (25.5, 200)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relative TNF-α expression</td>
<td></td>
<td>0.9 (0.6, 4.9)</td>
<td>4.9 (0.7, 9.7)</td>
<td>0.007</td>
<td></td>
<td>1.0 (0.5, 2.8)</td>
<td>5.3 (0.6, 8.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Relative IL-1β expression</td>
<td></td>
<td>1.0 (0.4, 2.3)</td>
<td>2.9 (0.3, 9.7)</td>
<td>0.02</td>
<td></td>
<td>1.1 (0.03, 6.0)</td>
<td>5.7 (1.1, 7.6)</td>
<td>0.005</td>
</tr>
<tr>
<td>Relative Cox-2 expression</td>
<td></td>
<td>1.0 (0.4, 2.5)</td>
<td>3.5 (1.2, 5.7)</td>
<td>0.001</td>
<td></td>
<td>1.0 (0.4, 3.7)</td>
<td>2.2 (1.6, 4.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Relative aromatase expression</td>
<td></td>
<td>1.2 (0.2, 5.8)</td>
<td>6.1 (0.04, 7.6)</td>
<td>0.007</td>
<td></td>
<td>0.9 (0.4, 2.7)</td>
<td>1.8 (0.8, 6.8)</td>
<td>0.009</td>
</tr>
<tr>
<td>Aromatase activity</td>
<td></td>
<td>90 (66, 112)</td>
<td>210 (146, 278)</td>
<td>&lt;0.001</td>
<td></td>
<td>98 (87, 154)</td>
<td>272 (177, 365)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NOTE: Inflammatory foci number of inflammatory foci per cm² of tissue; real-time PCR was used to quantify relative TNF-α, IL-1β, Cox-2, and aromatase transcript levels; aromatase activity, femtomoles/pg protein/hour. Values are summarized in median (range). P values are based on Wilcoxon rank-sum test, n = 10/gp.
Saturated Fatty Acids Activate the TLR4→NF-κB Axis in Macrophages Leading to Induction of Aromatase

Objectives

• To determine if CLS of the breast (CLS-B) exist in women and correlate with BMI.

• To investigate if increased levels of pro-inflammatory mediators and aromatase are present in the breast tissue of obese women.
Study Design

• Normal breast white adipose tissue was obtained from 30 women who underwent surgery.

• Routine H&E staining and CD68 IHC was performed.

CLS-B are Common in the Breasts of Overweight and Obese Women

Increasing BMI is associated with increased breast inflammation.

Aromatase expression and activity correlate better with breast inflammation than BMI.
NF-κB Binding Activity is Increased in a/w Breast Inflammation

Levels of Pro-inflammatory Mediators are Increased in Inflamed Breast Tissue
EP₂ and EP₄ are Important for PGE₂-mediated Induction of Aromatase Transcription

PGE₂ Levels are Increased in Inflamed Breast Tissue and Correlate with Aromatase Expression and Activity
Conclusions

• Inflammation (CLS-B) occurs in the breast tissue of most overweight and obese women.

• In both obese women and experimental models of obesity, breast inflammation was paralleled by elevated levels of pro-inflammatory mediators (TNF-α, IL-1β, COX-2, PGE₂).

• In obesity, activation of the TLR4→NF-κB pathway in macrophages is likely to be responsible for increased production of pro-inflammatory mediators leading, in turn, to elevated aromatase expression and estrogen synthesis.

Conclusions

• The obesity→inflammation→aromatase axis may help to explain the link between obesity and the increased risk of hormone receptor-positive breast cancer in postmenopausal women.

• CLS-B may represent a biomarker of breast cancer risk or poor prognosis.

• Strategies (lifestyle, diet, pharmacological) that disrupt the obesity→inflammation axis may be useful for reducing the risk of breast cancer or its progression.
Paracrine Interactions Between Macrophages and Other Cell Types Establish an Inflammatory Milieu in Obese Breast Adipose Tissue


CR Reverses Obesity Induced MG Inflammation

Celecoxib Suppresses Levels of PGE$_2$ and Aromatase Activity in the MG of Obese Mice

Human Intervention Studies

Schema

N = 10

Pre-intervention visit: History/physical, EKG, baseline blood tests
Post-intervention visit: Urine, blood, stool collection

Blood, urine, stool collection

Celecoxib 200 mg BID

Abdominal fat pad biopsy
CONTRIBUTORS

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