Rapid Reductions in Breast Density Following Tamoxifen Therapy as Evaluated by Whole Breast Ultrasound Tomography

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No Disclosures
Is breast density a modifiable risk factor that may relate to breast cancer outcomes?
Changes in Breast Density (BD) with Tamoxifen: IBIS-1

## Change in BD after Tamoxifen and Breast Cancer Outcomes: Summary of Evidence

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Age (years)</th>
<th># Events</th>
<th>Association with change in percent density</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBIS-1 chemoprevention trial (UK/Finland) Cuzick et al. <em>JNCI</em> 2011</td>
<td>Incident cancer</td>
<td>30-70</td>
<td>123</td>
<td>≥ 10% reduction vs. 0% OR: 0.32 (CI: 0.14 - 0.72)</td>
</tr>
<tr>
<td>Seoul National University (Korea) Kim et al. <em>Breast Cancer Res</em> 2012</td>
<td>Recurrence</td>
<td>24-77</td>
<td>80</td>
<td>≥ 10% reduction vs. &lt; 0% HR: 0.44 (CI: 0.22 - 0.91)</td>
</tr>
<tr>
<td>National Cancer Center (Korea) Ko et al. <em>BCRT</em> 2013</td>
<td>Recurrence</td>
<td>25-78</td>
<td>67</td>
<td>Reduction in BI-RADS BD HR: 0.35 (0.17 – 0.68)</td>
</tr>
<tr>
<td>Karolinska Institute (Sweden) Li et al. <em>JCO</em> 2013</td>
<td>Death</td>
<td>50-74</td>
<td>121</td>
<td>Q4 vs. Q1 HR: 0.50 (CI: 0.23 - 1.09)</td>
</tr>
</tbody>
</table>

*These data suggest that change in BD with tamoxifen could be a “biosensor” of risk reduction and treatment response.*
What Is the Prognostic Significance of BD Change After Tamoxifen Initiation?

Kaiser Permanente Northwest Case-Control Study

- ER+ breast cancers (1990-2008) treated with tamoxifen, age: 32-87 years
  - Cases (N=97): breast cancer death
  - Controls (N=252): matched on age, stage, year of diagnosis, follow-up time

Nyante SJ,...Gierach GL. *JNCI* 2015
# Breast Density Decline Associated with Reduced Risk of Breast Cancer Death

<table>
<thead>
<tr>
<th>Change in % BD $^a$</th>
<th>Cases / Controls</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;-0.5</td>
<td>36/86</td>
<td>Ref.</td>
</tr>
<tr>
<td>-8.7 to -0.5</td>
<td>45/82</td>
<td>1.36 (0.79, 2.34)</td>
</tr>
<tr>
<td>&lt;=-8.7</td>
<td>16/84</td>
<td>0.44 (0.22, 0.88)</td>
</tr>
</tbody>
</table>

$P$-trend: 0.04

$^a$ Tertiles, based on the distribution of change in percent density among controls

Nyante SJ, ... Gierach GL. *JNCI* 2015; Mullooly M, ... Gierach GL. *J Clin Oncol* 2016
How early can tamoxifen-related declines in breast density be detected?
Patterns of Change in BD among Tamoxifen Users

- Most of the density decline occurred within 12 months

- BD measurement at single time-point following tamoxifen initiation may identify patients with substantial declines

Nyante SJ,...Gierach GL. CEBP 2016.
The Ultrasound Study of Tamoxifen

**Enroll**  Women prescribed tamoxifen for clinical indications (n=74)

Screen negative comparison group matched on age, race, menopausal status (n=150)

**Collect**  Risk factor data, biologic specimens (saliva, blood), mammograms

**Ultrasound tomography (UST)**

- No ionizing radiation
- Sound speed: measure of physical properties of breast tissue

Transitional Studies of UST Sound Speed Estimates as a Surrogate for BD

• Accuracy
  – Is UST sound speed measuring what we think it’s measuring?
  – Compare UST sound speed to traditional measures of BD from mammography
Baseline Sound Speed and % BD Are Positively Correlated

Transitional Studies of UST Sound Speed Estimates as a Surrogate for BD

- **Accuracy**
  - Is UST sound speed measuring what we think it’s measuring?
  - Compare UST sound speed to traditional measures of BD from mammography

- **Reproducibility**
  - What is the rater reliability of UST sound speed estimates as a surrogate for volumetric breast density?
  - Estimation of density change over brief intervals requires excellent precision
Design of the UST Reliability Study

- One experienced rater
- Five trained raters
- For second masked review, UST scans were randomly ordered
- Repeated sampling design required to calculate major sources of variance

Study population included women from The Ultrasound Study of Tamoxifen (N=22)

Baseline Scan

Follow-Up Scan (1-13 months later)

Endpoint: Change in Sound Speed

Khodr Z, ...Gierach GL. Med Phys 2015.
Results: Excellent Rater Reliability of UST Sound Speed Estimates of BD

<table>
<thead>
<tr>
<th>UST Measure</th>
<th>A) Percent Variation (%)</th>
<th>B) ICC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subject</td>
<td>Scan</td>
</tr>
<tr>
<td>Sound Speed</td>
<td>86.0</td>
<td>7.5</td>
</tr>
<tr>
<td>Change in Sound Speed</td>
<td>62.6</td>
<td>--</td>
</tr>
</tbody>
</table>

Results suggest that UST is a reliable tool for estimating breast density and sensitively detecting changes in its value within individuals over time.

Khodr Z, ...Gierach GL. Med Phys 2015.
Assessing Interval Changes in Volumetric BD with Ultrasound Tomography (UST)

Baseline  
1-3 mos  
4-6 mos  
12 mos

Tamoxifen start

Short-term Longitudinal Study with Biomarker Endpoint

Khodr Z, Gierach GL. *Med Phys* 2015
Why Are Tamoxifen-Associated Declines in BD Associated with Improved BC Outcomes?

• Tamoxifen thought to inhibit development of metastases by blocking estrogen signaling through ER
• Tamoxifen metabolites bind to ER more avidly than parent drug
• ~30% to 50% of tamoxifen recipients demonstrate a decline in BD
• Women who do not efficiently metabolize tamoxifen could fail to show a change in density

Mammographic Density as a Biosensor of Tamoxifen Effectiveness in Adjuvant Endocrine Treatment of Breast Cancer: Opportunities and Implications

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