Hormone Replacement Therapy and High S Phase in Breast Cancer

Melody A. Cobleigh, MD
Frances E. Norlock, DO, MPH
Denise M. Oleske, PhD
Alexander Starr, MD

Prolonged postmenopausal hormone replacement therapy (HRT) is associated with increased incidence of breast cancer and, paradoxically, reduced breast cancer mortality. The biological rationale for this discrepancy has not been explored.

Objective To compare the prognostic characteristics of cancers arising in women who have used HRT with those in women who never have used HRT.

Design Prospective cohort study from December 1989 to November 1996.

Setting Teaching hospital in a large midwestern metropolitan area.

Patients Cohort of 331 postmenopausal women who presented consecutively with 349 invasive breast cancers.

Main Outcome Measures Estrogen receptor (ER) status (ER positive vs ER negative) and S phase (low vs high) for current HRT users vs never users.

Results The frequency of high S-phase fraction among cancers in women who were using HRT was markedly increased compared with that in women who had never used HRT (adjusted odds ratio [OR], 2.82; 95% confidence interval [CI], 1.04-7.66). However, the greater frequency of high S-phase fraction was limited to women with ER-positive cancers (for HRT users vs never users, OR, 5.25; 95% CI, 1.36-20.28; for ER-negative cancers in HRT users vs never users, OR, 1.08; 95% CI, 0.20-5.86).

Conclusions Use of HRT appears to stimulate growth of ER-positive but not ER-negative breast cancer as measured by S-phase fraction. The prognostic significance of high S-phase fraction in current HRT users who have ER-positive tumors is unknown.

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Statistical Analysis
Bivariate comparisons were assessed using a Yates corrected chi-square test. Crude odds ratios were computed to represent the likelihood of high S phase relative to the hypothesized high risk of a prognostic factor (HRT use, tumor size > 2 cm, ER-negative status, PR-negative status, aneuploidy, and nodal involvement). Logistic regression analysis was used to determine the multivariate likelihood of high S phase among HRT users, adjusting for age at diagnosis, tumor size,

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ER and PR status, ploidy, and nodal status. Model fit was evaluated.\(^1\) Tetraploid tumors were excluded because of small numbers. Analyses were performed using SPSS/PC+ software, Version 5.0 (SPSS Inc, Chicago, Ill). Probability values are 2-tailed, with \(P<.05\).

**RESULTS**

There were 349 breast cancers among 331 women (bilatent cancers included 4 synchronous and 14 metachronous). There were 142 current HRT (40.7%), 165 never (47.3%), 38 prior (10.9%), and 4 tamoxifen users (1.1%). Prior and tamoxifen users were excluded because of their small numbers.

Current users were significantly younger (mean [SD] age, 57 [7] years) than never users (mean [SD], 62 [9] years; \(P<.001\)) and more likely to have high S-phase cancers and PR-positive status (TABLE 1). Controlling for age did not change the significance of these associations. Other prognostic factors did not vary with HRT use.

S phase was evaluated by ER status and HRT use. Estrogen receptor–positive cancers were affected by HRT; nearly half of current users had high S-phase cancers compared with only about a fifth of never users. Use of HRT did not affect the S phase of ER-negative cancers; the majority had a high S phase (TABLE 2).

Estrogen receptor–negative status, aneuploidy, and current use of HRT correlated significantly with high S phase in the regression analysis (TABLE 3). When sorted by receptor status, the model confirmed a significant association of current HRT use with high S phase in ER-positive cancers only. Current users with ER-positive cancers were 5 times more likely to have a high S phase than never users (TABLE 4).

**COMMENT**

In this study, ER-positive cancers were more likely to have a high S phase in current users of HRT. To our knowledge, this is the first report of such an association. This result was expected based on preclinical models. Estrogen causes proliferation of ER-positive but not ER-negative human breast cancer cells in vitro\(^4\) and in vivo.\(^5\)

High S phase was independently and significantly predictive of breast cancer recurrence in 8 trials of 9901 women, while 4 trials including 1044 women found no such evidence.\(^6\)-\(^17\) History of HRT use was not included in these models.

In a large database of 127 000 breast cancers, high S phase correlated with aneuploidy and ER-negative and PR-negative status (these results were not stratified by HRT use).\(^18\) Our results support and extend those observations and suggest that high S phase is also more common in ER-positive cancers among current HRT users.

Use of HRT has been correlated with low S phase\(^19\); however, the results of that study were not stratified by receptor status. Use of HRT was associated with low S phase in ER-positive cancers, but the analysis did not control for other variables that affect S phase, such as aneuploidy and nodal status.\(^20\)

Others have evaluated the relationship between HRT and ER status of primary cancers. Although occasional correlations have been described,\(^21\)-\(^24\) most studies found no significant differences in ER profiles between users and nonusers of HRT.\(^19\),\(^25\)-\(^30\) Our study supports this consensus.

Relationships between HRT use and other prognostic characteristics have been reported. Although trends toward smaller tumors, negative nodal findings, and diploid/tetraploid can-

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**Table 1.** Characteristics of Current and Never Users of Hormone Replacement Therapy*  

<table>
<thead>
<tr>
<th>Age at diagnosis, mean (SD), y (n = 307)</th>
<th>56.62 (6.9)</th>
<th>61.92 (9.0)</th>
<th>&lt;.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size, cm (n = 263)</td>
<td>76</td>
<td>81</td>
<td>.60</td>
</tr>
<tr>
<td>Nodal status (n = 263)</td>
<td>88</td>
<td>85</td>
<td>.73</td>
</tr>
<tr>
<td>S phase (n = 173)</td>
<td>37</td>
<td>27</td>
<td>.02</td>
</tr>
<tr>
<td>Aneuploidy (n = 193)</td>
<td>49</td>
<td>53</td>
<td>.08</td>
</tr>
<tr>
<td>Estrogen receptor status (n = 294)</td>
<td>96</td>
<td>114</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Progesterone receptor status (n = 283)</td>
<td>86</td>
<td>79</td>
<td>.05</td>
</tr>
</tbody>
</table>

*Data are number of subjects unless otherwise noted.*

**Table 2.** S-Phase Determinations by Hormone Replacement Therapy Use and Receptor Status  

<table>
<thead>
<tr>
<th>Estrogen Receptor-Positive Status (n = 104)</th>
<th>Estrogen Receptor-Negative Status (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High S Phase</td>
<td>Low S Phase</td>
</tr>
<tr>
<td>Current users, No.</td>
<td>24</td>
</tr>
<tr>
<td>Never users, No.</td>
<td>9</td>
</tr>
<tr>
<td>Odds ratio (95% confidence interval)</td>
<td>4.67 (1.72-12.68)</td>
</tr>
</tbody>
</table>
HRT USE AND BREAST CANCER

Table 3. Multiple Logistic Regression Model for Predicting High S Phase*  

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>0.98 (0.92-1.04)</td>
<td>.43</td>
</tr>
<tr>
<td>Tumor size, ≥2 vs &lt;2 cm</td>
<td>1.03 (0.40-2.66)</td>
<td>.95</td>
</tr>
<tr>
<td>Estrogen receptor status, negative vs positive</td>
<td>6.12 (2.16-17.35)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ploidy, aneuploid vs diploid</td>
<td>2.91 (1.11-7.67)</td>
<td>.03</td>
</tr>
<tr>
<td>Nodal status, positive vs negative</td>
<td>1.19 (0.42-3.36)</td>
<td>.74</td>
</tr>
<tr>
<td>Hormone replacement therapy use, current vs never</td>
<td>2.82 (1.04-7.66)</td>
<td>.04</td>
</tr>
</tbody>
</table>

*Variables were considered and controlled for simultaneously (n = 107). CI indicates confidence interval.

Table 4. Multiple Logistic Regression Model for Predicting High S Phase Among Estrogen Receptor–Positive Patients Only*  

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>0.95 (0.88-1.04)</td>
<td>.25</td>
</tr>
<tr>
<td>Tumor size, ≥2 vs &lt;2 cm</td>
<td>0.68 (0.22-2.11)</td>
<td>.51</td>
</tr>
<tr>
<td>Ploidy, aneuploid vs diploid</td>
<td>4.46 (1.38-14.41)</td>
<td>.01</td>
</tr>
<tr>
<td>Nodal status, positive vs negative</td>
<td>0.96 (0.26-3.56)</td>
<td>.95</td>
</tr>
<tr>
<td>Hormone replacement therapy use, current vs never</td>
<td>5.25 (1.36-20.28)</td>
<td>.02</td>
</tr>
</tbody>
</table>

*Variables were considered and controlled for simultaneously (n = 75). CI indicates confidence interval.

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REFERENCES