Short-term Cessation of Hormone Replacement Therapy and Improvement of Mammographic Specificity

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A recent study by Laya et al. (1), comparing 8779 current, never, and former users of hormone replacement therapy (HRT), found a significant reduction in both the sensitivity and the specificity of mammography associated with current hormone administration. An accompanying editorial (2) suggested that the effects of HRT should be reversible, since the specificity and sensitivity for former users were identical to those for never users.

HRT causes an increase in mammographic density in 17%–73% of women that may be diffuse, focal, or multifocal (3–6). While diffuse or multifocal changes are not worrisome, new or enlarging focal, circumscribed masses or developing densities can be a sign of early breast carcinoma and may prompt biopsy (7–11). Biologic data demonstrate rapidly reversible stimulatory effects of estrogens and progesterones on mammary cell proliferation, both during the menstrual cycle and in hormonally deprived women (12). Therefore, as a routine practice, we have attempted to reverse focal mammographic changes that may be hormone induced by empirically discontinuing HRT for 2 weeks prior to biopsy. Our data suggest that short-term HRT cessation can induce regression of hormone-induced mammographic changes, and unnecessary biopsy can be avoided.

The article by Laya et al. (1) and the accompanying editorial (2) prompted a retrospective search of our mammography database. During the period from January 1995 through December 1996, a total of 19069 patients had mammograms and 545 had biopsies. We identified 48 women who had a new or enlarging, circumscribed mass (20 patients) or a developing density (28 patients) while currently using HRT. These patients underwent HRT cessation for 10–30 days (mean, 15.4 days) and then had a repeat mammogram. If the abnormality regressed, biopsy was not performed. The patient resumed HRT and was advised to continue routine screening, although she was asked to discontinue HRT for 2 weeks prior to future mammograms. If the abnormality persisted and a corresponding simple cyst was not identified on ultrasound examination, biopsy was recommended. One of the 48 patients had follow-up studies at another institution, and the findings, therefore, were unavailable for review. All patients received HRT for at least 1 year before the mammogram in question and had at least one previous mammogram.

Abnormalities unrelated to hormone-induced changes, including spiculated or irregular masses, suspicious calcifications, and palpable masses, underwent prompt biopsy rather than a trial of HRT cessation. If a benign cyst was identified initially, routine follow-up was recommended rather than HRT cessation.

Thirty-five (74%) of the 47 assessable patients had an interval decrease or resolution of the mammographic abnormality following hormone cessation (Fig. 1; Table 1). Twenty-six (74%) of these 35 patients have had 6–24 months (mean, 12.3 months) of mammographic follow-up, with no evidence of carcinoma. The remaining patients have not yet had follow-up mammograms performed.

Of the 12 patients who exhibited no interval change in their mammographic abnormality following HRT cessation, four had subsequent sonograms that demonstrated a corresponding simple cyst. For the remaining eight patients, biopsy was recommended. Histologic examination showed invasive lobular carcinoma (n = 1) (Fig. 1), typical hyperplasia (n = 4), fibrosis (n = 1), and normal breast parenchyma (n = 1). One

Note

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patient elected to have a 6-month follow-up rather than a biopsy, and no change was noted on the subsequent mammogram.

This retrospective study provides suggestive evidence that short-term HRT cessation can induce regression of hormone-induced mammographic changes and may avoid unnecessary biopsy and improve mammographic specificity. Mammographic sensitivity may also be increased by use of this technique, provided false-negatives do not increase. Because new, focal mammographic densities are common in women on HRT (3, 5), these abnormalities may be dismissed as hormone-induced changes, even though such changes usually carry a 9%–11% risk of being carcinoma (9). Therefore, short-term HRT cessation may improve confidence that a persistent abnormality is of more concern than ones that regress.

One concern with this diagnostic strategy is the possibility that a carcinoma may also regress in response to HRT cessation. This possibility seems especially plausible for tumors that may be strongly hormone receptor positive. Notably, in one case report of a patient

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**Table 1.** Mammographic response to cessation of hormone replacement therapy (HRT) according to type of abnormality and HRT*

<table>
<thead>
<tr>
<th>Mammographic abnormality</th>
<th>HRT type</th>
<th>No. of patients with</th>
<th>Decrease or resolution</th>
<th>No change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developing density</td>
<td>Estrogen alone</td>
<td>11</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Estrogen + progesterone</td>
<td>12</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Circumscribed mass</td>
<td>Estrogen alone</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Estrogen + progesterone</td>
<td>7</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown†</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>35</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

*By use of Fisher’s exact test (two-tailed), no statistically significant differences were found between the types of mammographic abnormality (P = .18) or the types of HRT (P = .31).

†Patient who was participating in a double-blinded study of HRT.
with a spiculated mass that was shown by fine-needle aspiration to represent breast cancer, marked regression of the mass occurred after 5 weeks of hormone withdrawal (13). Biopsy of abnormalities not likely to be hormone induced should not be delayed by an initial trial of HRT cessation. In our series, the only cancer was hormone receptor positive, yet it did not change with 2 weeks of HRT cessation. Since we currently have 6–24 months of follow-up data for 26 patients, it is unlikely that these individuals harbor occult neoplasms. The cessation interval may be important, with the optimum yet unknown. However, since the breast responds to cyclic fluctuations with menses, cessation of HRT for more than 2 weeks should not be necessary.

This study does have limitations. Although mammograms were not interpreted in a blinded fashion, the study reflects routine standards of mammographic interpretation in a high volume center. In spite of its preliminary nature, the study provides a strong impetus to initiate a prospective trial of short-term HRT cessation. A randomized trial with continued HRT or placebo administered in a double-blinded fashion prior to biopsy would be optimal. This approach would allow for assessment of spontaneous regression, although such regression is uncommon in our experience with patients not using HRT.

References


Notes

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