Estrogen plus progestin increased risk for breast cancer in postmenopausal women


**Question**

In postmenopausal women, does estrogen-plus-progestin hormone therapy (HT) increase the risk for abnormal mammographic results and diseases of breast cancer?

**Design**

Randomized (allocation concealed*), blinded (clinicians, participants, data collectors, outcome assessors, and monitoring committee), placebo-controlled trial with a mean 5.6-year follow-up (Women’s Health Initiative [WHI]).

**Setting**

40 U.S. clinical centers.

**Participants**

16,608 postmenopausal women who were 50 to 79 years of age (mean age 63.3 y). Exclusion criteria were previous hysterectomy, breast cancer, or probable survival < 3 years. Follow-up data were available for 15,931 women (95.9%).

**Intervention**

Women were allocated to 1 daily tablet of conjugated equine estrogen, 0.625 mg, and medroxyprogesterone acetate, 2.5 mg (n = 8506), or placebo (n = 8102).

**Main Outcome Measures**

Incidence of breast cancer (total, invasive, and in situ) and abnormal mammography results.

**Main Results**

Analysis was by intention to treat. Women who received HT had a greater incidence of total and invasive breast cancer than did women who received placebo; in situ breast cancer cases were not increased (Table). The increase in invasive breast cancer with HT was seen across almost all risk categories. Invasive breast tumors were larger in the HT group (mean 1.7 cm vs 1.5 cm, *P* = 0.04) and were diagnosed at a more advanced stage (regional or metastatic, compared with local, 25% vs 16%, *P* = 0.04) than in the placebo group. Women who received HT also had a higher proportion of abnormal mammogram results. The difference was seen at 1 year (9.4% vs 5.4%, *P* < 0.001) and continued throughout the study (total study period 31.5% vs 21.2%, *P* < 0.001).

**Conclusion**

In postmenopausal women, estrogen plus progestin hormone therapy increased cases of total and invasive breast cancer and abnormal mammogram results.

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For correspondence: Dr. R.T. Chlebowski, Harbor-UCLA Research and Education Institute, Torrance, CA, USA. E-mail rchlebowski@rei.edu.

*See Glossary.

**Estrogen-plus-progestin hormone therapy (HT) vs placebo for incidence of breast cancer in postmenopausal women at mean 5.6 years†**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Cases of breast cancer</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All breast cancer</td>
<td>245</td>
<td>1.24 (1.02 to 1.50)</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>199</td>
<td>1.24 (1.01 to 1.54)</td>
</tr>
<tr>
<td>In situ breast cancer</td>
<td>47</td>
<td>1.18 (0.77 to 1.82)</td>
</tr>
</tbody>
</table>

†CI defined in Glossary.

**Commentary**

The study by Chlebowski and colleagues gives detailed information regarding breast cancer risk in late postmenopausal women using estrogen-plus-progestin HT. No increased risk for breast cancer death was reported in HT users, and the diagnosis of metastatic breast cancer was observed in 1% of HT users compared with 2% of placebo users. The authors emphasized that HT users had larger tumors than placebo users (0.2 cm larger with 10% greater node involvement [*P* ≤ 0.04]). The recently released Million Women Study [1] found that current HT therapy, particularly estrogen plus progestin, was associated with increased risk for breast cancer. However, past use was not associated with such risk. It is becoming clear that current estrogen-plus-progestin HT carries greater breast cancer risk than estrogen alone. Of note, the estrogen-only arm of the WHI is still ongoing.

Women and clinicians are receiving the message that HT increases breast cancer risk. Placing this in perspective for the menopausal woman (2) is important because there will continue to be women who want to use HT. In women with a uterus requiring progestin opposition, it is likely that less use of synthetic progestins and more use of localized vaginal-uterine preparations will occur, particularly if it is proven that estrogen alone is safer from the breast cancer perspective. Because HT users had a substantially greater risk for abnormal mammography results than placebo users (9.4% vs 5.4%, *P* < 0.001), should women on HT stop using it for 2 weeks before an annual mammogram? It has been suggested that short-term cessation of HT improves mammographic specificity (3). Although screening mammography is the current gold standard, a way to detect breast cancer before finding an abnormality on mammography is needed. Ductal lavage, recently approved by the Food and Drug Administration, can be used as a risk-assessment tool for women at high risk for breast cancer who have negative results on mammography. This may help menopausal women to make well-informed decisions regarding HT, the use of tamoxifen for breast cancer chemoprevention, and other decision options related to the breast (4).

Holly L. Thacker, MD
Cleveland Clinic Foundation
Cleveland, Ohio, USA

**References**