Menopausal Hormone Therapy Influence on Breast Cancer Outcomes in the Women’s Health Initiative

Rowan T. Chlebowski, MD, PhD; Aaron K. Aragaki, MS; and Garnet L. Anderson, PhD

Abstract
The Woman’s Health Initiative has conducted 2 full-scale, placebo-controlled clinical trials to determine the influence of menopausal therapy on breast cancer incidence and outcome. Estrogen plus progestin use in postmenopausal women with a uterus increases breast cancer incidence and deaths from breast cancer. Despite a short-term reduction in risk after stopping estrogen plus progestin use, an increase in breast cancer risk persists postintervention. Estrogen-alone use in postmenopausal women with prior hysterectomy reduces breast cancer incidence and reduces deaths from breast cancer. The reduced breast cancer risk persists for several years after stopping estrogen-alone use but is lost in late postintervention. These findings suggest recalibration of breast cancer risk and benefit consideration for both regimens, with estrogen plus progestin use associated with greater risk and estrogen-alone use associated with greater benefit. Use of either regimen in clinical practice requires careful consideration of all clinical risks and benefits. (J Natl Compr Canc Netw 2015;13:917–924)
event for medical conditions believed to be under potential hormone therapy influence also included stroke, pulmonary embolism, colorectal cancer, endometrial cancer (in the combined hormone therapy trial), hip fracture, and death. A comprehensive update of study findings was recently published.

The Estrogen Plus Progestin Trial

The estrogen plus progestin trial was stopped after 5.6 years median intervention when significantly more harm than benefit for estrogen plus progestin use was identified (Figure 1). Although a modest increase in breast cancer with combined hormone therapy was anticipated, other breast cancer findings differed substantially from expectations. During the initial years of follow-up, fewer breast cancers were seen in the estrogen plus progestin group, with the incidence curves crossing at approximately 3 years (Figure 2) and a statistically significant linear trend for increase seen during the intervention ($P=.01$). During the 5.6 years of intervention, estrogen plus progestin increased breast cancer risk by 24% ($P=.003$). In sensitivity analyses, which censored women 6 months after they became nonadherent, the breast cancer increase was 49% ($P<.001$). With additional post-intervention follow-up, deaths from breast cancer were also significantly increased (hazard ratio [HR], 1.96; 95% CI, 1.00–4.04; $P=.049$)(Table 1).

In contrast to most expectations, the increase in breast cancer was not limited to hormone receptor positive and lower-stage cancers. The tumors in the estrogen plus progestin group were larger and had more lymph node involvement. With cumulative follow-up, numerically more breast cancers in all

<table>
<thead>
<tr>
<th>Event</th>
<th>Median 5.6 y</th>
<th>Median 13 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>1.29 (1.02–1.63)</td>
<td>1.09 (0.96–1.24)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1.24 (1.01–1.53)</td>
<td>1.28 (1.11–1.48)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.41 (1.07–1.85)</td>
<td>1.16 (1.00–1.35)</td>
</tr>
<tr>
<td>PE</td>
<td>2.13 (1.39–3.25)</td>
<td>1.26 (1.00–1.59)</td>
</tr>
<tr>
<td>Endometrial</td>
<td>0.83 (0.47–1.47)</td>
<td>0.67 (0.49–0.91)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.63 (0.43–0.92)</td>
<td>0.80 (0.63–1.01)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.66 (0.45–0.98)</td>
<td>0.81 (0.68–0.97)</td>
</tr>
<tr>
<td>Global index</td>
<td>1.15 (1.03–1.28)</td>
<td>1.06 (1.00–1.13)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.97 (0.81–1.16)</td>
<td>0.99 (0.91–1.08)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Median 7.1 y</th>
<th>Median 13 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.91 (0.75–1.12)</td>
<td>0.94 (0.82–1.09)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>0.79 (0.61–1.02)</td>
<td>0.79 (0.65–0.97)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.39 (1.08–1.77)</td>
<td>1.15 (0.97–1.37)</td>
</tr>
<tr>
<td>PE</td>
<td>1.34 (0.87–2.06)</td>
<td>1.15 (0.87–1.51)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1.08 (0.75–1.55)</td>
<td>1.13 (0.85–1.51)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.61 (0.41–0.91)</td>
<td>0.91 (0.72–1.15)</td>
</tr>
<tr>
<td>Global index</td>
<td>1.01 (0.91–1.12)</td>
<td>1.02 (0.94–1.09)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.03 (0.93–1.13)</td>
<td>0.99 (0.90–1.10)</td>
</tr>
</tbody>
</table>
categories were seen in the estrogen plus progestin group, including estrogen receptor–positive, estrogen receptor–negative, HER2-positive, and triple-negative cancers (Table 2). Given the adverse effects on cancer size and lymph node status, the lower incidence seen in the first several years in the combined hormone therapy intervention group likely reflects diagnostic delay rather than actual reduction in risk.

During the trial, annual mammography and clinical breast examination were mandated, with study medication refill dependent on their completion. As a result, mammography adherence was high and closely comparable in the placebo and the estrogen plus progestin groups. During intervention, estrogen plus progestin increased the frequency of abnormal mammograms (35% vs 23%; \( P < .001 \)), interfered with breast cancer detection through adverse influence on receiver operating characteristics curves (\( P = .02 \)), and increased the risk of breast biopsies (10.0% vs 6.1%; \( P < .001 \)).

Although observational studies have generally reported no excess breast cancer risk associated with estrogen plus progestin use in obese and African American women, analyses in the WHI randomized trial evaluating estrogen plus progestin found no interaction with body mass index and race/ethnicity. Thus, no breast cancer safety has been established for estrogen plus progestin use in those 2 populations.

The increase in breast cancer risk persisting through 8 years of postintervention follow-up also suggests a potential influence of estrogen plus progestin on breast cancer development (Table 3). Although the increase in breast cancer risk emerged after approximately 3 years of intervention, because of the diagnostic delay, a safe interval for estrogen plus progestin use with respect to breast cancer risk cannot be determined. Because alternative imaging strategies are available with increased and/or differ-

### Table 1 Menopausal Hormone Therapy and Breast Cancer Outcomes in the Intervention Phase of the 2 Women’s Health Initiative Clinical Trials

<table>
<thead>
<tr>
<th>Category</th>
<th>Estrogen Plus Progestin</th>
<th>Estrogen Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>757</td>
<td>1.24 (1.01–1.53)</td>
</tr>
<tr>
<td>Deaths from breast cancer</td>
<td>37</td>
<td>1.96 (1.00–4.05)</td>
</tr>
<tr>
<td>Deaths after breast cancer</td>
<td>82</td>
<td>1.57 (1.01–2.48)</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>182</td>
<td>1.29 (0.83–2.02)</td>
</tr>
<tr>
<td>Benign proliferative breast disease</td>
<td>277</td>
<td>1.74 (1.35–2.25)</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; NS, not significant.
ential sensitivity compared with conventional mammography (ultrasound, tomosynthesis, MRI), future studies could explore the efficacy of these screening strategies on breast cancer stage in combination with hormone therapy users.

**Clinical Significance**

After reports of adverse effects of estrogen plus progestin in patients with breast cancer from the WHI and the Million Women Study, menopausal hormone therapy use rapidly and substantially declined in the United States, which was associated with the first decrease in breast cancer incidence in more than 20 years. This decrease was attributed to the declining use of menopausal hormone therapy. Subsequently, numerous reports attempting to link hormone therapy use, mammogram frequency, and breast cancer risk largely supported the original hypothesis.

Nonetheless, questions remained, including whether mammography use was changing during this period and whether such a rapid reduction in breast cancer risk was biologically feasible. To address these issues, Chlebowski et al examined the period immediately before and after when women in the estrogen plus progestin trial were instructed to stop their study pills. The sudden stopping of estrogen plus progestin use resulted in a complex influence on breast cancer incidence. Although mammography use remained closely comparable in both randomization groups, a rapid decrease in breast cancer incidence was seen within 2.5 years of postintervention follow-up. When fit as constant effects, the HRs are similar in the intervention and the early postintervention period (HR, 1.24 and 1.23, respectively; Table 3), but when modeled as time-dependent effects, the estrogen plus progestin HR increases throughout the intervention period and subsequently decreases during the postintervention period.

Based on both preclinical and clinical modeling, an estimated 94% of breast cancers diagnosed during the intervention period in the estrogen plus progestin trial are assumed to be preexisting at study entry despite the normal screening mammogram. Thus, the rapid decrease in breast cancer incidence likely represents preclinical cancers that are responding to the sudden change in reproductive hormone levels similar to that seen for oophorectomy or aromatase inhibitor use with established breast cancer.

However, with additional postintervention follow-up, a seemingly paradoxical situation arose. Despite the decreasing HR trend seen during the early postintervention period, the summary (constant) HR for estrogen plus progestin influence on breast cancer incidence remained increased and became significantly so when estimated for the entire postintervention period, and was comparable with the intervention period. A possible explanation would be that preclinical cancers present when the estrogen plus progestin ended responded and remained undetectable for approximately 2 years. Subsequently, perhaps either regrowth or resumed growth occurred. A plausible mechanism for the postintervention finding has been proposed, based on progestin stimulation of breast stem/progenitor cells.

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### Table 2 Breast Cancer in the Women’s Health Initiative Hormone Therapy Trials by Hormone Receptor and HER2 Status

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Estrogen + Progestin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>Estrogen Alone</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All invasive</td>
<td>385</td>
<td>293</td>
<td>1.25 (1.07–1.46)</td>
<td>151</td>
<td>199</td>
<td>0.77 (0.62–0.95)</td>
</tr>
<tr>
<td>ER-positive</td>
<td>308</td>
<td>230</td>
<td>1.27 (1.07–1.51)</td>
<td>110</td>
<td>149</td>
<td>0.75 (0.59–0.96)</td>
</tr>
<tr>
<td>ER-negative</td>
<td>48</td>
<td>33</td>
<td>1.40 (0.90–2.18)</td>
<td>25</td>
<td>31</td>
<td>0.81 (0.48–1.38)</td>
</tr>
<tr>
<td>PR-positive</td>
<td>262</td>
<td>194</td>
<td>1.29 (1.07–1.55)</td>
<td>92</td>
<td>112</td>
<td>0.84 (0.63–1.10)</td>
</tr>
<tr>
<td>PR-negative</td>
<td>86</td>
<td>62</td>
<td>1.31 (0.95–1.82)</td>
<td>41</td>
<td>63</td>
<td>0.66 (0.45–0.98)</td>
</tr>
<tr>
<td>Triple-negative</td>
<td>26</td>
<td>14</td>
<td>1.78 (0.93–3.41)</td>
<td>16</td>
<td>14</td>
<td>1.14 (0.56–2.34)</td>
</tr>
<tr>
<td>HER2-positive</td>
<td>54</td>
<td>26</td>
<td>2.00 (1.25–3.19)</td>
<td>23</td>
<td>16</td>
<td>1.50 (0.79–2.83)</td>
</tr>
<tr>
<td>HER2-negative</td>
<td>233</td>
<td>161</td>
<td>1.37 (1.12–1.68)</td>
<td>89</td>
<td>121</td>
<td>0.74 (0.56–0.97)</td>
</tr>
</tbody>
</table>

Abbreviations: ER, estrogen receptor; HR, hazard ratio; PR, progesterone receptor.
event, taken together, the findings indicate that a woman taking estrogen plus progestin for approximately 5 years will be at increased breast cancer risk for many years after discontinuation (Table 3).14

The WHI Observational Study: Estrogen Plus Progestin
Parallel studies were conducted in the WHI Observational Study cohort of more than 93,000 postmenopausal women.28 In the WHI Observational Study cohort, estrogen plus progestin use was also associated with a higher breast cancer risk (HR, 1.55; 95% CI, 1.41–1.70; P<.001), consistent with findings from the randomized trial.16

To reconcile differences in breast cancer characteristics seen between the WHI randomized clinical trial and most observational studies, roles for several potential confounding factors were identified, including absence of mammogram clearance before cohort entry and consideration of hysterectomy, bilateral oophorectomy, and especially prior hormone therapy use. As in many other cohorts, current hormone users were eligible for entry in the WHI observational study cohort. In analyses including the entire cohort, substantially more estrogen receptor–positive cancers were seen in combined hormone therapy users compared with nonusers, a finding similar to that seen in most observational studies. However, when analyses were limited to women who began estrogen plus progestin use only after entering the cohort, more aggressive breast cancers were seen in these women, a finding similar to that seen in the randomized trial.28 It is likely that including current hormone therapy users introduces potential confounding. A woman who has been on estrogen plus progestin for several years before entering a cohort has a “guarantee time” against development of aggressive breast cancer, because a breast cancer diagnosis would have precluded entry in the cohort. Thus, many observational studies have been unable to identify associations with estrogen plus progestin and aggressive hormones, because their analyses include women who were using hormones on cohort entry.

WHI: The Estrogen Alone Trial
In the WHI randomized trial evaluating estrogen alone in postmenopausal women with prior hysterectomy, intervention ended after 7.1 years (median) when stroke increase was observed with no overall clinical benefit, as reflected in the global index (Figure 1).12

During the intervention period, a trend was seen toward a lower breast cancer risk in the estrogen alone group.29 In contrast to the findings for estrogen plus progestin, estrogen alone did not significantly interfere with mammogram detection of breast cancer nor did it increase breast biopsy frequency.30 With additional postintervention follow-up, a statistically significant lower breast cancer incidence was seen with use of estrogen alone.31 There was a suggestion of a somewhat greater reduction in breast cancer incidence with the use of estrogen alone for women beginning therapy further from menopause (>5 years from menopause: HR, 0.65; 95% CI, 0.48–0.89, vs <5 years from menopause: HR, 0.89; 95% CI, 0.66–1.20, but the interaction P value was not significant [P=.13]).31 This outcome differs from the preponderance of observational studies, including recent reports from large cohorts32,33 in which longer duration of estrogen alone use has consistently been associated with an increase in breast cancer incidence.

In the WHI trial, with longer follow-up, deaths from breast cancer were also significantly reduced in the estrogen alone group (HR, 0.37; 95% CI, 0.13–0.91; P=.03), supporting the concept of an actual reduction in risk (Table 1).31

Throughout the 7.1 years of active intervention, the HR for breast cancer incidence in the estrogen
alone group remained below 1. There has been 5.8 years (median) of postintervention follow-up. During the initial 2.75 years of early postintervention follow-up, the HR became lower than the summary HR seen during active intervention (Table 3). This finding suggests that, similar to the effect seen in the estrogen plus progestin trial, preclinical breast cancers present at the time estrogen-alone use was discontinued also showed a clinical response to the sudden change in reproductive hormone environment.

The lower HR for breast cancer incidence for the use of estrogen alone persists for several years after stopping but is ultimately lost during late postintervention follow-up (HR, 0.55; 95% CI, 0.34–0.89 vs HR, 1.17; 95% CI, 0.73–1.87 for early vs late postintervention, respectively; P interaction=.04; Table 3). As a net result, the HR for breast cancer during the intervention phase was the same as the cumulative HR during the postintervention period (0.79 vs 0.79, respectively). Thus, a postmenopausal woman with a prior hysterectomy considering estrogen-alone use for climacteric symptoms initiated close to menopause can be reassured by these breast cancer findings. In clinical practice, full discussion of all risks and benefits of estrogen-alone use are needed in women considering short-term use. Currently, it is not possible to reconcile these randomized clinical trial results with those from the preponderance of observational studies.

Several small/moderately sized randomized trials have also evaluated menopausal hormone therapy, often with intermediate end points. However, several of these trials have also reported on breast cancer findings. In the ESrogen for the Prevention of re-infarction trial (ESPRIT) that randomized 1017 women to either placebo or estradiol valerate, 2 mg/d, fewer breast cancers were seen in the treatment group after more than a decade of follow-up (7 vs 15 cases vs HR, 0.47; 95% CI, 0.19–1.15). In another randomized trial involving 192 women in Denmark, fewer breast cancers were seen in the estrogen-alone (17-beta-estradiol, 2 mg/d) group (10 vs 17 cases; HR, 0.58; 95% CI, 0.271.29).

The opposite effects of estrogen plus progestin and estrogen alone on breast cancer incidence are illustrated in Figure 2, in which the Kaplan-Meier curves for breast cancer incidence over the 13-year cumulative follow-up period are superimposed for the 2 interventions. The placebo controls have closely comparable breast cancer incidence plots, whereas the plots from the 2 hormone therapy trials diverge in opposite directions.

**Menopausal Hormone Therapy and Intermediate Markers of Breast Cancer Risk**

Ductal carcinoma in situ (DCIS), benign breast disease (BBD), and higher mammographic breast density are all associated with increased breast cancer risk. The influence of estrogen alone and estrogen plus progestin on these end points and on new-onset breast tenderness was examined in the WHI hormone therapy trials.

The clinical trial findings for DCIS were very similar to those for invasive breast cancer. More cases of DCIS were seen in the estrogen plus progestin group than in the placebo group (103 vs 79 cases, respectively; HR, 1.23; 95% CI, 0.80–1.73), and fewer cases were seen in the estrogen-alone group (37 vs 46 cases, respectively; HR, 0.81; 95% CI, 0.53–1.25), but these differences were not statistically significant in either trial (Table 1).

The findings for BBD and hormone therapy use contrast with those for invasive breast cancer, in which estrogen alone and estrogen plus progestin had opposite effects on breast cancer incidence. For BBD, both estrogen plus progestin and estrogen alone resulted in statistically significant increases in BBD incidence of approximately the same magnitude (Table 1). For breast density, WHI ancillary studies in 400 participants in each trial showed that although the increase in mammographic breast density was greater (4.9% increase at 2 years) in the estrogen plus progestin trial, a statistically significant increase in breast density (1.7% increase at 2 years) was also seen in the estrogen-alone trial. Thus, estrogen plus progestin and estrogen alone had similar influence on breast cancer risk factors of BBD and increased breast density, but opposite effects on both breast cancer incidence and deaths.

The potential role of new-onset breast tenderness 1 year after hormone therapy use was also examined as a potential intermediate marker of breast cancer risk. New-onset breast tenderness was significantly higher among women on active therapy than in those on placebo (relative risk, 2.15 for estrogen alone and 3.07 for estrogen plus placebo). New-
onset breast tenderness during the use of estrogen plus progestin was associated with a significantly increased subsequent breast cancer risk, but new-onset breast tenderness during the use of estrogen alone was not. 45

**Endogenous Sex Hormone Levels and Exogenous Hormone Therapy**

Higher levels of sex hormones, including estradiol, estrone, and estrone sulfate, are associated with increased breast cancer risk in postmenopausal women. 46, 47 A nested case-control study within the WHI randomized clinical trials examined associations among sex hormone levels, menopausal hormone therapy use, and breast cancer risk. In the trial evaluating estrogen plus progestin, women with lower pretreatment endogenous estrogen levels were at greatest breast cancer risk with estrogen plus progestin compared with women with higher levels (odds ratio [OR]: 2.7 for lowest quintile [95% CI, 1.28–4.79] vs 0.96 [95% CI, 0.44–2.09] for the highest quintile; P interaction=.04). 47 In the WHI trial evaluating estrogen alone, the nearly 2-fold increase in sex hormone–binding globulin seen after estrogen-alone use is hypothesized to offset the large increases in estrogen levels seen, which perhaps could account for some of the reduction in breast cancer risk that is associated with estrogen-alone use. 48 Additional studies are needed to evaluate this provocative hypothesis.

**Summary**

Estrogen plus progestin increases breast cancer incidence, 15, 16 interferes with breast cancer detection, 10 and increases deaths from breast cancer. 28 Because of the interference on mammographic breast cancer detection, a safe interval for breast cancer risk cannot be determined. Nonetheless, when used for the duration of the WHI estrogen plus progestin trial (5.6 years [median], 3.4 years [median adherence], and 13 years follow-up), the increase in breast cancer incidence was 2.7% in the estrogen plus progestin group (228 cases in 8506 women) and 2.1% in the placebo group (168 cases in 8102 women). A full discussion of issues regarding presenting absolute risk versus relative risk reduction in an appropriate clinical context is beyond the scope of this review. However, on a population basis, a therapy that increases deaths from breast cancer requires cautious use, especially because no net chronic disease benefit was seen with estrogen plus progestin use.

Clearly, some women with limiting climacteric symptoms will benefit from combined hormone therapy use, but this is an individualized decision to be informed by an understanding of the overall risks and benefits and revisited at regular intervals. Estrogen-alone use decreases breast cancer incidence. Available evidence is insufficient to support use of estrogen-alone for primary breast cancer prevention or that of any other disease. However, a woman with prior hysterectomy and climacteric symptoms can be assured that estrogen-alone use for a short duration is relatively safe and can provide symptom relief.

**Acknowledgments**

The authors would like to thank the WHI investigators, staff, and trial participants for their outstanding dedication and commitment.

**References**

breast cancer incidence and mortality in postmenopausal women.


