Is new-onset breast tenderness after the start of hormone therapy a sign of elevated cancer risk?

Yes According to this analysis of data from the Women's Health Initiative (WHI), women who experienced new-onset breast tenderness, as assessed 12 months after the initiation of conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA), had a significantly higher risk of breast cancer than did women taking CEE plus MPA who did not report such tenderness (hazard ratio [HR], 1.48; 95% confidence interval [CI], 1.08–2.03; $P = .02$).

Crandall CJ, Aragaki AK, Chlebowski RT, et al. New-onset breast tenderness after initiation of estrogen plus progestin therapy and breast cancer risk. Arch Intern Med. 2009;169:1684–1691.

FAST TRACK

Women who had new-onset breast tenderness after initiating CEE plus MPA had a higher risk of breast cancer than those who did not experience such tenderness after starting CEE plus MPA

EXPERT COMMENTARY

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Breast tenderness is a common side effect of postmenopausal hormone therapy (HT); generally, it is dose-dependent. In this study by Crandall and colleagues, investigators assessed self-reported breast tenderness at the beginning of the WHI and after 12 months of HT, exploring any association between that tenderness and the risk of breast cancer. Here is what they found:

- Among women who reported no breast tenderness at study entry, the incidence of breast tenderness after 12 months was three times higher in those assigned to HT than in those assigned to placebo (36.1% vs 11.8%; $P < .001$).
- Women who reported the onset of breast tenderness after starting HT were older and more likely to be black or Hispanic than were women who did not.
- More than 75% of women who reported new breast tenderness (most often rated as mild) had been assigned to HT.
- Women taking HT who reported new breast tenderness had a risk of breast cancer 48% higher than those who did not report this complaint ($P = .02$).
- New-onset breast tenderness in women assigned to the placebo group was not associated with an elevated risk of breast cancer.

Does breast tenderness reflect an increase in cell proliferation?

Earlier studies have linked breast tenderness in women taking CEE plus MPA to high mammographic density, an independent risk factor for breast cancer. They have also established a link between estrogen–progestin therapy and breast cell proliferation. Therefore, as Crandall and colleagues observe, "breast discomfort

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Counsel women who are considering or continuing estrogen–progestin hormone therapy (HT) about its risks (including a modestly increased risk of breast cancer) and benefits. Also counsel them that breast tenderness commonly occurs after initiation of HT.

During follow-up visits, any woman reporting breast tenderness should be advised that this side effect suggests that her risk of breast cancer may be higher than that of women who use HT but do not experience breast tenderness. This information may factor into decisions about HT continuation and dosage, as well as strategies for breast-cancer surveillance.

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may be a clinical manifestation of increased proliferation that is manifest radiographically as increased breast density."

Keep in mind that the original WHI estrogen–progestin trial demonstrated that CEE plus MPA is associated with eight additional cases of breast cancer per 10,000 woman-years—a modest increase in risk. Although the study by Crandall and colleagues suggests that new-onset breast tenderness further increases the risk of breast cancer among users of estrogen–progestin therapy, the absolute magnitude of this increased risk is modest.

New-onset breast tenderness has a sensitivity and specificity similar to those of the Gail model for predicting the risk of invasive breast cancer. In this study, based on a mean follow-up of 5.6 years, the sensitivity and specificity of new-onset breast tenderness were 41% and 64%, respectively, and the positive predictive value was 2.7%. In comparison, using a threshold risk of breast cancer of 1.67% over 5 years, the Gail model has sensitivity, specificity, and a positive predictive value of 44%, 66%, and 6.6%, respectively.