Oestrogen plus progestogen increased risk of breast cancer in postmenopausal women

Chlebowski RT, Hendrix SL, Langer RD, *et al.* Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* 2003;**289**:3243–53.

Q In postmenopausal women, does oestrogen plus progestogen hormone therapy increase the risk of abnormal mammographic results and diagnosis of breast cancer?

METHODS

- **Design:** randomised, placebo controlled trial (Women's Health Initiative).
- **Allocation:** concealed.
- **Blinding:** blinded (clinicians, participants, data collectors, outcome assessors, and monitoring committee).
- **Follow up period:** mean 5.6 years.
- **Setting:** 40 US clinical centres.
- **Patients:** 16 608 postmenopausal women who were 50–79 years of age (mean age 63 y). Exclusion criteria: previous hysterectomy, breast cancer, or probable survival <3 years.
- **Interventions:** 1 daily tablet of conjugated equine oestrogen, 0.625 mg, and medroxyprogesterone acetate, 2.5 mg (Prempro, Wyeth Ayerst, Philadelphia, PA, USA) (n=8506) or placebo (n=8102).
- **Outcomes:** incidence of breast cancer (total, invasive, and in situ) and abnormal mammography results.
- **Patient follow up:** 96%.

MAIN RESULTS

Analysis was by intention to treat. Women who received oestrogen plus progestogen 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 oestrogen plus progestogen was seen across almost all risk categories. Invasive breast cancers were larger in the oestrogen plus progestogen group (mean 1.7 cm v 1.5 cm, $p = 0.04$) and were diagnosed at a more advanced stage (regional or metastatic [compared with local] 25% v 16%, $p = 0.04$) than in the placebo group. Women who received oestrogen plus progestogen also had a

higher proportion of abnormal mammography results. The difference was seen at 1 year (9.4% v 5.4%, $p < 0.001$) and continued throughout the study (total study period 32% v 21%, $p < 0.001$).

CONCLUSION

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

A modified version of this abstract appears in *ACP Journal Club*.

Commentary

The complex issues surrounding hormone replacement therapy have been escalating over the past decade. Initial results of the Women's Health Initiative (WHI) trial released in 2002¹ have served to further complicate the decisions made by prescribers and potential consumers of hormone therapy. The WHI report by Chlebowski *et al* provides specific details about breast cancer outcomes for the oestrogen plus progestogen and placebo groups. Similar results regarding hormone therapy and breast cancer have been reported in European studies.^{2 3}

It was previously believed that the increased risk of breast cancer with hormone therapy was seen in women with longer term (>5 y) use. These recent results reveal unexpected findings of early development of invasive breast cancers with the use of oestrogen plus progestogen. Additionally, the use of combined hormone therapy resulted in higher rates of mammographic abnormalities, adding to the emotional and economic burden for both patients and providers.

Future reports of the WHI trial results will help to discern the survival outcomes for the 2 groups and may provide insight about the use of oestrogen alone hormone therapy. In the interim, the results of the WHI to date provide a convincing argument against the use of oestrogen plus progestogen. It seems the increased risk of breast cancer and mammographic abnormalities is truly not worth the potential benefit derived from the therapy.

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Oestrogen plus progestogen (Oest + Prog) v placebo for postmenopausal women*

Outcomes at mean 5.6 years	Oest + Prog	Placebo	Hazard ratio (95% CI)
Cases of breast cancer (all)	245	185	1.24 (1.02 to 1.50)
Cases of invasive breast cancer	199	150	1.24 (1.01 to 1.54)
Cases of in situ breast cancer	47	37	1.18 (0.77 to 1.82)†

*CI defined in glossary.

†Not significant.