Postmenopausal hormone replacement therapy for chronic disease prevention: results from the Women's Health Initiative trial

Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288:321-33.

Background: The risks and benefits of long-term postmenopausal hormone replacement therapy (HRT) with estrogen alone or combined with progestin have long been a source of controversy. Chronic diseases in which HRT has been felt to be beneficial include coronary artery disease (CAD) and osteoporosis. Practitioners prescribing HRT to postmenopausal women have had to weigh these potential benefits against the risks known (increased incidence of venous thromboembolism) or thought to be associated with HRT (breast and endometrial cancers). To date, many studies of HRT in cardiovascular disease prevention have been observational in design or have focused on intermediate outcomes such as serum lipid levels. In the 1998 HERS (Heart Estrogen/Progestin Replacement Study) report, HRT in women with established CAD was associated with an increased risk of CAD events within the first year of treatment, but no change in risk overall.[1] The effect of HRT on the risk of CAD and other chronic diseases in postmenopausal women without established cardiovascular disease remained unknown.

Question: What are the health risks and benefits of long-term estrogen–progestin HRT in healthy postmenopausal women with an intact uterus?

Design: The Women's Health Initiative (WHI) began a series of large, population-based, primary prevention trials designed to determine the risks and benefits of a number of interventions (low-fat diet, calcium and vitamin D supplementation, and HRT) in healthy postmenopausal women. In the current study,[2] which was ended early, 16 608 women aged 50–79 who had an intact uterus were randomly assigned to either once daily estrogen–progestin (conjugated equine estrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg) or placebo. Among those excluded were women with a history of breast cancer, a history of other cancer (apart from nonmelanoma skin cancer) within the previous 10 years, or any medical condition associated with a predicted survival of less than 3 years. The primary outcomes were the occurrence of CAD events (nonfatal myocardial infarction and CAD-related death) and invasive breast cancer. Secondary outcomes included osteoporotic fractures, cardiovascular disease other than CAD, and endometrial and colorectal cancer. To ascertain outcome events, subjects completed semi-annual self-administered questionnaires and attended annual follow-up clinic visits.

Analysis was by time-to-event methods, using the intention-to-treat principle. Outcome adjudicators were blinded to treatment status. Interim analyses were conducted semi-annually for consideration of stopping the trial, with upper boundaries for adverse outcome rates having been prespecified.

Results: The mean age of the subjects at enrolment was 63.3 (standard deviation 7.1) years. There were no significant demographic or clinical differences at baseline between the HRT and placebo groups. The prevalence of cardiovascular disease was low, with 1.6% and 1.9% of the HRT and placebo recipients, respectively, reporting prior myocardial infarction. The trial was stopped after the tenth interim analysis because the prespecified upper boundary for breast cancer risk in the HRT group had been exceeded and the global index of benefits and risks of HRT showed a net harm (hazards ratio 1.15, nominal 95% confidence interval 1.03–1.28). At the time the trial was stopped, the mean duration of follow-up was 5.2 years (range 3.5–8.5). A significant proportion of the subjects had stopped the study medication at some time during the trial (42% in the HRT group, 38% in the placebo group).

Women taking HRT had an excess risk of both cardiovascular disease and breast cancer. Compared with the placebo group, the HRT group had a 29% higher CAD rate (37 v. 30 per 10 000 person-years), a 41% higher stroke rate (29 v. 21 per 10 000 person-years), a more than two-fold higher rate of venous thromboembolism (34 v. 16 per 10 000 person-years) and a 26% higher rate of breast cancer (38 v. 30 per 10 000 person-years). There was no difference between groups in endometrial cancer rates (5 v. 6 per 10 000 person-years) or all-cause mortality (52 v. 53 per 10 000 person-years). Beneficial effects of HRT included a 33% reduction in the rate of hip fractures (10 v. 15 per 10 000 person-years) and a 37% reduction in the rate of colorectal cancer (10 v. 16 per 10 000 person-years). The summary global index, however, showed a 15% higher outcome event rate in the HRT group (170 v. 151 per 10 000 person-years). The time-to-event analysis showed that, although the event curves for cardiovascular disease and hip fracture diverged within the first 1 to 2 years of treatment, the curves for breast cancer remained similar for about 4 years before diverging.

Commentary: This is the first randomized controlled trial designed to assess the risks and benefits of HRT when prescribed for primary prevention of chronic disease. Despite a high dropout

rate in the HRT group (42%), which would tend to underestimate treatment effects (beneficial and harmful), the trial showed a net harm. The trial did not address the benefit of short-term HRT in relieving postmenopausal symptoms, nor did it allow determination of the relative influence of estrogen versus progestin on disease event rates. A parallel WHI trial of estrogen alone versus placebo in postmenopausal women who have undergone hysterectomy is underway, and its results will help to answer the latter question.

Practice implications: HRT with combined estrogen–progestin causes net harm when used for an average of 5.2 years. Although event rates are low, reductions in the risk of fracture and colorectal cancer are outweighed by increases in the risk of cardiovascular disease and breast cancer. HRT remains an effective treatment for moderate or severe postmenopausal symptoms; however, the results of this trial support a recommendation to limit its use to as short a period as possible.

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References

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HEALTH AND DRUG ALERTS

Tamoxifen for breast cancer prevention: safety warning

Reason for posting: Tamoxifen is used as adjuvant hormonal therapy for breast cancer[1,2] and may be useful for primary prevention in some women at high risk of the disease (including those with ductal carcinoma in situ [DCIS]).[3–5] The US Food and Drug Administration recently issued a warning emphasizing that physicians need to advise women that serious and fatal adverse effects, including uterine cancer, stroke and pulmonary embolism,[6] have occurred in some women taking the drug for breast cancer prevention.

The drug: Tamoxifen is a nonsteroidal agent with anti-estrogenic properties that is used to treat estrogen-receptor–positive tumours[1,2] and DCIS.[4] It also has a low affinity for androgen receptors, inhibits prostaglandin synthetase and displays estrogenic-like effects on some body systems, including the bones, endometrium and blood lipids.[7] Tamoxifen interacts with coumadin,[7] erythromycin, cyclosporin, nifedipine and diltiazem.[8] Associated adverse effects include hot flashes, nausea and vomiting, gynecologic changes (e.g., oligomenorrhea, amenorrhea, endometrial hyperplasia, ovarian cysts, fibroids, vaginal dryness or discharge, and pruritus vulvae), bone and tumour pain, hypercalcemia, depression, lightheadedness, headache, alopecia, rash, liver disturbances, cataracts, leukopenia, thrombocytopenia, neutropenia, deep vein thrombosis and pulmonary embolism.[7]

The Gail model can identify women at high risk of breast cancer (those with a 5-year risk of more than 1.67%)[5] so that they can be offered chemoprevention. The National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial enrolled 13 388 such high-risk women (all over 35 years old) and randomly assigned them to receive either tamoxifen or placebo for 5 years.[9] Invasive breast cancer was less common in the tamoxifen group than in the placebo group (3.4 v. 6.8 per 1000 woman-years, relative risk [RR] 0.51, 95% confidence interval 0.39–0.66).[9] However, 2 smaller studies — the Italian Tamoxifen Prevention Study (n = 5408) and the Royal Marsden Hospital Tamoxifen Randomized Chemoprevention Trial (n = 2471) — did not show similar risk reductions (RR 0.92 and 0.94 respectively).[3] No trial has yet shown a reduction in breast cancer mortality. Adverse effects identified in these trials included endometrial cancer, deep vein thrombosis, pulmonary emboli and cataracts.[3] However, a recent long-term follow-up study (median 6.9 years) of women in the NSABP P-1 trial revealed that the tamoxifen group had an increased rates of uterine sarcoma and stroke as well as endometrial adenocarcinoma and pulmonary embolism (Table 1).[6,8]

What to do: Although the Gail model has not been validated for routine screening, it may allow a preliminary estimate of baseline breast cancer risk (an online risk assessment tool is available at bcra.nci.nih.gov/brc).

Table 1: Incidence of serious adverse events in the NSABP P-1 Breast Cancer Prevention Trial[6,8]

	Group; rate per 1000 woman-years	
Adverse event*	Tamoxifen *n = 6707*	Placebo *n = 6681*
Endometrial adenocarcinoma	2.20	0.71
Uterine sarcoma	0.17	0.00
Stroke	1.43	1.00
Pulmonary embolism	0.75	0.25

Note: NSABP = National Surgical Adjuvant Breast and Bowel Project.
*Includes deaths.