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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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.

Tamoxifen is not appropriate for breast cancer prevention in women at low risk of the disease (5-year risk less than 1.66%),[3] and discussions about modifiable risk factors, including dietary fat and alcohol intake,[10] physical inactivity,[11] breast-feeding[12] and postmenopausal hormone replacement exposure[13] may be appropriate. Women at higher risk (especially those with a 5-year risk of more than 5%[3]) who consent to treatment after appropriate appraisal of its risks and benefits may be considered for chemoprevention,[3] recognizing the limitations of the evidence (studies have excluded women with thrombophilia) and the fact that tamoxifen is not licensed in Canada for this indication. Many women offered tamoxifen for chemoprevention will decline treatment, often because of a fear of side effects.[14] The role, safety and efficacy of raloxifene, an agent with a risk of deep vein thrombosis similar to that of tamoxifen but no apparent effect on the endometrium, is currently under investigation as an alternative chemopreventative agent.[15]

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