Tamoxifen for the Prevention of Breast Cancer in High-Risk Women

Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel project P-1 Study. J Natl Cancer Inst 1998; 90:1371-88.

Clinical question **Does tamoxifen prevent breast cancer in high-risk women?**

Background Breast cancer is a major worry for many patients, but preventive strategies are limited to the encouragement of breast-feeding, clinical breast examination, and mammography. Recent studies have documented that women with breast cancer who are taking tamoxifen have a lower incidence of breast cancer in the contralateral breast, raising the possibility that tamoxifen may be useful as a preventive agent. This randomized controlled trial evaluates the efficacy of tamoxifen in preventing breast cancer in high-risk women.

Population studied Women with a high risk of breast cancer (n = 13,175) were enrolled at 131 sites in the United States and Canada. Three groups of women were included: (1) those older than 60 years; (2) those with a history of lobular carcinoma in situ; and (3) those with a >1.6% risk of the development of breast cancer in 5 years, as calculated by a computerized prediction tool incorporating patient age, number of first-degree relatives with breast cancer, nulliparity or age at first live birth, a history of breast biopsy, and age at menarche. Subjects had to have a life expectancy of more than 10 years, a recent mammogram with no evidence of breast cancer and no recent hormonal therapy. Sixty-nine percent were older than 60 years, and 56.8% had at least one first-degree relative with breast cancer. Thus, the patients seem to be representative of patients in family practice at high risk for breast cancer.

Study design and validity This was a double-blind placebo-controlled randomized trial. Subjects received placebo or tamoxifen 20 mg per day for an average of 47 months. Details of follow-up examinations are not described. Slightly more patients taking tamoxifen stopped their medication (23.7% vs 19.7%). Overall follow up for outcomes was excellent (98%).Analysis was by intent to treat. Overall, the study design is strong. Weaknesses include: (1) lack of information about how end points were identified; (2) lack of attention to potentially confounding variables, such as breast-feeding, risk factors for coronary disease, and fractures that may influence outcomes, and (3) low power for secondary outcomes.

Outcomes measured The primary outcome was the incidence of invasive breast cancer; secondary outcomes included the incidence of side effects, noninvasive breast cancer, endometrial cancer, myocardial infarction, bone fractures, vascular events, depression, and overall mortality. Quality of life, health care utilization, and cost data were not reported.

Results The groups were similar at onset. Patients taking tamoxifen were significantly less likely to develop invasive breast cancer (relative risk [RR]=0.49; 95% confidence interval [CI], 0.39-0.66; number needed to treat [NNT]=77), noninvasive breast cancer (RR=0.50; 95% CI, 0.33 to 0.77; NNT=200), and all breast cancer (NNT=56). Risk reduction was similar in all subgroups. Unfortunately, patients taking tamoxifen had substantial increases in bothersome hot flashes (NNT=6 for "quite a bit" or "extremely") and bothersome vaginal discharge (NNT=11 for "quite a bit" or "extremely"), as well as cataracts (RR = 1.14; 95% CI, 1.01 - 1.29; NNT=77), endometrial cancer (RR=2.53; 95% CI, 1.35 - 4.97; NNT=322), and pulmonary embolus (RR=3.0; 95% CI, 1.15 - 9.27; NNT=500). The likelihood of depression, coronary events, or bone fractures was similar in both groups. Overall mortality was lower in the tamoxifen group (57 vs 71), but not significantly so (RR=.81; 95% CI, .56 - 1.16).

Recommendations for clinical practice **This study provides good evidence that tamoxifen reduces the incidence of breast cancer in high-risk women. However, the absolute benefit of treatment was small, follow-up was fairly short, and there was no effect on mortality. Furthermore, tamoxifen has significant side effects and caused serious, though relatively rare, adverse effects such as endometrial cancer, pulmonary emboli, and cataracts. Combined with 2 recent smaller trials that found no benefit, the overall message is that benefits of tamoxifen as a preventive agent are quite limited. Clinicians should offer tamoxifen only to motivated, high-risk women. For the few women for whom tamoxifen is appropriate, clinicians should perform baseline endometrial sampling, document informed consent about side effects and long-term health risks, and monitor closely.**

This study raises a broader issue regarding counseling about breast cancer risk in office practice: Is it valuable to provide patients with individual assessments of risk of breast cancer? Such assessments are increasingly a part

of routine care for mild hypertension and hyperlipidemia. This study does not answer this question, but the National Cancer Institute is making available the risk assessment software used in this trial at http://cancertrials.nci.nih.gov.

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Carotid Endarterectomy for Symptomatic Moderate Stenosis

Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. N Engl J Med 1998; 339:1415-25.

Clinical question Is carotid endarterectomy indicated for patients with symptomatic and moderate (< 70%) stenosis?

Background The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST), both reported in 1991, showed the striking clinical benefit of surgery over drug therapy for patients with symptomatic carotid stenoses > 70%.[1,2] These studies also clearly demonstrated the lack of benefit of carotid endarterectomy (CEA) for patients with mild lesions (0% to 29%). It is not clear, however, whether patients with moderate stenosis (30% to 70%) benefit from surgery. Recent evidence-based guidelines from both the Stroke Council of the American Heart Association and the Canadian Neurosurgical Society consider such patients "uncertain candidates for CEA."[3,4]

Population studied These investigators enrolled 2226 patients with < 70% carotid stenosis by angiography who had either transient ischemic attack (TIA) or nondisabling stroke in the previous 180 days. Patients were excluded for cardiac lesions likely to cause cardioembolism, prior ipsilateral CEA, severe internal carotid artery stenosis, or any medical illness that would preclude a 5-year life expectancy. The average age was 66 years, with 15% of subjects older than 75 years. Patients were enrolled from 1987 to 1996.

Study design and validity This was an international randomized clinical trial in 106 centers. Patients were randomized after angiography to the medical arm (n = 428) or surgical/CEA arm (n = 430) of the study. Patients were stratified by degree of stenosis, and there were no significant differences between the groups in baseline variables. The average duration of follow-up was 5 years; complete outcome measures were available for 99.7% of enrolled patients. All patients were given antiplatelet treatment throughout the study; hypertension and hyperlipidemia were treated, when present, in both groups. Analysis was by intention-to-treat. Patients in the medical arm were offered CEA if their lesions progressed to >70% stenosis, and these crossover patients were appropriately analyzed in the medical group.

Outcomes measured The primary outcomes were fatal and nonfatal stroke ipsilateral to the stenosis for which the patient was randomized. Outcome assessments (territory, type, severity, and duration of all strokes, and cause of death) were effectively blinded. Secondary outcomes included rates of perioperative disabling stroke and death at 30 and 90 days.

Results For symptomatic patients with 50% to 69% stenosis, the failure rate (any ipsilateral stroke) was 15.7% in the surgical group and 22.2% in the medical group (P = .045). The number needed to treat (NNT) to prevent one ipsilateral stroke over 5 years was 15 (95% CI, 11-29). Subgroup analysis showed that the benefit of CEA over medical treatment is greater in men than women, greater in patients with stroke than those with TIA, and greater in patients with hemispheric opposed to retinal symptoms. The highly expert surgeons in this series achieved perioperative combined death or disabling stroke rates of 2.8% at 30 days and 2.0% at 90 days. There was no benefit for CEA in patients with stenoses <50%.

Recommendations for clinical practice **Endarterectomy is of marginal benefit for symptomatic patients with carotid stenosis between 50% and 69%. If the combined surgical risk of death and disabling stroke exceeds 2%, this benefit is lost completely. We should refer these patients only to surgeons whose patients have low rates of complications as determined by independent audits.**

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