

How do we interpret the results of the Breast Cancer Prevention Trial?

Richard G. Margolese, MD

The results of the Breast Cancer Prevention Trial (BCPT)¹ must be interpreted carefully. Critics tell us we should be cautious in prescribing tamoxifen for women in general. True, but it is important not to get bogged down in the kinds of controversies that marked the launch of the study.

The results of clinical trials are applicable only to populations that resemble the trial participants. Although we should not begin to broaden the use of tamoxifen to women with a low or normal risk of breast cancer, it is clear that women with a significantly elevated risk stand to benefit from tamoxifen prophylaxis. The toxic effects observed in the BCPT were exactly as previously experienced² and as predicted for this study. Relative to the risk of breast cancer among the participants, the risk of uterine cancer was low. Furthermore, all the participants in whom uterine cancer developed had stage I tumours, except for one participant in the placebo group, who had stage IV disease at the time the uterine cancer was detected and subsequently died. Although it is too early to be sure, this may be evidence for the value of introducing surveillance and screening with endometrial biopsies or ultrasound during the course of tamoxifen prophylaxis. Although uterine cancer is relatively uncommon and easier to cure than breast cancer, one can never feel comfortable about increasing the risk of uterine cancer. Nevertheless, some women may choose to run this risk if, for example, their grandmother, mother and sister all had breast cancer. Obviously, women with less conspicuous risk profiles need careful counselling, but this also means not exaggerating the risks.

Although cost-effectiveness is important, it is not the only criterion we should use in deciding whether to implement a public health measure. The cost of tamoxifen therapy for every woman with risk factors for breast cancer would of course be enormous. This strategy is not what the BCPT investigators are proposing, nor should they be criticized as if they were. Their study demonstrated over the 6-year trial period a 45% reduction in the incidence of breast cancer among women who received tamoxifen as compared with the women who received placebo. The difference in breast cancer incidence between the treatment and placebo arms became apparent early in the trial and increased steadily, to the point where scientific and ethical considerations dictated that the trial be terminated early. For women at risk, all the evidence we have points toward the benefit of tamoxifen prophylaxis.

Some commentators feel that stopping the trial early was unfortunate, but this represents a misunderstanding of the trial design. The trial was stopped when its predetermined end point was reached. That end point was a 40% reduction in cancer incidence, not any specific time period. The trial was stopped earlier than foreseen, but not prematurely.

The importance of the BCPT is not so much that 80-odd cases of breast cancer were apparently prevented but that it demonstrated that it is possible to slow or preempt carcinogenesis with reasonable safety. Tamoxifen is not the end of the cancer prevention effort any more than sulfa drugs were the end of the development of antibiotics. Women who are good candidates for tamoxifen cancer prevention should be encouraged to enrol in the second prevention trial. There are participating centres in 7 Canadian provinces and in all 50 US states. This trial



Editorial

Éditorial

Dr. Margolese is Director of Oncology at the Sir Mortimer B. Davis-Jewish General Hospital and Herbert Black Professor of Surgical Oncology at McGill University, Montreal, Que. He is a member of the Steering Committee of the Breast Cancer Prevention Trial.

CMAJ 1998;158:1613-14

‡ See related article page 1615



will compare tamoxifen with raloxifene, a drug shown to be useful in preventing osteoporosis and which seems to lack the stimulatory effect that tamoxifen has on the endometrium. A clinical trial is necessary to confirm preliminary evidence that raloxifene diminishes breast cancer incidence and to show whether it is as efficacious in doing so as tamoxifen. Because there is no placebo group, all women enrolled in this trial will receive an active agent. Thus, the trial will compare a drug recently demonstrated to reduce the occurrence of breast cancer with another that may be safer but whose total effectiveness is not yet measured.

Continuing research on growth factors, retinoids and other switch points in the biochemical pathways that control cellular proliferation will all give rise to the development of new candidate drugs for cancer prevention. Enrolling women at high risk for breast cancer in these future trials is likely to benefit them directly and to benefit all women indirectly by providing more and better information on breast cancer prevention.

The public has a natural tendency to misinterpret risks. A good example is the widespread concern about nuclear power plants — which have not caused any deaths in the Western world — while deaths and illnesses that result from the mining, processing, transporting and burning of coal are overlooked. The projected 1-in-9 lifetime risk of breast cancer is widely repeated and alarms many women; the flip side of this statistic — that approximately 90% of

women will *not* get breast cancer — is not perceived. Prescribing tamoxifen to prevent breast cancer is viewed as a riskier enterprise than prescribing it to treat the disease, even though its benefits as a preventive agent may be more important than its use in therapy. Many thousands of women begin hormone replacement therapy during menopause to prevent some of the degenerative diseases associated with aging and to prevent hot flashes, accepting the mild increase in the risk of breast cancer that this entails. Many others use birth control pills, accepting their risks, which include pulmonary embolism. Using tamoxifen to prevent breast cancer should be viewed in a similar context.

Dr. Margolese has received consultation fees from a manufacturer of a drug mentioned in this article.

References

1. National Cancer Institute. Breast Cancer Prevention Trial shows major benefit, some risk [Web site news release]. Available: <http://cancertrials.nci.nih.gov> (accessed 1998 May 13).
2. Fisher B, Constantino C, Redmond R, Poisson D, Bowman J, Couture J, et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. *N Engl J Med* 1989;320:479-84.

Reprint requests to: Dr. Richard G. Margolese, Sir Mortimer B. Davis-Jewish General Hospital, 3755 Côte-Ste-Catherine, Montreal QC H3T 1E2; fax 514 340-8302; rm@onc.jgh.mcgill.ca

CLINICAL AND INVESTIGATIVE MEDICINE
MÉDECINE CLINIQUE ET EXPÉRIMENTALE

Association Médicale Canadienne / Canadian Medical Association

CLINICAL AND INVESTIGATIVE MEDICINE

Clinical and Investigative Medicine, the official journal of the Canadian Society for Clinical Investigation, is a peer-reviewed journal with an international reputation for excellence in research and experimental medicine. Established in 1977, *Clinical and Investigative Medicine* is published 6 times a year for the Society by the Canadian Medical Association and is available online at: www.cma.ca/cim.

CMA Member Service Centre
tel 888 855-2555 or 613 731-8610 x2307
fax 613 731-9102
cmamsc@cma.ca