Tamoxifen and breast cancer prevention: What should you tell your patients?

Editorial

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Vivek Goel, MD, MSc

Dr. Goel is with the Department of Public Health Sciences, University of Toronto, and the Institute for Clinical Evaluative Sciences, Toronto, Ont.

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On Apr. 6, 1998, the US National Cancer Institute released preliminary results of the Breast Cancer Prevention Trial (BCPT).[1] These results included a 45% reduction in the incidence of breast cancer among participants in the tamoxifen arm of the trial as compared with those in the placebo control arm. Scrutiny by the trial's Endpoint Review, Safety Monitoring and Advisory Committee resulted in a decision to unblind the study and release the findings. The preliminary results received widespread publicity, and as a result many women may ask their physicians whether they should take tamoxifen to reduce their risk of breast cancer. It will take some time before the investigators review the results in detail and publish a peer-reviewed article. To assist physicians in the interim, this article briefly reviews the publicly released BCPT data and summarizes considerations for Canadian physicians who may be asked about tamoxifen prophylaxis.

Tamoxifen has been used for over 20 years in the treatment of breast cancer. It is believed to slow or stop the growth of breast cancer cells through its anti-estrogenic action. It has been shown to reduce the risk of recurrent breast cancer and of contralateral breast tumours. Outside of breast tissue it actually has a weak estrogenic effect, resulting in benefits similar to those of hormone replacement therapy.[2,3]

The BCPT enrolled 13 388 women at 300 sites across the US and Canada and randomly assigned them to receive either placebo or tamoxifen.[1] Women were eligible for the study if they were over the age of 60 or if their risk of breast cancer was calculated to be at least as great as that of a 60-year-old woman. (This is equivalent to a 1.7% risk of breast cancer over 5 years.) For women under 60, risk was calculated by using a model that took into account the number of first-degree relatives with breast cancer, age at menarche, parity, age at delivery of first child, number of breast biopsies, history of atypical hyperplasia and history of lobular carcinoma in situ.

The trial was not without controversy[4] and indeed was temporarily halted for congressional hearings while emerging evidence of a link between tamoxifen and endometrial cancer was reviewed.[5,6] Some centres withdrew from the study at that time.

The interim results that led to the termination of the trial after an average of about 4 years of follow-up showed 85 cases of invasive breast cancer in the tamoxifen arm compared with 154 in the placebo arm.[1] There were 31 and 50 cases respectively of noninvasive ductal carcinoma in situ. The reduction in breast cancer risk was demonstrated across all age groups. Tamoxifen also had a beneficial effect on fractures of the hip, wrist and spine, of which there were 47 and 71 cases respectively. Although a beneficial impact on cardiovascular outcomes was expected, none was observed in the interim results, given the relatively short follow-up period.

There were 33 cases of endometrial cancer in the tamoxifen group compared with 14 in the placebo group. It should be noted that about 37% of participants in each group had undergone a hysterectomy before enrolment. There were 30 cases of deep vein thrombosis (DVT) and 17 cases of pulmonary embolism in the tamoxifen arm, compared with 19 and 6 cases in the placebo arm. Two women, both in the tamoxifen arm, died of pulmonary embolism.

These interesting results must be considered carefully. Women at high risk for breast cancer have limited options to reduce their risk.[7] It has not been established

to what extent lifestyle factors such as diet and physical activity influence breast cancer risk, or to what extent their modification may reduce risk. Other agents are under consideration for chemoprevention, such as retinoids and special oral contraceptives. Regular surveillance with mammography can reduce breast cancer mortality, but this has not been established for women younger than 50. Breast self-examination and clinical examination may be beneficial but are not proven. The only other option is prophylactic mastectomy, which is unacceptable to many women.

Thus the promise of chemoprevention is one that many may look upon favourably. However, as the BCPT results show, there are clear risks associated with its use. Although endometrial cancer can be detected with regular surveillance, it is still potentially fatal. Similarly, DVT can be detected early with regular monitoring, which allows complications such as embolism to be averted with anticoagulation therapy. However, avoiding these adverse effects will require vigilance, invasive tests and treatments. Furthermore, iatrogenic outcomes are perceived to be worse than those that occur naturally.[8]

Physicians must also recognize that the trial participants were at high risk for breast cancer; hence the results do not necessarily apply to the entire population. Even if the relative risk reduction were the same for the general population as for the study sample, it would be applied to a lower baseline breast cancer risk; therefore, the risk–benefit ratio, in absolute terms, would change drastically, assuming that the rate of adverse events remained the same in a low-risk breast cancer population. We should also bear in mind that women with different levels of risk may have quite different responses to tamoxifen. A recent study suggests that women with some *BRCA1* mutations are more likely than others to have hormone-resistant tumours, which may be less responsive to tamoxifen prophylaxis.[9]

On the basis of the interim finding of a 5-year cumulative breast cancer incidence of 33 per 1000 women in the control arm and 18 per 1000 in the tamoxifen arm, about 67 women at high risk would have to take tamoxifen for 5 years to prevent 1 case of invasive cancer. An additional adverse event, either endometrial cancer or DVT, would occur in about 1 of every 130 women taking tamoxifen for 5 years. Several more would undergo investigations for suspicious symptoms. An analysis of the risks and benefits of tamoxifen prophylaxis suggests that even with very generous assumptions in favour of the drug, the absolute benefit is quite small.[10]

Tamoxifen has other adverse effects that must be noted.[2,3] It has been suggested that women taking tamoxifen may have an increased risk of cataracts and depression. Although animal studies have suggested a link with liver cancer, this has not been confirmed in clinical studies. Animal studies have also suggested that tamoxifen may be teratogenic. More common side effects, experienced by 15% to 20% of women taking tamoxifen, include hot flashes, irregular menstrual periods, menorrhagia, nausea, vomiting, light-headedness and dizziness.

Because the BCPT was halted early and women in the placebo arm are being offered the opportunity to begin taking tamoxifen, its long-term benefits, such as an effect on survival, will be more difficult to establish. There is reason to believe that the survival benefit could be smaller than the reduction in incidence, given that tamoxifen may selectively avert neoplasms with a better prognosis — that is, those that are not resistant to tamoxifen. Moreover, the efficacy of tamoxifen adjuvant therapy may be reduced in women who are already taking tamoxifen at the time of diagnosis.[11] Trials now under way in Britain and Italy will continue to study tamoxifen prophylaxis and may supply answers to these questions. However, participation in these trials may be compromised by the publicity surrounding the BCPT.[11]

On the basis of the Ontario Drug Benefit Formulary price for generic tamoxifen (40¢ per pill), preventing 1 case of cancer over 5 years with daily doses for 67 women would cost about $49 000. The costs of additional monitoring, tests and treatments for complications would also have to be included in a full economic evaluation. The cost-effectiveness of this agent in the prevention of cancer needs to be considered before policies can be developed.

More chemopreventive agents are on the horizon. Raloxifene, which is currently used in the treatment of osteoporosis, may have the potential to reduce breast cancer risk without increasing endometrial cancer risk.[12] This drug is much more expensive than tamoxifen. A trial comparing this drug with tamoxifen is planned to begin this fall.

What is a physician to do when faced with a woman seeking a prescription for tamoxifen to reduce her risk of breast cancer? Women should be informed about the risks and benefits of this drug, the need for long-term use and the need for surveillance for adverse effects. The lack of evidence of benefit in women in the general population should be emphasized. Use of tamoxifen for cancer prevention outside of trials should be discouraged until further data on its risks and benefits are assessed.

At the policy level, tamoxifen requires regulatory approval for use for this indication. Guidelines will need to be developed for its prophylactic use, and breast cancer treatment groups in provincial cancer agencies are well positioned to take the lead in developing such guidelines. However, it is important to recognize that population-based cancer prevention strategies are also matters of public health significance. Therefore, guidelines and policies will need to be developed jointly by cancer treatment and public health agencies. Finally, given the com-

plexities of the issue, decision support tools based on such guidelines will be required for both consumers and physicians.

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Reprint requests to: *Dr. Vivek Goel, 12 Queen's Park Cres. W, Toronto ON M5S 1A8; fax 416 978-8299; vivek.goel@utoronto.ca*

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