

CAN BREAST CANCER BE PREVENTED?

Robert K. Stuart, MD

Despite recent medical progress in the treatment of breast cancer, one-third of newly diagnosed patients receiving optimal medical management will ultimately die of the disease. And although treatment advances have also reduced the morbidity of breast cancer surgery, many women, especially in developing countries, still have reason to fear that breast cancer therapy will leave them disfigured. These limitations of treatment have encouraged a new focus on breast cancer prevention.

Primary and Secondary Prevention

The evidence is compelling that a woman can take steps to reduce her risk of dying from breast cancer. Utilizing mammography with or without clinical breast examination, regular screening of women aged 50-69 years leads to a reduction in breast cancer mortality of 25%-30% at 10-12 years after initiation of screening.¹ Women in the age range of 40-49 years may also benefit from screening, but the estimated effect is smaller, a 17% reduction in mortality at 15 years from the start of screening.² These are examples of *secondary prevention*—early detection reduces the mortality and morbidity of breast cancer but not the incidence of the disease. True *primary prevention* of breast cancer requires a reduction in risk of developing breast cancer in the first place.

The concept that breast cancer can be prevented is supported by the wide geographical variability in breast cancer rates and by migration studies that suggest environmental and/or lifestyle determinants of breast cancer risk. For instance, breast cancer rates are very low in Japan compared to North America, but descendants of Japanese immigrants to the USA acquire risk similar to that of North Americans within two generations.³⁻⁵ In addition, many studies show support for a model of breast carcinogenesis in which an accumulation of multiple somatic mutations results in the final malignant phenotype. An appealing prediction of this model is that there are multiple steps in carcinogenesis where a preventive action could have a salutary effect.⁶

Prophylactic Mastectomy

Heretofore, the only available method of primary prevention of breast cancer has been prophylactic mastectomy, a controversial procedure with ambiguous indications and uncertain efficacy. Subcutaneous mastectomy rarely results in removal of all breast tissue, with retained tissue commonly found under the nipple-areola complex and in the tail of the breast.⁷ Even total or simple mastectomy, where an ellipse of skin including the nipple-areola complex is resected with the underlying breast, may fail to remove all breast tissue. The development of breast cancer has been reported after both types of mastectomy, as late as 15 years after surgery.^{8,9} The actual risk reduction that is provided by prophylactic mastectomy is presumed to be substantial but cannot be precisely measured due to uncertainty of pre-treatment risk, variable indications, and incomplete follow-up.¹⁰ Even if risk reduction could be quantified, medical, cultural and financial issues make this approach unfeasible in clinical practice for most women.

Hormonal Factors

Breast cancer risk is clearly related to hormonal factors. After premature menopause by ovarian ablation, the risk of subsequent breast cancer is reduced by up to 75%, with the greatest reduction in young, thin, nulliparous women.¹¹ Other associations of breast cancer risk with hormonal events are accepted, although weaker. Later menarche (after 14 compared to 11 or younger) and young age at first birth (under 20 versus over 35), are also associated with reductions in breast cancer risk of 20%-50%.¹²

Such lifestyle factors as a high-fat diet and a sedentary existence, which are linked to a higher risk of breast cancer, may be related to hormonal factors. Stringent dietary fat reduction, to less than 20% of total calories from fat, results in significant lowering of blood estradiol levels in post-menopausal women,¹³ and moderate exercise reduces the frequency of ovulation among adolescent girls.¹⁴ These findings further

support the hypothesis that breast cancer risk may be lowered by hormonal manipulation.

Chemoprevention

Because of inherent difficulties in implementing lifestyle modifications and the poor acceptance of prophylactic mastectomy, attention has turned to chemoprevention. The first drug to undergo large-scale testing is the anti-estrogen tamoxifen. Multiple controlled trials of adjuvant tamoxifen therapy of women with breast cancer have shown that tamoxifen not only improves freedom from relapse but also reduces by 47% the risk of a new primary cancer in the contralateral breast.¹⁵ Based on this and other evidence, the National Surgical Adjuvant Breast and Bowel Project (NSABP) randomized 13,338 women with increased risk of breast cancer but no previous cancer diagnosis to either daily tamoxifen or placebo for five years.¹⁶

In April 1998, the Breast Cancer Prevention Trial (BCPT) was halted after a monitoring committee concluded that their interim analysis results met the criteria for early stopping. After a mean follow-up of only four years, 213 women in the placebo group developed breast cancer (154 with invasive cancers) compared to only 116 women (85 with invasive cancers) in the tamoxifen group. This 46% reduction in incidence is almost identical to the 47% reduction in contralateral cancers among women treated with adjuvant tamoxifen after surgical treatment for breast cancer. The results were announced to the press and posted electronically to a government web site (<http://cancertrials.nci.nih.gov/>), and they will be published soon in traditional journal format.

In addition to the reduced breast cancer incidence, there was a 34% decrease in bone fractures favoring the tamoxifen group, confirming previous observations of tamoxifen's estrogen-like effect on bone mineralization.¹⁷ These positive effects were partly balanced by an increased incidence in women aged 50 years and above of endometrial cancer and thrombotic events. In the tamoxifen group there were 33 endometrial cancers and 47 thrombotic episodes compared to 14 endometrial cancers and 25 thrombotic episodes in the placebo group. The 19 additional cases of endometrial cancer must be weighed against the 97 cases of breast cancer (69 invasive cancers) that were avoided.

The early stopping of the BCPT prompted the publication of interim analyses of two European trials of tamoxifen prevention, one from England¹⁸ and one from Italy.¹⁹ Both failed to detect any reduction in breast cancer incidence among the women taking tamoxifen compared to those taking placebos. How does

one account for the striking differences between the BCPT and the two European trials?

An editorial in the same issue of the *Lancet*²⁰ pointed out differences among the three trials that might explain the conflicting results. The Italian trial had problems with compliance (26% dropped out, most in the first year), as well as a low rate of new cancers detected. There were 41 cases of breast cancer among 5408 subjects (0.7%) compared to 329 among 13,388 women (2.5%) in the BCPT. In the British trial the size of the study population was much smaller (2741 evaluable subjects), although the incidence of breast cancer (2.8%) was similar to that of the BCPT. Both European trials had age distributions skewed toward younger subjects than the BCPT. Since the preventive effect in the BCPT was confined to estrogen receptor positive tumors, which are more common in older women, the age shift could account for some of the difference among the trials.

The most interesting hypothesis for the differences in outcomes relates to the eligibility criteria for the three trials. The European trials, especially the British study, determined high risk for breast cancer mainly on family history. The BCPT gave more weight to personal risk factors, such as menarche at 11 or younger, first live birth at 25 or older, a history of benign breast biopsies, especially biopsies showing atypical hyperplasia, or a history of lobular carcinoma in situ. One possibility is that tamoxifen may be more effective in preventing sporadic breast cancers and less effective in preventing breast cancers resulting from a genetic predisposition. There is evidence that the effects of well-recognized hormonal risk factors may be modified by genetic predisposition. In one large longitudinal study,²¹ the traditional hormonal effects in breast cancer risk were confirmed only among women *without* a family history of breast cancer in a mother or sister. In other words, women *with* this type of strong family history of breast cancer apparently were not protected by later menarche, young age at first pregnancy, or artificial menopause. This represents an important area of research that will be addressed by analysis of genetic risk factors among the studies' participants, such as mutations in the BRCA1 and BRCA2 genes, whose normal function seems to involve suppression of breast cancer development.^{22,23}

In the final analysis, the BCPT is robust and its results are biologically consistent with previous observations. There is little reason to doubt its conclusions.

Who should take tamoxifen to prevent breast cancer?

The decision to take tamoxifen for primary prevention of breast cancer is a serious matter that

should not be undertaken lightly. In North America, home of the BCPT trial participants, women should be considered for tamoxifen therapy only if they fulfill the eligibility criteria for the BCPT. Volunteers were eligible for the BCPT if they were age 60 and older *or* had a diagnosis of lobular carcinoma in situ (at any age). Women in these categories have approximately a 1.7% risk of developing breast cancer in their next five years of life. For all other women, a computer program determined eligibility by identifying those with a similar degree of high risk based on the following factors:

1. Number of first-degree relatives with previously diagnosed breast cancer.
2. Age at menarche.
3. Parity and age at first delivery.
4. Number of prior benign breast biopsies, especially with diagnosis of atypical hyperplasia.

Therefore, a North American woman aged 60 or more or a younger woman with a diagnosis of lobular carcinoma in situ should be considered for five years of tamoxifen therapy. Other women require a more sophisticated risk assessment that soon will be made available by the NSABP. The final decision must include consideration of the woman's risk for thromboembolic disease and for uterine carcinoma, as well as her risk for breast cancer. Finally, tamoxifen therapy is not a substitute for annual mammographic screening and periodic clinical breast examinations. This type of screening has been proven to reduce *mortality* from breast cancer, something not yet proven for tamoxifen therapy.

It is more difficult to make recommendations for women in other parts of the world. The geographic variability in breast cancer risk, which may reflect a complex combination of genetic, environmental, dietary, and lifestyle factors, argues against generalization of the North American experience to all parts of the world. The interim analyses of the two European tamoxifen trials^{19,20} lend support to this argument. In fact, for a European woman who fits the eligibility criteria for the British or Italian trials, there is now good reason to argue against prescription of tamoxifen outside of a clinical trial.

For women in Saudi Arabia, there is evidence that the lifetime risk of breast cancer is closer to that seen in Japan than to the North American risk. The average age-adjusted incidence rates per 100,000 population for female breast cancer are 89.2 for (white) women in the United States and 21.9 for women in Japan.²⁴ The Saudi Arabian National Cancer Registry 1994-1996 Report will show that the age-adjusted incidence rate for Saudi women is 14 cases per 100,000 population.²⁵ Therefore, for Saudi women in general, the best use of

tamoxifen now is probably its traditional role as adjuvant therapy of breast cancer and for the prevention of a second primary breast cancer among breast cancer survivors. More research, especially in specific populations, is needed before widespread use of tamoxifen can be recommended for primary prevention of breast cancer.

Robert K. Stuart, MD

Chairman

Department of Oncology (MBC-64)

King Faisal Specialist Hospital
and Research Centre

P.O. Box 3354

Riyadh 11211, Saudi Arabia

References

1. Fletcher SW, Black W, Harris R, et al. Report of the International Workshop on Screening for Breast Cancer. *J Natl Cancer Inst* 1993;85:1644-56.
2. National Institutes of Health Consensus Development Panel: National Institutes of Health Consensus Development Conference Statement: breast cancer screening for women ages 40-49, January 21-23, 1997. *J Natl Cancer Inst* 1997;89:1015-26.
3. Parkin DM. Cancer of the breast, endometrium, and ovary: geographic correlations. *Europ J Cancer Clin Oncol* 1989;25:1917-25.
4. Dunn JE. Breast cancer among American Japanese in the San Francisco Bay area. *J Natl Cancer Inst Monograph* 1977;47:157-60.
5. Kliever EV, Smith KR. Breast cancer mortality among immigrants in Australia and Canada. *J Natl Cancer Inst* 1995;87:1154-61.
6. Boone CW, Kelloff GJ, Freedman LS, et al. Intraepithelial and postinvasive neoplasia as a stochastic continuum of clonal evolution, and its relationship to mechanisms of chemopreventive drug action. *J Cell Biochem* 1993;17:14-25.
7. Goldman L, Goldwyn R. Some anatomic considerations of subcutaneous mastectomy. *Plast Reconstruct Surg* 1973;51:501a.
8. Goodnight J, Quagliana J, Morton D. Failure of subcutaneous mastectomy to prevent the development of breast cancer. *Surg Oncol* 1984;26:198-202.
9. Holleb A, Montgomery R, Farrow J. The hazard of incomplete simple mastectomy. *Surg Gynecol Obstet* 1954;121:819-24.
10. Pennisi V, Capozzi A. Subcutaneous mastectomy data: a final statistical analysis of 1500 patients. *Aesthet Plast Surg* 1989;13:15-22.
11. Trichopoulos D, MacMahon B, Cole P. Menopause and breast cancer risk. *J Natl Cancer Inst* 1972;48:605-13.
12. Henderson BE, Bernstein L. Endogenous and exogenous hormonal factors. In: Harris JR, Lippman ME, Morrow M, Hellman S, eds. *Diseases of the Breast*. New York: Lippincott-Raven, 1996:185-200.
13. Prentice R, Thompson D, Clifford C, et al. Dietary fat reduction and plasma estradiol concentration in healthy postmenopausal women. *J Natl Cancer Inst* 1990; 82:129-34.
14. Bernstein L, Ross RK, Lobo RA, et al. The effects of moderate physical activity on menstrual cycle patterns in adolescence: implications for breast cancer prevention. *Brit J Cancer* 1987;55:681-5.
15. Nayfield SG, Karp JE, Ford LG, et al. Potential role of tamoxifen in prevention of breast cancer. *J Natl Cancer Inst* 1991;83:1450-9.
16. Redmond CK, Wickerham DL, Cronin W, et al. The NSABP breast cancer prevention trial (BCPT): a progress report. *Proc Amer Soc Clin Oncol* 1993;12:69a.
17. Love RR, Barden HS, Mazess RB, et al. Effect of tamoxifen on lumbar spine bone mineral density in postmenopausal women after 5 years. *Arch Int Med* 1994;154:2585-8.
18. Powles T, Eeles R, Ashley S, et al. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. *Lancet* 1998;352:98-101.
19. Veronesi U, Maisonneuve P, Costa A, Sacchini V, Maltoni C, Robertson C, et al., on behalf of the Italian Tamoxifen Prevention

STUART

- Study. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. *Lancet* 1998;352:93-7.
20. Pritchard KI. Is tamoxifen effective in prevention of breast cancer? *Lancet* 1998;352:122-3.
 21. Colditz GA, Rosner BA, Speizer FE. Risk factors for breast cancer according to family history of breast cancer. *J Natl Cancer Inst* 1996;88:365-71.
 22. Easton DF, Bishop DT, Ford D, et al. Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. *Amer J Human Genetics* 1993;52:678-701.
 23. Struwing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *New Engl J Med* 1997;336:1401-8.
 24. Trichopoulos D, Lipworth L, Petridou E, Adami H. Epidemiology of cancer. In: De Vita VT, Hellman S, Rosenberg SA, editors. *Cancer: Principles and Practice of Oncology*. Philadelphia: Lippincott-Raven, 1997:236.
 25. Dr. Nasser Al-Hamdan, personal communication.