4. Veronesi U, Maisonneuve P, Costa A, *et al*. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. *Lancet* 1998, **352**, 93–97.
5. Powles TJ, Hickish T. Tamoxifen therapy and carcinogenic risk. *J Natl Cancer Inst* 1995, **87**, 1343–1344.
6. Fisher B, Costantino JP, Wickerham LD, *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**, 1371–1388.
7. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998, **351**, 1451–1467.

Breast cancer prevention: the next steps

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The public health implications of the Breast Cancer Prevention Trial (BCPT-NSABP-P1) results are enormous. From the general oncological perspective, this is the first trial in history to demonstrate with the highest level of evidence (i.e. a prospective randomised double-blinded phase III trial) the efficacy of primary chemoprevention in inhibiting the development of breast cancer in a high-risk population. Selection of appropriate candidates for preventive use of tamoxifen is essential because: (1) the potential users are 'healthy' women; and (2) tamoxifen has toxicities which, though infrequent, can be serious or life-threatening. As a result, the decision regarding who should be considered for preventive tamoxifen must address two issues. First, who is expected to benefit from the drug based on her membership in the tested target population; and second, to what extent do the observed risks of tamoxifen, its toxicities, compete with its potential benefits in a given individual?

To facilitate the selection of appropriate high-risk women for tamoxifen use, the National Cancer Institute (NCI) developed a formal method for assessing breast cancer risk into a 'risk disk'. The risk disk incorporates those features of the Gail model [1] that served as eligibility criteria for entry into the BCPT into a computer model for estimating an individual's 5-year and projected lifetime risks for developing breast cancer (NCI Cancer Information Service; NCI Website). However, the fact that the BCPT demonstrated the efficacy of tamoxifen in reducing breast cancer incidence in high-risk women in the face of infrequent but serious toxicities prompted the synthesis of the multiple effects of tamoxifen into a unified risk–benefit model for individualising estimated outcomes for a particular woman [2]. Accordingly, Gail and colleagues [3] subjected the risks (primarily endometrial cancer, stroke, pulmonary embolism and deep vein thrombosis and some lesser toxic side-effects) and benefits (breast cancer and fracture reduction) of tamoxifen as observed in the BCPT to a quantitative analysis that yielded an estimate of the relative risks of this drug for specific clinical endpoints. The groups that benefit most from preventive tamoxifen include younger women at higher risk and women over 50 years of age who do not have a uterus [3,4]. In contrast, the risk–benefit ratio is far less clear for women who are 50 years of age or older who are postmenopausal, have not had a hysterectomy, and have no history of lobular carcinoma *in situ* (LCIS), atypical hyperplasia (AH) or ductal carcinoma *in situ* (DCIS) [5]. Importantly, both the risk disk and the quantitative risk–benefit model are merely tools in the decision-making process for an interested woman. A woman's final decision regarding whether or not to implement preventive tamoxifen must involve discussions with her physician and other knowledgeable health professionals and interested parties [2,3].

The benefits and risks of tamoxifen revealed by the BCPT have also stimulated the next step, a clinical breast cancer prevention trial that will compare the now established standard for prevention, tamoxifen, to raloxifene, a second generation SERM approved for the prevention of osteoporosis in postmenopausal women [6–8]. Women assigned to the raloxifene group of the MORE (Multiple Outcomes of Raloxifene Evaluation) osteoporosis study [7] showed a decreased incidence of breast cancer as a secondary endpoint [9], suggesting raloxifene as an appropriate candidate SERM for testing against tamoxifen. Raloxifene has similar desirable effects to tamoxifen on biochemical markers of cardio-

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vascular risk [10] and may be less stimulatory to the uterus [6,11]. Accrual to the Study of Tamoxifen and Raloxifene (STAR) NSABP P-2 began in July 1999 at almost 500 centres in North America. Eligible women must be postmenopausal women, 35 years or older and have an increased risk reflected in a $\geqslant 1.66\%$ projected 5-year probability of developing invasive breast cancer according to the breast cancer Risk Assessment Profile (RAP) generated by the NSABP Biostatistical Center. The RAP incorporates Gail model criteria, as well as a history of benign breast biopsies, LCIS and AH, as well as general health status, personal and family medical history and lifestyle. The plan is to randomise 22 000 eligible women to tamoxifen 20 mg or raloxifene 60 mg per day for 5 years. Study endpoints include invasive and noninvasive breast cancer, cardiovascular disease, endometrial cancer, bone fractures and vascular events.

Appendix

NCI Website. Available at: http://www.nci.nih.gov. Access for sign-up form for 'risk disk'. Accessed October 1999.

References

1. Gail MH, Brinton LA, Byar DP, *et al*. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst* 1989, **81**, 1879–1886.
2. Chlebowski RT, Collyar D, Somerfield MR, *et al*. American society of clinical Oncology technology assessment on breast cancer risk reduction strategies: tamoxifen and raloxifene. *J Clin Oncol* 1999, **17**, 1939–1955.
3. Gail MH, Costantino JP, Bryant J, *et al*. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. *J Natl Cancer Inst* 1999, **91**, 1829–1846.
4. 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**, 1371–1378.
5. Fisher B. National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial: a reflective commentary. *J Clin Oncol* 1999, **17**, 1632–1639.
6. Delmas PD, Bjarnason NH, Mitlak BH, *et al*. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *New Engl J Med* 1997, **337**, 1641–1647.
7. Ettinger B, Black DM, Mitlak BH, *et al*. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene. Results from a 3-year randomized clinical trial. *JAMA* 1999, **282**, 637–650.
8. Khovidhunkit W, Shoback DM. Clinical review: clinical effects of raloxifene hydrochloride in women. *Ann Intern Med* 1999, **130**, 431–439.
9. Cummings SR, Eckert S, Krueger KA, *et al*. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. *JAMA* 1999, **16**, 2189–2197.
10. Walsh BW, Kuller LH, Wild RA, *et al*. Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. *JAMA* 1998, **279**, 1445–1451.
11. Draper MW, Flowers DE, Huster WJ, *et al*. A controlled trial of raloxifene (LY139481) Hcl: impact on bone turnover and serum lipid profile in healthy postmenopausal women. *J Bone Mineral Res* 1996, **11**, 835–842.

Update on raloxifene to prevent endometrial-breast cancer

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Abstract

In the mid 1980s when tamoxifen was shown to be associated with endometrial neoplasia there was a renewed interest in another SERM compound, raloxifene. Experimental animal data suggested that raloxifene did not stimulate the endometrium as tamoxifen does while having similar anti-oestrogenic effects in breast tissue as tamoxifen. Clinical data has now shown that raloxifene does not stimulate the endometrium in postmenopausal women. It results in no hyperplasia, no increase in endometrium thickness or polyp formation and virtually no proliferation. Further studies are necessary to see if long-term raloxifene use will reduce the risk of endometrial cancer. In studies of raloxifene as treatment for osteoporosis, when viewed as a secondary endpoint there was a significant reduction in risk of new onset breast cancer. Further studies with breast cancer as a primary endpoint are ongoing (the STAR Trial). © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: SERMs; Raloxifene; Tamoxifen; Endometrial Cancer; Breast Cancer; Transvaginal ultrasound; Sonohysterography

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