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Breast cancer prevention: results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) breast cancer prevention trial (NSABP P-1: BCPT)

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Breast cancer is the most common non-cutaneous cancer (29%) and the second highest cause of cancer deaths (16%, second only to lung cancer) among women in the US [1]. Despite advances in the treatment of breast cancer and a recent downward trend in breast cancer mortality with a levelling off of breast cancer incidence [1,2], this disease remains a major public health problem, prompting increasing emphasis on early detection and prevention. The oestrogen responsiveness of breast tumours suggested the use of a therapeutic antagonist to the action of oestrogen, a selective oestrogen receptor modulator, or SERM, in the prevention of breast cancer [3]. Accumulating evidence from breast cancer treatment trials pointed to the ability of the first SERM, tamoxifen, to prevent second primary breast cancers in the contralateral breast in women being treated in the adjuvant setting for established invasive disease [4–8].

Encouraged by this data, in 1992 the NSABP started the Breast Cancer Prevention Trial (P-1: BCPT) to test the ability of tamoxifen to prevent breast cancer in women at increased risk for the disease [9]. The study randomised 13 388 women 35 years of age or older who were at increased risk for breast cancer according to Gail model [10] risk factors (family history, age and personal history (i.e. age at first birth, age at menarche, previous breast biopsies)) to tamoxifen 20 mg per day or placebo for 5 years. Recruitment and retention of such a large number of healthy participants presented a major challenge which was successfully met by the NSABP during its implementation of this trial. The resulting data showed that through 69 months of follow-up tamoxifen reduced the risk of invasive breast cancer, primarily oestrogen receptor (ER)+ tumours, by 49% (two-sided $P < 0.00001$) with a cumulative incidence of 175 versus 89 cases of invasive breast cancer in the placebo and tamoxifen groups respectively. The decrease in breast cancer incidence occurred in all age groups and all eligible risk categories. Tamoxifen reduced the risk of noninvasive breast cancer by 50%, with 69 versus 35 cases in the placebo and tamoxifen arms, respectively (two-sided $P < 0.002$). The benefits of tamoxifen were most prominent in participants with a history of lobular carcinoma *in situ* (LCIS; 56% reduction in risk) and atypical hyperplasia (AH; 87% reduction in risk). As a secondary endpoint, tamoxifen reduced the incidence of fractures (hip, radius, spine) by 19%, approaching but not reaching statistical significance. Another secondary endpoint, the rate of ischaemic heart disease, was unaffected by tamoxifen. The major toxicity was an increase in the rate of endometrial cancer (risk ratio 2.53, 95% CI: 1.35–4.97), as previously demonstrated in treatment trials with tamoxifen. The rates of stroke, pulmonary embolism and deep vein thrombosis were elevated in the tamoxifen group. Toxicities were most evident in women over 50 years of age. Based on the BCPT results, the Food and Drug Administration approved tamoxifen for use in the reduction of breast cancer incidence in women at increased risk for this disease.

The updated results of two smaller European studies evaluating the breast cancer preventive efficacy of tamoxifen versus placebo were published shortly before publication of the BCPT results [11,12]. Neither study yielded statistically significant results regarding the efficacy of tamoxifen as a preventive, or risk reducing, agent, in apparent contradiction to the results of the BCPT. Among 2471 women followed for a median of 70 months in the Royal Marsden trial, a relative risk of 1.06 was observed for the tamoxifen versus the placebo group. In the Italian trial 5408 women were followed for a median of 46 months. A variety of explanations have been offered for the discrepancy in outcomes, including poor compliance in the Italian study; strong family

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history, suggestive of genetically determined disease, in the British study; and the use of hormone replacement therapy in both the British and Italian trials, 42% and 14% respectively. The most cogent explanation is the substantially lower statistical power of the two European trials, which together had fewer than half the number of events of the BCPT (111 breast cancer cases in the British plus Italian trials versus 265 events in the BCPT). In view of this, the BCPT results remain the most definitive with regard to tamoxifen's role as the new standard of care for the chemoprevention of breast cancer in appropriately selected women.

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Update on tamoxifen to prevent breast cancer. The Italian Tamoxifen Prevention Study

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The Italian Tamoxifen Prevention Study included healthy women aged 35–70 years who had had a total hysterectomy for reasons other than neoplasm. Women were randomised to receive tamoxifen 20 mg day or placebo for 5 years. The preliminary results of the study after a median of 46 months show no difference in the incidence of breast cancer between the two arms [1]. Of the 41 cases of breast cancer that have occurred so far, 22 cases were in the placebo group and 19 cases in the tamoxifen group. There was an increased risk of venous vascular events (38 women on tamoxifen versus 18 women on placebo, $P = 0.0053$), mainly consisting of superficial phlebitis, and 15 versus 2 cases of severe hypertriglyceridaemia in the tamoxifen and placebo arms respectively ($P = 0.0013$).

Among women on tamoxifen for more than 1 year, there was a trend towards a beneficial effect of tamoxifen (11 in the tamoxifen arm versus 19 in the placebo arm, $P = 0.16$).

Interestingly, a borderline significant reduction of breast cancer was observed among women who were hormone replacement therapy (HRT) users and received tamoxifen. Compared with the 8 cases of breast cancer occurring among the 390 HRT users who were on placebo, there was 1 case of breast cancer among the 362 HRT users who were receiving tamoxifen (RR = 0.13, 95% CI: 0.02–1.02). Although our study was regarded as being affected by a higher dropout rate, a subsequent analysis comparing all three primary prevention trials of tamoxifen indicate that the number of discontinuations

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