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

A. Decensi [a,*], B. Bonanni [a], N. Rotmensz [b], C. Robertson [b], A. Guerrieri-Gonzaga [a], S. Mora [a], S. Diani [a], M. Cazzaniga [a], A. Costa [a] on behalf of the Italian Investigators

[a] *Chemoprevention Unit, European Institute of Oncology, via Ripamonti 435, 20141 Milan, Italy*
[b] *Division of Epidemiology and Biostatistics, European Institute of Oncology, via Ripamonti 435, 20141 Milan, Italy*

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

* Corresponding author. Tel.: +39-0257-489-861; fax: +39-0257-489-809.
E-mail address: andrea.decensi@ieo.it (A. Decensi).

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for reasons other than major events was 20.7, 28.8 and 35.5% in the Italian, NSABP and Marsden trials, respectively [2]. The dropout rate was higher during the first year after recruitment (2% per month in the first year versus 1% in years 2–5).

Since several women left the study voluntarily for menopausal symptoms, the combination of tamoxifen and HRT might reduce the side-effects of tamoxifen. Moreover, their combination could reduce the risks of either agent, such as breast and endometrial cancer [3]. To provide further insight into this combination, we assessed the effect of tamoxifen and transdermal HRT on several cardiovascular risk factors, including blood cholesterol levels, within the trial [3]. Compared with small changes in the placebo group, tamoxifen was associated with changes in total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol of −9, −14 and −0.8%, respectively, which were similar in continuous HRT users and never HRT users. By contrast, the decrease induced by tamoxifen of total and LDL cholesterol was blunted by two thirds in women who started HRT while on tamoxifen. Thus, the beneficial effects of tamoxifen on cardiovascular risk factors are unchanged in current HRT users, while they might be attenuated in women who start transdermal HRT while on tamoxifen. While tamoxifen can reduce the risk of breast cancer associated with HRT use, HRT could, alternatively, reduce tamoxifen's adverse events (i.e. vasomotor and urogenital symptoms and, possibly, endometrial cancer). Preliminary results from the trial also indicate that the HRT use can maintain a higher compliance rate. These findings provide the background for future investigations on the combination of tamoxifen and HRT in order to reduce the risks while retaining the benefits of both agents.

We also studied the biological activity of tamoxifen in order to establish a dosing schedule with a better risk: benefit ratio [4,5]. We measured the blood concentrations of tamoxifen and its main metabolites in a dose titration study in 105 healthy women (placebo, tamoxifen 10 mg alternate days, 10 mg/day and 20 mg/day). Drug levels measured after two months of treatment were correlated with the changes in surrogate biomarkers of cardiovascular or breast cancer risk, including insulin-like growth factor-I. The means (± standard deviation (S.D.)) for tamoxifen and N-desmethyltamoxifen (metabolite-X) concentrations (ng/ml) were dose-related, being, respectively: 0 and 0 with placebo, 26.8±15.1 and 43.7±22.5 with 10 mg every other day, 51.2±24.1 and 90.7±48.0 with 10 mg/day and 136.0± 52.7 and 230.6±75.0 with 20 mg/day of tamoxifen. At variance, the biomarker changes were of comparable magnitude at any drug concentration except for platelet count and triglycerides levels, the latter showing a trend to an increase with increasing tamoxifen concentrations. We, therefore, conclude that a 80% reduction in blood concentrations does not appear to affect the activity of tamoxifen on biomarkers of cardiovascular or breast cancer risk, and may in fact have a more favourable safety profile. Additional studies are warranted to determine the most appropriate dose of this agent.

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A brief review of the breast cancer prevention trials

J. Cuzick [a,*], A. Howell [b]

[a] *Imperial Cancer Research Fund Statistics and Epidemiology Unit, 61 Lincoln's Inn Fields, London WC2A 3PX, UK*
[b] *Department of Medical Oncology, Manchester Christie Hospital, Manchester, UK*

* Corresponding author. Tel.: +44-20-7269-3006; fax: +44-20-7269-3429.
E-mail address: j.cuzick@icrf.icnet.uk (J. Cuzick).

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