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

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Table 1
Demographic data from the four breast cancer prevention trials

	n	Med. FU months	Per cent age < 50 years	Per cent first-degree relative	Per cent HRT use on study	Invasive breast cancer	
						Tamoxifen	Placebo
P1	13 388	55	37	57	< 10	89	175
RMH	2471	70	62	96	26	34	36
Italian	5408	36	38	12	12	19	22
IBIS[a]	5596	26	51	91	22	(83)	

[a] Accrual ongoing ratio (as of 1 October 1999).

1. Introduction

Following the observation that tamoxifen reduced the incidence of contralateral breast cancer when used after surgery, it was suggested that the prevention of breast cancer in high-risk women might be possible [1,2]. A pilot study was initiated under the auspices of the United Kingdom Coordinating Committee for Cancer Research (UKCCCR) at the Royal Marsden Hospital (RMH) under the direction of Trevor Powles. The early results of this trial have now been reported along with a similar Italian study [3,4]. As a result of the favourable compliance data and lack of unexpected toxicities in the RMH trial [5], the UKCCCR launched its main trial, the International Breast Cancer Intervention Trial (IBIS) in 1992. A similar trial was initiated in the USA in 1992 under the auspices of the National Surgical Adjuvant Breast and Bowel Project (NSABP). All trials were placebo controlled studies of 5 years of tamoxifen. The early results of the NSABP trial — P1 (prevention 1) were reported recently [6]. The results of this study differed from those of the RMH and Italian studies; this review is an attempt to explain these differences. While IBIS has not completed recruitment we do have some demographic data from the trial and, thus we can make some comparisons between all 4 prevention trials. The characteristics of the 4 trials are shown in Table 1.

2. Breast cancer reduction

The early results of three tamoxifen studies have been reported [4–6] see (Table 1). The IBIS trial is due to recruit until the end of 2000 and will report 1 or 2 years later. P1 shows a clear dramatic reduction (OR = 0.51; 95% CI: 0.39–0.66) in the incidence of invasive cancers in the tamoxifen-treated arm. This result is very similar to the reduction in contralateral tumours reported in the overview of tamoxifen adjuvant trials [7]. The RMH and Italian trials do not show appreciable treatment effects. In the RMH trial, the incidence curves for invasive cancers for the two arms are superimposable [3]. When the Italian trial is analysed according to whether subjects took medication for longer than 1 year, there were indications of an effect (19 versus 11 OR = 0.58) although the numbers are small and this is a subgroup comparison. Also, there was one case of breast cancer in the tamoxifen + HRT group compared with 8 in the placebo + HRT group ($P = 0.02$).

The incidence reduction in the P1 trial is almost exclusively restricted to oestrogen receptor (ER)-positive tumours. In the P1 trial, this reduction was 67% in this group (OR = 0.33; 95% CI: 0.22–0.45) whereas there was a slight increase of ER-negative tumours (OR = 1.22, 95% CI: 0.74–2.03).

3. Conclusion

Perhaps the main conclusion is that there are no clear conclusions at this stage. The differences between the trials are sufficiently large to be difficult to attribute to chance, but this is still a real possibility. None of the demographic variables clearly explain the differences, although there are important variations. The P1 result is biologically plausible and equivalent to the risk reduction seen in the contralateral breast in the adjuvant tamoxifen trials (EBCTCG). The RMH trial is relatively small and follow-up in the Italian trial relatively short. Results from the IBIS trial will be crucial to our interpretation of the European data. If this trial is negative, it might suggest that hereditary at risk breasts are relatively unresponsive to tamoxifen. If positive it may point to a relative lack of power in the other European trials as a cause of their negativity.

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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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