

Endocrine prevention of breast cancer: the jury is half in

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Following the report that tamoxifen significantly reduced the incidence of cancer in the normal breast contralateral to one with cancer (Cuzick *et al.* 1985), four prevention trials, each with a similar design, were established. Three of these were reported recently (USA (Fisher *et al.* 1998), Italy (Veronesi *et al.* 1998), UK (Powles *et al.* 1998)) and a fourth (the International Breast Intervention Study: IBIS) is due to finish recruitment of 7000 subjects next year. Each trial is randomised and double blind comparing 20 mg of tamoxifen with a placebo daily for five years. The recent overview of adjuvant trials showed that five years of tamoxifen reduced contralateral breast cancer by 49% and confirms this period of treatment as the most optimal (Early Breast Cancer Trialists' Collaborative Group 1998).

The UK pilot trial began in October 1986 as a prelude to the main IBIS study which began in November 1993. The USA trial (BCPT: Breast Cancer Prevention Trial (NSABP)) started in June 1992 and the Italian study in October 1992. These start dates reflect median follow-up times in each trial, which in the recent publications were 54.6 months (USA), 30.5 months (Italy) and 70.0 months (UK). Median follow-up is related to rate of entry; the relatively long period in the USA trial reflects a very rapid rate of entry in the early stages, whereas the European trials had slower recruitment.

The size and follow-up duration of the trial are proportional to the number of events in terms of invasive and *in vivo* breast cancers found. Despite the follow-up of a median of about four and a half years, the USA trial has the greatest number of events by far (Table 1). The Italian

trial has more numbers than the UK trial, but a relatively short follow-up (about two and a half years) and thus fewer events.

The number of events is increased if women at high risk of breast cancer are entered. In the USA trial subjects had to be 60 or over or, if younger, to have equivalent risk to a 60-year-old. Only women after hysterectomy were entered into the Italian study: 48.3% had bilateral oophorectomy and 18.6% had unilateral oophorectomy. Thus many women in this trial were at decreased risk of breast cancer because of an induced menopause, compared with women in the general population. This is reflected in the small number of invasive breast cancers seen (19 on Tamoxifen vs 22 on placebo), producing a trial of low power compared with the USA study. The UK study entry was based mainly on a moderate family history (usually one first degree relative with a breast cancer before the age of 50) or a history of excision of a benign tumour.

There was a highly significant reduction in the numbers of invasive and *in vivo* cancers in the USA trial in women treated with tamoxifen, whereas there was no significant effect in either the Italian or the UK trials. All three studies were analysed on an intention to treat basis. Approximately 23%, 26% and 35% of patients stopped treatment in the USA, Italian and UK studies respectively. Such compliance is not surprising, considering the highly controversial nature of the trials, but they affect the power of the smaller trials more than the large USA study.

With one markedly positive study and two negative ones, can we make any judgements concerning the preventative value of tamoxifen? The USA trial is most

Table 1 Characteristics of the three reported tamoxifen prevention trials

	USA (June 1992-July 1998)		ITALY (Oct 1992-July 1997)		UK (Oct 1986-April 1996)	
	Tamoxifen	Placebo	Tamoxifen	Placebo	Tamoxifen	Placebo
No. randomised	6681	6707	2700	2708	1238	1233
Stopped treatment (%)	23.7	19.7		40.1	30.1	
Median follow-up (months)		54.6		30.5		70.0
HRT allowed		No		Yes (? %)		Yes (41.6 %)
Invasive cancers	89	175	19	22	30	32
<i>In situ</i> cancers	35	69	?	?	4	4
Breast cancer deaths	3	6	0	0	4	1

Table 2 Numbers of invasive tumours

Trial	Tamoxifen	Placebo	Relative risk
NSABP	89	175	0.51
UK	30	32	0.94
Italy	19	22	0.86
Total	138	229	0.6
Contralateral	93	175	0.53

important because of its size. The relative risk of invasive breast cancer in tamoxifen-treated patients in the USA study is 0.51 (Table 2). There is a small reduction in relative risk in the other two studies. However, when the numbers of tumours from all three studies are summated, the relative risk reduction by tamoxifen remains highly significant at 0.60. This is equivalent to the risk reduction by tamoxifen in the incidence of contralateral breast cancers in the adjuvant trials (Table 2).

Tamoxifen prevention trials to date therefore suggest that tumours may be prevented. In the USA study *in vivo* cancers were also greatly reduced (Fisher *et al.* 1998). Do these benefits and others, such as the increase in bone density and reduction in lipids (Powles *et al.* 1989 and Powles *et al.* 1996) outweigh the side effects of tamoxifen? The side effects reported in the three recent papers are summarised in Table 3. In the USA study subjects were asked a large series of questions concerning day to day side effects on a five point scale. Forty-six percent of tamoxifen users reported hot flushes (flashes) as being 'quite a bit' or 'extremely' bothersome, whereas this was reported in 28.7% of controls. Other continuous side effects were relatively minor. Development of a preventative agent which reduced flushes is of the highest importance. There was also an excess of embolic events (110% increase) and endometrial cancer (140% increase). However, in all three studies there was, importantly, no excess of non-cancer deaths.

In summary, the reports of these three trials is a milestone in our efforts to reduce the incidence of breast cancer. The USA trial is of the greatest importance because of its size and the exemplary thoroughness with

which it was conducted by the NSABP under Bernard Fisher. The apparent negative results of the Italian and UK trials should be seen in the context of their relative (to the USA trial) lack of power and their small influence on the overall effect when the three studies are combined (Table 2). The major question is whether the reduction in incidence of breast cancer, similar to that seen in the contralateral breast in the adjuvant tamoxifen trials (Early Breast Cancer Trialists Collaborative Group 1998), will translate into a survival advantage for women. Unfortunately, the USA trial will not contribute to answering this question, since it is now unblinded and women can opt for treatment if in the control arm. The Italian and UK trials will contribute to the answer and their results can be combined with the IBIS study (includes 7000 subjects) to answer the survival question. In addition it will be of importance to see if IBIS produces a similar reduction in the incidence of breast cancer.

The future lies in confirmation of the USA results, and, if confirmed, trials of antioestrogens with a better side effect profile compared with tamoxifen. Raloxifene, which is less uterotrophic, will be compared with tamoxifen in the next NSABP trial. New pure anti-oestrogens in development may contribute by producing a greater inhibitory effect on the breast (Bramley *et al.* 1997).

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Table 3 Reported side effects of tamoxifen in the three prevention trials

	USA		ITALY		UK	
	Tamoxifen	Placebo	Tamoxifen	Placebo	Tamoxifen	Placebo
Hot flushes (%)	45.7	28.7	—	—	—	—
Vaginal discharge (%)	12.4	4.5	—	—	—	—
Depression (%)	8.8	9.0	—	—	—	—
Cardiac events	71	62	—	—	—	—
Vascular events	35	41	9	5	—	—
Fractures	91	114	—	—	—	—
Embolic events	40	19	38	18	7	4
Endometrial cancer	36	15	—	—	4	1
Non-breast cancer deaths	54	65	6	9	5	5

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