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RESULTS OF THE CANCER RESEARCH CAMPAIGN ADJUVANT TRIAL FOR PERIOPERATIVE CYCLOPHOSPHAMIDE AND LONG-TERM TAMOXIFEN IN EARLY BREAST CANCER REPORTED AT THE TENTH YEAR OF FOLLOW-UP

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Over 2 000 patients with early breast cancer were recruited into a trial between 1980 and 1985. This trial was of a factorial 2 × 2 design to investigate the benefits of a short course of perioperative cyclophosphamide or tamoxifen 20 mg daily for 2 years. At the tenth year of follow-up no significant benefit is noted for perioperative cyclophosphamide, however the main effect analysis for adjuvant tamoxifen demonstrates a significant improvement in disease-free survival which increases with time during the follow-up period. These results are in keeping with the World Overview of Trials of Adjuvant Tamoxifen. However, this study is unique, having a large number of node negative patients and over 500 premenopausal women in a comparison of tamoxifen and control. The relative risk reductions for the node negative patients for disease-free survival are greater than for the node positive patients. This might suggest that the absolute benefit for adjuvant tamoxifen is similar in both groups of patients, bearing in mind the increased risk of relapse with the node positive patients. No trend for interaction emerges according to age or menopausal status suggesting an identical benefit for premenopausal women. Of particular interest is the development of contralateral breast cancer. The initial overall effect which emerged at the third year of follow-up ceases to be apparent. However, subgroup analysis according to menopausal status suggests a trend for interaction with a reduction in the risk of contralateral breast cancer in the postmenopausal women and an increase in the risk of contralateral breast cancer in premenopausal women. Plausable mechanisms exist to explain this difference in outcome and these data need to be checked against other large trials of adjuvant tamoxifen at a time when we are considering the chemoprophylaxis of breast cancer in high risk premenopausal women.

Key words: Breast cancer, adjuvant therapy, tamoxifen, perioperative cyclophosphamide.

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The Cancer Research Campaign Adjuvant Trial for Early Breast Cancer began recruitment in 1980. The design of this trial repeated both the Nolvadex Adjuvant Trial Organisation (NATO) for adjuvant tamoxifen and the Scandinavian Trial of Perioperative Cyclophosphamide. Thus, patients were randomised to four groups; control, tamoxifen 20 mg daily for two years, perioperative cyclophosphamide 5 mg per kg for 6 days following surgery, and a fourth group receiving both treatments. A more detailed description of this trial is in earlier reports (1, 2).

Special features of this trial, were the inclusion of all operable cases of early breast cancer irrespective of menopausal or nodal status. The 2 × 2 design also allowed an analysis for the 'main effect' of perioperative cyclophosphamide and the 'main effect' of adjuvant tamoxifen. A four-way comparison was also possible although the smaller numbers and the potential for multiple subset analyses weaken the statistical power of this kind of analysis and will not be the subject of the paper.

From 1st May 1984 following data published by the NATO (1983) tamoxifen trial, clinicians were given the option to prescribe tamoxifen for all patients, with randomization only into the cyclophosphamide part of the trial. Therefore only 1 912 patients out of 2 230 were eligible for the tamoxifen main effect analysis.

Other important features of this study which have already been reported were the significant effects that were demonstrated for disease-free survival in node negative as well as node positive patients, and furthermore this was the first and to date the largest trial looking at the effect of tamoxifen alone in premenopausal women. Also this trial was the first to show an effect on the incidence of contralateral breast cancer amongst women exposed to long-term tamoxifen (3). The CRC trial is now in its tenth year of follow-up and this new report concentrates on three important areas: the role of tamoxifen in premenopausal women, the relative risk reduction amongst node negative and node positive patients, and the possible interaction between menopausal status and long-term tamoxifen therapy on the incidence of contralateral breast cancer.

Table 1

Comparison of treatment groups

	Control	Tamoxifen
No. of patients (%)	965 (50.5)	947 (49.5)
Mean age (yrs)	55.4	54.8
Path.tumour <2 cm (%)	267 (27.7)	268 (28.3)
Node positive (%)	372 (38.5)	401 (42.3)
Premenopausal (%)	323 (33.5)	353 (37.3)
Median follow-up (yrs) (range)	7.8 (5.0–10.6)	

Results

Earlier publications failed to demonstrate any significant impact on perioperative cyclophosphamide in overall survival, although there was a transient improvement in the disease-free interval (1, 2). The most recent analysis confirms this lack of effect, thus for the purpose of this publication we will concentrate on the effect of tamoxifen on disease-free and overall survival.

Table 1 describes the demographic details, the number of patients at risk and the duration of follow-up. A total of 1 912 patients were recruited to this trial between 1980 and 1985 including 932 node negative patients and 676 premenopausal patients. There are two possible ways of analysing the data for patients receiving tamoxifen, either the main effect analysis which includes patients taking tamoxifen alone or tamoxifen plus perioperative cyclophosphamide, or alternatively the single strata analysis comparing patients taking tamoxifen only with the untreated controls.

Fig. 1 shows the main effect analysis for disease-free survival which included all 1 912 patients, whereas Fig. 2 shows the disease-free survival for the tamoxifen versus

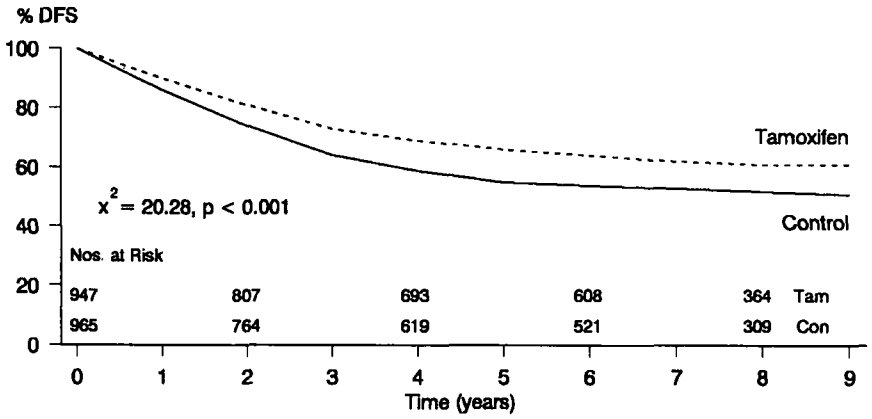

Fig. 1. Tamoxifen main effects analysis—Disease-free survival.

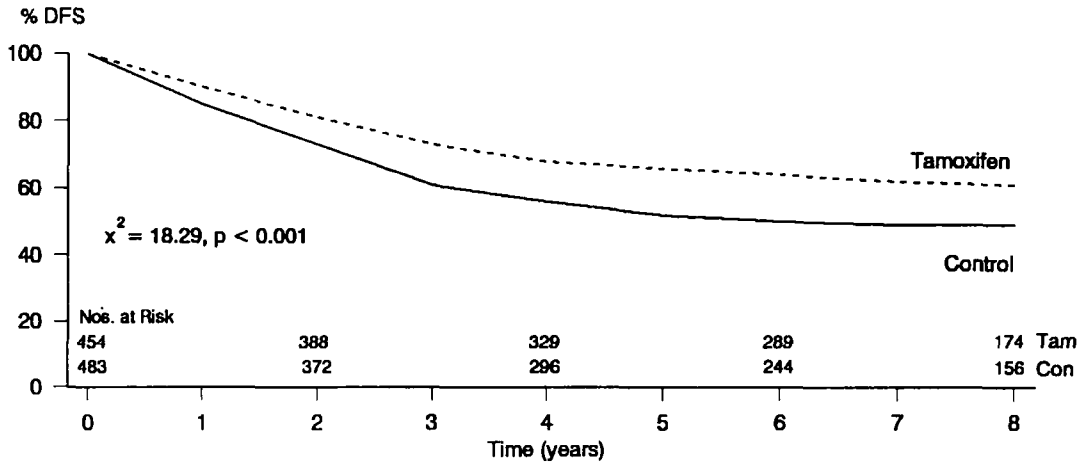

Fig. 2. 'Tamoxifen vs. control' analysis—Disease-free survival.

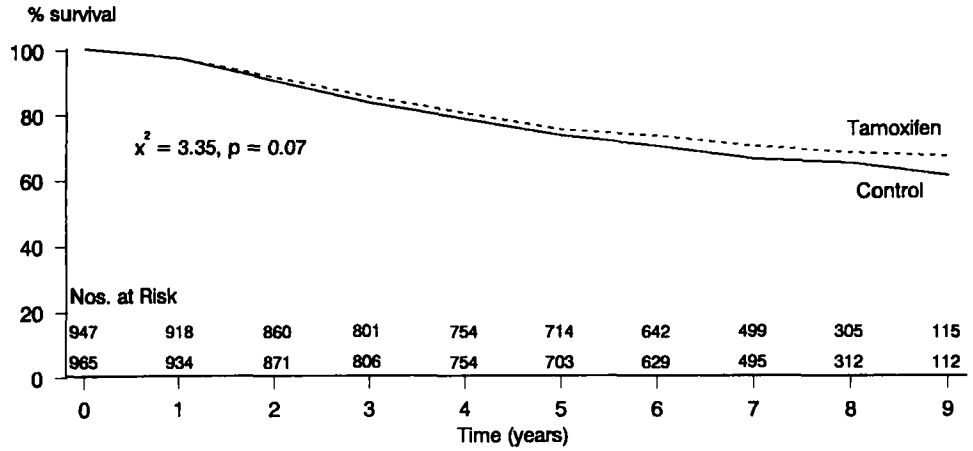

Fig. 3. Tamoxifen main effects analysis—Overall survival.

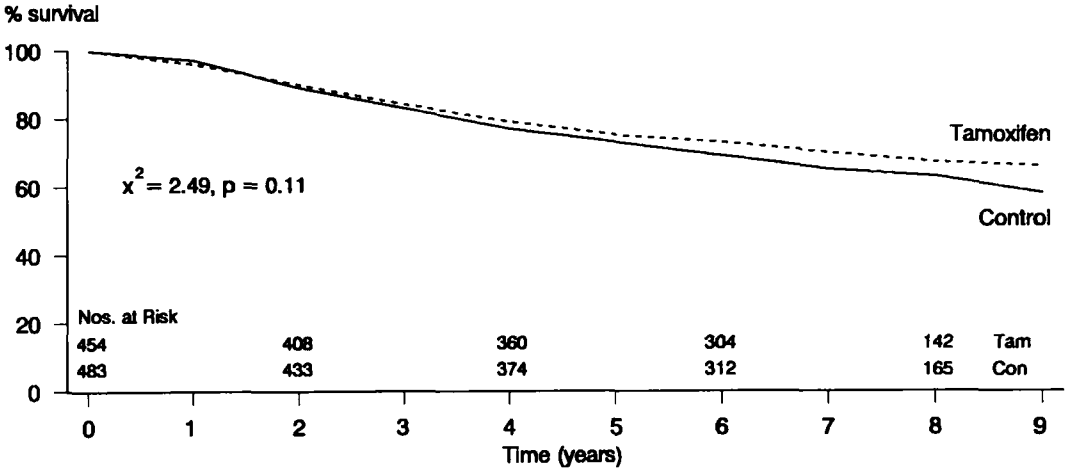

Fig. 4. 'Tamoxifen vs. control' analysis—Overall survival.

control analysis, which only contains data from 937 patients. The results for these comparisons are almost identical as were the results for overall survival, illustrated in Figs 3 and 4. For that reason all further analyses consider the 'main effect' of tamoxifen (which includes the tamoxifen plus perioperative cyclophosphamide group against the two control groups, half of whom were exposed to perioperative cyclophosphamide).

Subgroup main effect analyses were therefore carried out for patients divided according to nodal status, age,

Table 2

Stratified analysis — Disease-free survival

	RR	χ^2	*p*-value	χ^2(int)	*p*-value
All patients	0.73 (0.63–0.85)	20.28	<0.001		
Nodal status					
negative	0.60 (0.47–0.77)	16.96	<0.001		
positive	0.76 (0.63–0.92)	7.88	<0.01	2.41	0.12
Age					
<50	0.84 (0.64–1.08)	1.86	0.17		
⩾50	0.68 (0.58–0.81)	20.19	<0.001	1.60	0.20
Menstrual status					
premenopausal	0.72 (0.57–0.91)	7.52	<0.01		
postmenopausal	0.72 (0.59–0.87)	11.88	<0.001	0.00	1.00
Tumour size					
<2 cm	0.71 (0.42–1.18)	1.77	0.18		
⩾2 cm	0.75 (0.64–0.87)	13.49	<0.001	0.04	0.84

RR = relative risk
χ^2(int) = χ^2-test for interaction

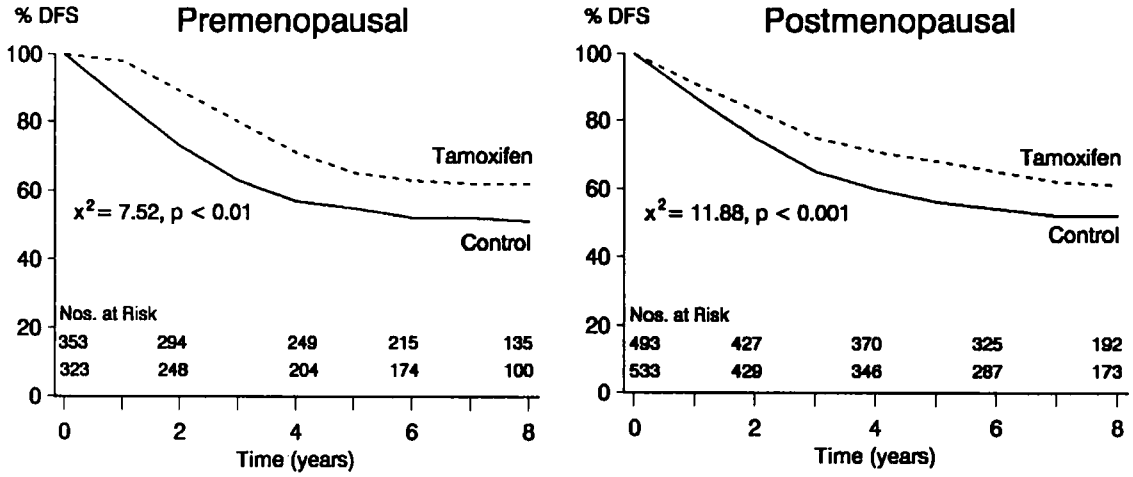

Fig. 5. Stratification for menstrual status—Disease-free survival.

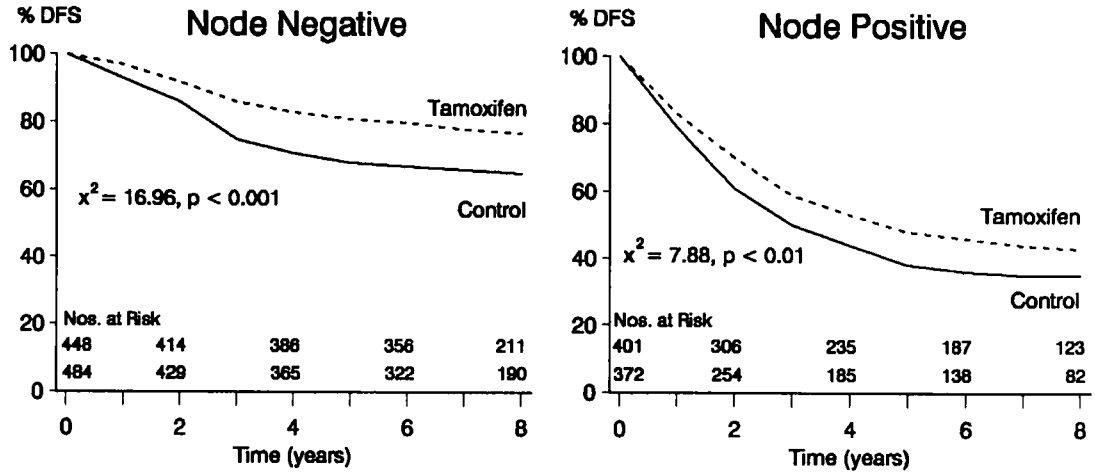

Fig. 6. Stratification for nodal status—Disease-free survival.

Table 3

Incidence of contralateral breast cancer

	RR	χ^2	p-value	χ^2(int)	p-value
All patients	0.85 (0.48–1.52)	0.31	0.58		
Age					
<50	1.78 (0.64–4.91)	1.22	0.27		
≥50	0.60 (0.30–1.21)	2.04	0.15	3.00	0.08
Menstrual status					
premenopausal	1.41 (0.60–3.32)	0.60	0.44		
postmenopausal	0.49 (0.22–1.09)	3.04	0.08	3.08	0.08

RR = relative risk
χ^2(int) = χ^2-test for interaction

menopausal status and tumour size categories. These results are illustrated in Table 2 and Figs 5 and 6. Table 2 also provides the statistical tests for interaction within these subgroups. Turning first to the subgroup analysis based on menopausal status, Fig. 5 clearly illustrates the significant effect of tamoxifen on prolonging the disease-free interval in premenopausal women, and at a glance it can be seen that there is no material difference on this outcome based on menopausal status.

Fig. 6 shows the two subgroups based on nodal status. Again a significant reduction in the time to relapse is seen in both node negative and node positive patients. However, on this occasion there is an impression that the impact of adjuvant tamoxifen for node negative cases is greater than that for node positive patients but it is not sufficient to 'eye-ball' the life tables. Formal statistical tests for interaction are required. Table 2 illustrates that the relative risk reduction for disease-free survival is identical in both pre- and postmenopausal women, whereas there is a trend favouring the node negative cases which fails to reach conventional levels of significance using the χ^2-test for interaction.

Table 3 describes the incidence of contralateral breast cancers in the main effect analysis for all patients, whereas Fig. 7 shows the same type of analysis for the patients stratified according to menopausal status. The significant trend for the reduction in contralateral breast cancers amongst patients taking tamoxifen that emerged at the three-year follow-up has disappeared with time (3). However, a non-significant reduction in the incidence of contralateral breast cancer persists amongst postmenopausal patients ($p = 0.08$). In contrast the incidence of contralateral breast cancers amongst premenopausal women receiving tamoxifen is increased, although not significantly so. Fig. 8 illustrates the comparison of the relative risk for developing contralateral breast cancer according to age or

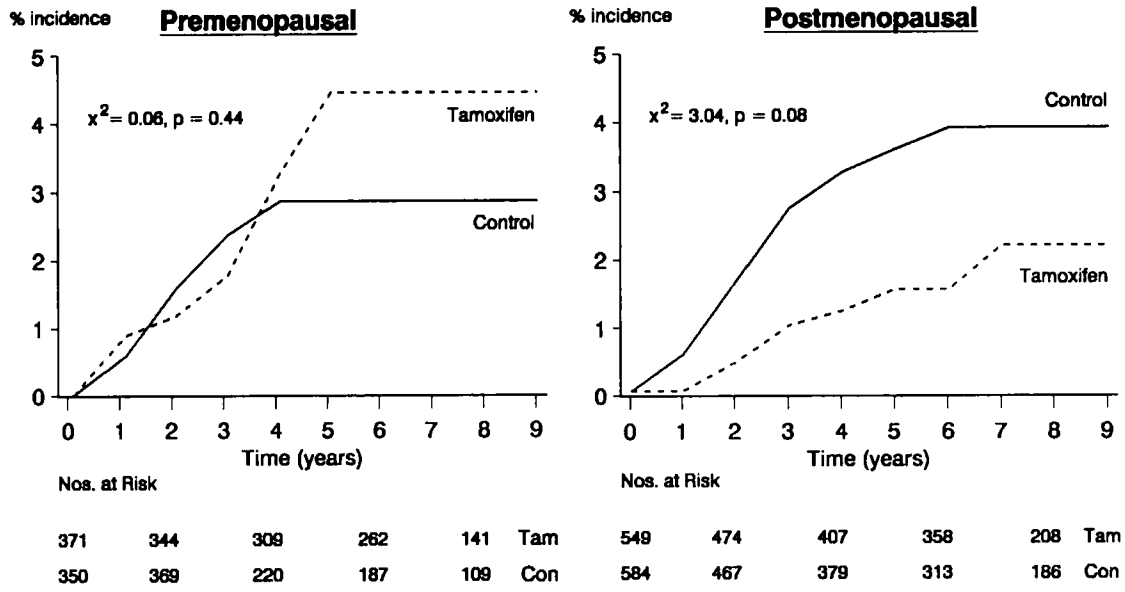

Fig. 7. Incidence of contralateral breast cancer.

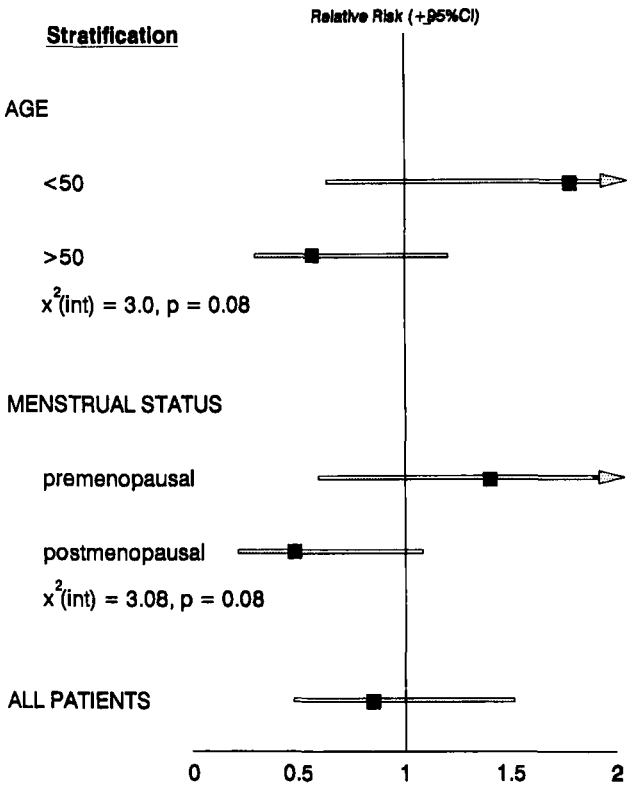

Fig. 8. Contralateral breast cancer—Relative risks.

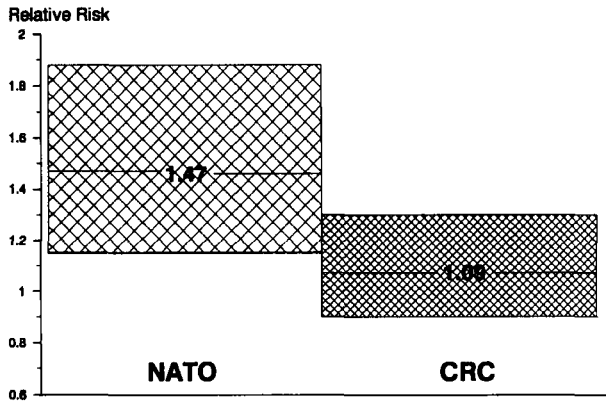

Fig. 9. NATO & CRC Trials—Survival at 4 years.

menstrual status. There is a clear trend suggesting an interaction favouring the postmenopausal women which just fails to reach conventional levels of statistical significance.

Discussion

These data once again demonstrate the unequivocable beneficial effect of two years of tamoxifen on the disease-free survival amongst patients with early breast cancer. As with the World Overview, the results seem to improve with time and there is as yet no suggestion of a rebound (4). Nor is there as yet any significant improvement in overall survival, although the results look more promising now than they did at the last publication (1). These data appear to be inconsistent with the results originally published for the NATO Trial, which showed a much earlier and more promising improvement in the overall survival rates in the tamoxifen treated group (5). However, expressing the results as relative risk reduction, the 95% confidence intervals between the two studies overlap to a degree that fails to suggest a genuine heterogeneity (Fig. 9).

Of greater importance in this analysis is the demonstration that tamoxifen has a significant impact in reduction of the risk of relapse amongst premenopausal women which is identical to that for postmenopausal women. These data are counter to popular prejudice and appear to lie outside the reported results of the World Overview. However, it must be emphasised that in the World Overview, patients from trials where tamoxifen was added to chemotherapy were included together with trials where tamoxifen was compared with a control group. A more detailed and sophisticated reading of the World Overview demonstrate consistency of this result with that of the other trials where the tamoxifen effect in the premenopausal group was not confounded by the synchronous administration of long-term polychemotherapy (6).

Two years ago the National Cancer Institute issued a medi-alert based on the results from two American trials, suggesting that adjuvant systemic therapy might also be of value in node negative patients, in addition to the conventional practice for node positive patients. We note with irony that no such clinical alert appeared after the first description of the CRC Trial three years before that, when we had demonstrated the value of adjuvant tamoxifen on node negative patients. This new analysis reinforces this result and furthermore suggests a trend where the relative risk reduction is somewhat greater in the node negative patients. Bearing in mind that node positive patients relapse at a faster rate, it is likely that the absolute benefits for adjuvant tamoxifen might be rather similar in these two subgroups. If that is the case, then adjuvant tamoxifen could be ethically and logically prescribed for all patients with early breast cancer irrespective of nodal and menopausal status.

The CRC Trial did not include an analysis of oestrogen receptor (ER) status of the primary breast cancer, and so we are not in a position to comment on the continuing controversy of the relevance of ER status in selecting patients for adjuvant tamoxifen (7).

Finally, the most interesting aspect of this new analysis concerns the incidence of contralateral breast cancer. We recognise that there is a potential for the misdiagnosis of this event, particularly in patients who have already relapsed at other sites. However, on most occasions when the Trials Centre was notified of a new contralateral breast cancer, our Clinical Trial Coordinators contacted the surgeon and pathologist involved and ascribed the new event

as either a new primary in the opposite breast, or a component of widespread metastatic disease which was not eligible for the analysis for contralateral breast cancer. (A more detailed analysis of these cases is in progress involving a search through the hospital records and a review of the pathology slides).

It is interesting to note that the overall effect on contralateral breast cancer, which was originally described by Cuzick & Baum (3), has disappeared. This would be in keeping with the animal models described by Jordan (8), which suggest that breast cancer could remain suppressed at a subclinical level for as long as the subject was exposed to tamoxifen, but on withdrawing the drug the occult malignancy could re-emerge. Such a simplistic interpretation of the data can be challenged when looking at the subgroups divided according to menopausal status. A rather striking difference emerges between the pre- and postmenopausal women which just fails to reach conventional levels of significance using the χ^2-test for interaction. A sustained reduction in contralateral breast cancers appears in the postmenopausal women with a relative risk of 0.49 (0.22–1.09), whereas the premenopausal women demonstrated a relative risk of 1.41 (0.60–3.32). A plausible and biological explanation exists if this is a true effect. Premenopausal women on long-term tamoxifen develop a sustained elevation of oestradiol. This is not coupled with an associated increase in the sex hormone binding globulin (C. Jordan, 1991, personal communication). Therefore the breast epithelial cells are exposed to high levels of free oestradiol, as long as the patient is receiving the drug. Clearly this trend has to be checked out against the overview data for the non-confounded trials of tamoxifen versus control in premenopausal women. As well as having biological significance, these data might have an effect on the planned recruitment of high-risk premenopausal women to the trials of the chemoprophylaxis of breast cancer with tamoxifen.

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