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The Effect of Adjuvant Tamoxifen: The Latest Results from the Cancer Research Campaign Adjuvant Breast Trial

Cancer Research Campaign Breast Cancer Trials Group

The CRC Adjuvant Breast Trial, launched in 1980 to repeat both the Nolvadex Adjuvant Trial Organisation tamoxifen trial and the Scandinavian trial of perioperative cyclophosphamide trial, randomised 2230 stage I or II early breast cancer patients in a 2 × 2 factorial design to investigate the benefits of a short course of perioperative cyclophosphamide or tamoxifen daily for 2 years. At a median follow-up of 7.8 years, 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 over 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 node positive patients. This might suggest that the absolute benefit for adjuvant tamoxifen is similar in both groups of patients, bearing in mind the increase risk of relapse with node positive patients. No trend for interaction emerges according to age or menopausal status suggesting an identical benefit for pre and postmenopausal women. Similar relative risk reductions are seen when the data are stratified according to tumour size, suggesting a similar positive benefit may be seen for all patients irrespective of tumour size. Of particular interest is the incidence 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 a marginal increase in the risk of contralateral breast cancer in premenopausal women. Plausible mechanisms exist to explain this difference in outcome and these data need to be confirmed or refuted by other large trials of adjuvant tamoxifen especially at this time when the chemoprophylaxis of breast cancer in high risk premenopausal women by tamoxifen is being considered.
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INTRODUCTION

THE CANCER Research Campaign Adjuvant Breast Trial began recruitment in 1980. The aim of the trial was to repeat both the Nolvadex Adjuvant Trial Organisation (NATO) trial for adjuvant tamoxifen [1] and the Scandinavian trial of perioperative cyclophosphamide (SACSG) [2]. Patients were randomised to one of four treatment groups; control, tamoxifen 20 mg daily for 2 years, perioperative cyclophosphamide 5 mg per kg for 6 days immediately following surgery and a fourth group receiving both treatments at the aforementioned dose levels.

The trial was designed so as to be easily incorporated within district general hospitals and not just within specialist centres; therefore all operable cases of early breast cancer irrespective of menopausal or nodal status were eligible. By utilising a 2 × 2 factorial design the main effects of either adjuvant tamoxifen or perioperative cyclophosphamide could be studied. A 4-way comparison was also possible although the smaller numbers and the greater number of comparisons (six instead of two) weaken the statistical power of this kind of analysis and these data will not be included here.

From 1 May 1984 following data published by the NATO tamoxifen trial [1], clinicians were given the option to prescribe tamoxifen for all patients, with randomisation only into the cyclophosphamide arm of the trial. Therefore only 1912 patients out of 2230 were eligible for the tamoxifen main effect analysis.

This trial is the largest addressing the issue of the effect of tamoxifen in premenopausal women not also given adjuvant chemotherapy and has already demonstrated a significant benefit for disease-free survival in node negative as well as node positive patients. Also, this trial was the first to show an effect on the incidence of contralateral breast cancer amongst women exposed to 2 years of tamoxifen [3]. The CRC trial now has a median follow-up of 7.8 years and this report concentrates on several important areas; the role of tamoxifen in premenopausal women, the relative risk reduction amongst node negative and node positive patients and also according to clinical tumour sizes at presentation, and the possible interaction between adjuvant tamoxifen therapy, menopausal status and the incidence of contralateral breast cancer.

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Table 1. Comparison of treatment groups

	Control (%)	Tamoxifen (%)
No. of patients	965 (50.5)	947 (49.5)
Mean age (years)	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 (years) (range)	7.8 (5.0–10.6)	

PATIENTS AND METHODS

Entry to the trial began in January 1980 and was open to all women under 75 years of age, with stage I or II (T1-2, NO-1, MO) breast cancer, irrespective of menstrual or nodal status. The primary treatment initially was either a Patey mastectomy with full axillary clearance and no radiotherapy or a simple mastectomy with axillary sampling and radiotherapy for node positive cases. In 1983 a third primary treatment option was offered—local excision plus axillary sampling and radiotherapy. Clinicians were asked prospectively to nominate their policy and to adhere to it for all patients.

The only stratification carried out at randomisation was for participating clinicians. For the purpose of analysis, patients were classified as premenopausal if their last menstrual period was less than 2 years prior to entry into the trial.

A more detailed description of the trial protocol has been described [3, 4].

RESULTS

Earlier analyses failed to demonstrate any significant impact by perioperative cyclophosphamide on overall survival, although improvement in the disease-free interval has been reported [3, 4]. The current analysis does not demonstrate any significant advantage for patients receiving perioperative cyclophosphamide which will therefore, not be further discussed.

1912 patients were recruited to the tamoxifen comparison of this trial between 1980 and 1985 including 773 node positive patients and 676 premenopausal patients.

Table 1 shows the comparison of the two patient groups (tamoxifen and no tamoxifen) with regards to demographic and prognostic factors. There is no suggestion of inbalance between the groups.

The main effect lifetable analysis for disease-free survival which included all 1912 patients, showed a significant advantage for tamoxifen-treated patients ($x^2 = 20.28, P < 0.001$, Fig. 1).

Subgroup analyses have been carried out for patients stratified according to nodal status, age, menopausal status and tumour size categories. Results are illustrated in Table 2 and Figs 2, 3 and 4. Table 2 also provides the statistical tests for treatment interactions within these subgroups. Regarding menopausal status, Fig. 2 clearly demonstrates the significant effect of

Table 2. Stratified analysis—disease free survival

	RR	χ^2	P	χ^2 (int)	P
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.

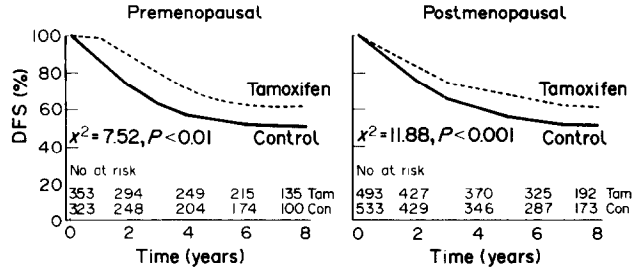

Fig. 2. Stratification for menstrual status—disease free survival.

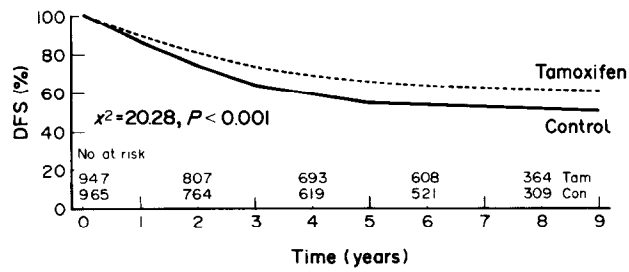

Fig. 1. Tamoxifen main effects analysis—disease free survival.

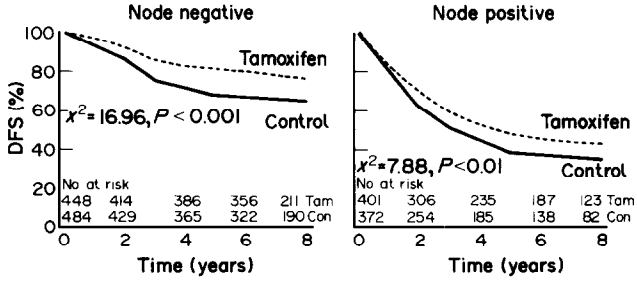

Fig. 3. Stratification for nodal status—disease free survival.

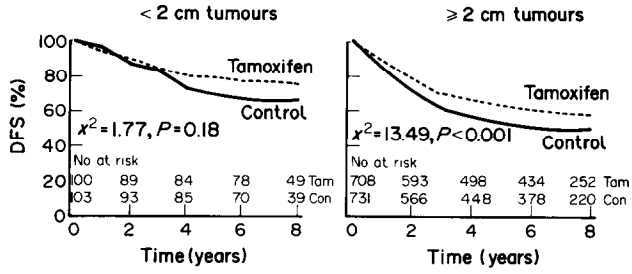

Fig. 4. Stratification for tumour size—disease free survival.

tamoxifen in prolonging the disease-free interval in premenopausal women, as well as postmenopausal, the relative risks being identical. When patients are stratified according to nodal status a significant increase in time to relapse is seen for both node negative and node positive patients treated with tamoxifen (Fig. 3). There is a suggestion that the effect of adjuvant tamoxifen in node negative cases is greater than that in node positive patients as shown by the lower relative risk for the node negative cases. However, this fails to reach conventional levels of significance using the χ^2 test for interaction (Table 2).

Analyses stratified according to tumour size at presentation show a statistically significant increase in disease free survival for patients with larger tumours (> 2 cm) treated by tamoxifen, but those with smaller tumours do not appear to benefit at least up to 3 years (Fig. 4). However, Table 2 shows that the relative risk reductions appear to be very similar for both groups, although the data for tumours < 2.0 cm does not reach statistical significance as shown by the confidence intervals crossing unity. This suggests a similar positive benefit is seen for patients with smaller tumours receiving tamoxifen, and the test for interaction shows no evidence of difference between the relative risks.

Figure 5 shows the probability of incidence of contralateral breast cancers in a main effect analysis for all patients, whereas Fig. 6 shows the data expressed as relative risks for patients stratified for both menopausal status and age. The significant reduction in contralateral breast cancers amongst patients taking tamoxifen that emerged at the 3 year follow-up [5] has now disappeared. However, a reduction in the incidence of contralateral breast cancer persists amongst postmenopausal patients, although does not quite attain conventional statistical significance (RR = 0.49, P = 0.08) but the incidence amongst premenopausal women receiving tamoxifen is not reduced and may

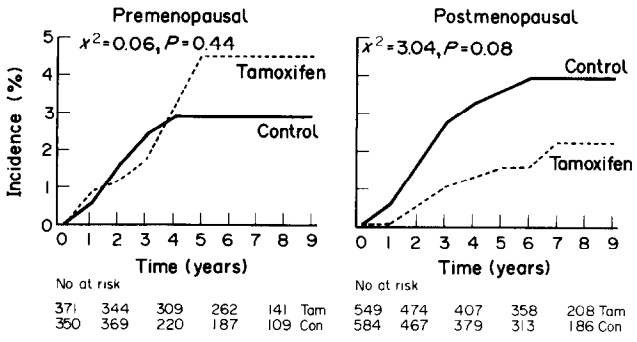

Fig. 5. Incidence of contralateral breast cancer. The numbers at risk are greater than previous menstrual status analysis, as patients with unknown menstrual status who were ≤ 45 years were classified as premenopausal, and those > 55 years as postmenopausal.

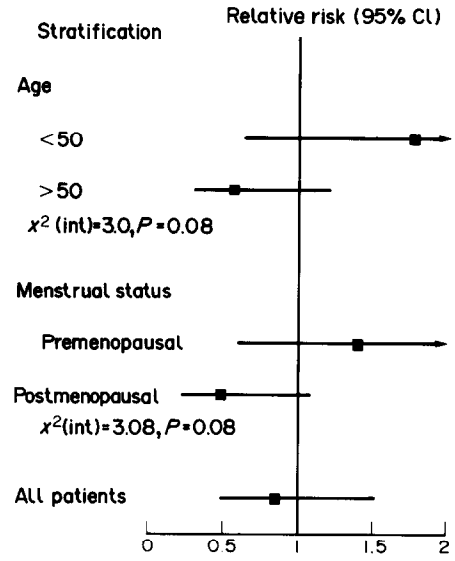

Fig. 6. Contralateral breast cancer—relative risks.

even be marginally increased, although this does not reach conventional levels of statistical significance (RR = 1.41, P = 0.44). Figure 6 illustrates the comparison of the relative risk for developing contralateral breast cancer according to age or menstrual status. There is a trend suggesting an interaction but this just fails to reach statistical significance.

The results for overall survival for all patients (shown in Fig. 7) still just fail to reach significance even with the 645 deaths that have now occured.

DISCUSSION

These data once again demonstrate the unequivocable beneficial effect of 2 years of tamoxifen on the disease-free survival amongst patients with early breast cancer [6]. As with the World Overview, the results seem to improve with time and as yet there is no suggestion of a rebound on withdrawal of tamoxifen therapy.

No significant improvement in overall survival has been demonstrated for patients within this trial. This appears to be inconsistant with the results originally published from the NATO trial, which showed much earlier a promising improvement in the overall survival rates in the tamoxifen treated group [7]. 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. 8).

The demonstration that tamoxifen has a significant impact on the reduction of the risk of relapse amongst premenopausal

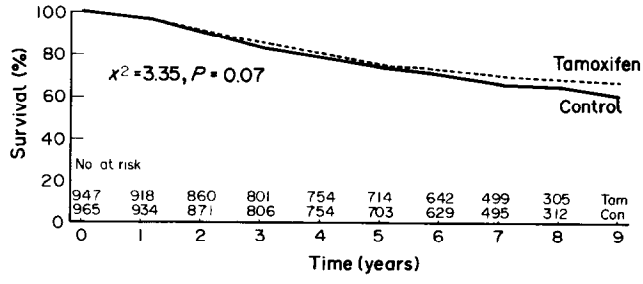

Fig. 7. Tamoxifen main effects analysis—overall survival.

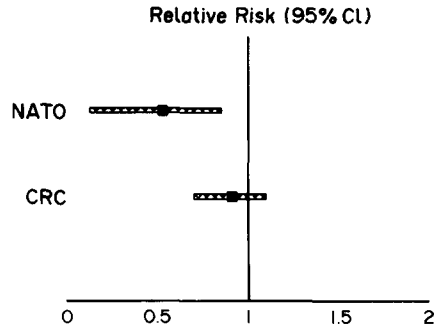

Fig. 8. NATO and CRC trials—relative risks for survival at 4 years.

women which is identical to that for postmenopausal women is very important. 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 no-adjuvant therapy control group. A more detailed and sophisticated reading of the World Overview Data demonstrate consistency of this result with that of other trials where the tamoxifen effect in the premenopausal group was not confounded by the synchronous administration of long-term polychemotherapy [8].

Two years ago the National Cancer Institute issued a medialert 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. Three years before that, the first analysis of the CRC Trial 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 greater for 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.

Regarding tumour size, it may be concluded from these data that patients presenting with larger tumours are more likely to respond to tamoxifen. However, when the relative risks are calculated they are very similar for both groups, suggesting the benefit of tamoxifen is irrespective of tumour size. The lack of significance may just be because of the fewer events, especially in the first 3 years, do not provide power in a maximum follow-up period of about 10 years. These data are particularly pertinent as with the advent of the National Screening Programme, the treatment of patients presenting with small primary tumours becomes increasingly important.

A further interesting aspect of this new analysis concerns the incidence of contralateral breast cancers. 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, the 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 review audit of these cases is in progress).

It is interesting to note that the overall effect on contralateral breast cancer, which was originally described by Cuzick and Baum, [5] has disappeared. This would be in keeping with the animal models described by Jordan and his colleagues, which suggest breast cancer cells could remain suppressed at a subclinical level for as long as the subject is exposed to tamoxifen, but on withdrawing the drug the occult malignancy could reemerge [10]. 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 [11]. Therefore the breast epithelial cells are exposed to high levels of free oestradiol, as long as the patient is receiving the drug and these high levels compete with tamoxifen for the oestrogen receptors. Clearly this trend has to be compared with the overview data for the non-confounded trials of tamoxifen versus control in premenopausal women. As well as 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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