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Original Paper

Tamoxifen in High-risk Premenopausal Women with Primary Breast Cancer Receiving Adjuvant Chemotherapy. Report from the Danish Breast Cancer Co-operative Group DBCG 82B Trial

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Following modified radical mastectomy, pre- and perimenopausal (amenorrhoea for <5 years) patients with stage II or III breast cancer received CMF (cyclophosphamide 600, methotrexate 40, 5-fluorouracil 600 mg/m^2 intravenously (i.v.) every 4 weeks, 9 cycles). The effect on recurrence-free survival (RFS) and overall survival (OS) of the addition of adjuvant tamoxifen (TAM) to adjuvant chemotherapy was examined by randomisation either to no additional treatment ($n = 314$), or concurrently TAM 30 mg daily for 1 year ($n = 320$). 40% had positive, 12% negative and 48% unknown receptor status. One year after surgery 21% versus 35% (CMF + TAM versus CMF) were still menstruating ($P < 0.01$). With a median follow-up of 12.2 years there was no difference in RFS (10-year RFS 34% versus 35%, $P = 0.81$) or OS (45% versus 46%, $P = 0.73$). In a Cox proportional hazards model, tumour size, number of metastatic lymph nodes, frequency of metastatic nodes in relation to total number of nodes removed, degree of anaplasia, age, and menostasia within the first year after operation were significant independent prognostic factors for RFS, and the same factors except age for OS. No significant interactions with TAM were seen. Thus, in this group of pre- and perimenopausal high-risk early breast cancer patients with heterogeneous receptor status given CMF i.v., concurrent TAM for 1 year did not improve the outcome. These results do not exclude that receptor positive patients may benefit from adjuvant TAM for longer periods given sequentially to chemotherapy. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: breast-neoplasms, chemo-endocrine therapy, CMF, tamoxifen, adjuvant, premenopausal
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INTRODUCTION

A PREVIOUS study accruing patients in the period 1977–1982 and conducted by the Danish Breast Cancer Co-operative Group (DBCG) showed that addition of adjuvant chemotherapy to modified radical mastectomy and postoperative loco-regional radiotherapy significantly prolonged time to recurrence and survival in premenopausal high risk early breast cancer patients [1–4]. These findings were subsequently substantiated in meta-analyses of the available randomised studies [5].

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From a theoretical point of view it might be advantageous to combine treatment modalities with different mechanisms of action in the setting of adjuvant treatment in order to avoid or postpone development of resistance to the treatment. Findings from phase III trials in advanced breast cancer indicate that the combination of cytotoxic treatment and endocrine therapy might be superior to chemotherapy alone at least with regard to the rate of response [6–10]. Consequently, the effect of tamoxifen (TAM) in addition to adjuvant chemotherapy in pre- and perimenopausal patients was studied in the DBCG 82B-study. This study randomised patients to chemotherapy versus chemotherapy plus locoregional radiotherapy versus chemotherapy plus TAM. The results achieved with radiotherapy have recently been published [11].

In the present study, we report the findings of the comparison of chemotherapy plus tamoxifen with chemotherapy alone. Preliminary results have been published previously [3].

PATIENTS AND METHODS

Since 1977 the diagnosis, surgical, and oncological treatment of early breast cancer in Denmark has been standardised and registered, population based and nationwide, by the DBCG organisation [12, 13]. The present study was conducted within the frameworks of this organisation. The design and eligibility criteria have been recently described [11]. In short, the study included pre- and perimenopausal women with histologically verified invasive carcinoma of the breast and high risk of recurrence. Pre- and perimenopausal patients were those with amenorrhoea for less than 5 years, or hysterectomy and age below 55 years. High risk status was defined as axillary lymph node metastases, primary tumour >5 cm and/or tumour involvement of skin or pectoral fascia. The patients had no evidence of disseminated disease as judged from physical examination, biochemical tests, chest X-ray, bone scintigraphy or radiological bone survey, and were not allowed to have earlier or concomitant malignant disease including bilateral breast cancer.

Surgery consisted of modified radical mastectomy with partial axillary lymph node dissection (median number of removed lymph nodes: six). Tumours were histologically classified according to the World Health Organization (WHO) [14] and ductal carcinomas were graded according to Bloom and Richardson [15]. Oestrogen- and/or progesterone receptor status was assessed biochemically in approximately half the cases. Tumours were considered receptor positive if oestrogen and/or progesterone receptor status was positive (i.e. (≥10 fmol receptor protein per mg cytosol protein).

The study was approved by the national ethical committee. Following verbal informed consent, patients were randomised in the oncological centres by a closed envelope system (with no stratification for prognostic variables) to receive postoperative chemotherapy with CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2 and 5-fluorouracil 600 mg/m^2 given intravenously (i.v.) every 4 weeks for a total of nine cycles) alone or combined with TAM, 30 mg daily orally for 1 year. The adjuvant systemic therapy was to start 2–4 weeks after surgery.

Patients were followed-up by history and physical examination (plus paraclinical examinations whenever indicated) at regular intervals until first recurrence, death, the occurrence of a new primary cancer, 10 years of follow-up, or 1 September 1996, whichever came first. Patients were further followed-up for vital status by linkage to the Central Population Register until 1 September 1996. Diagnostic, therapeutic and follow-up data were reported to and processed by the Danish Breast Cancer Co-operative Group (DBCG) data centre. To validate the quality of follow-up data all events reported until June 1992 were cross-checked with original hospital records [16]. The occurrence of new primary cancers (both as first event or subsequently) was assessed through 1994 by linkage with the Danish Cancer Registry.

Frequencies were compared by χ^2-tests. Recurrence-free survival (RFS) and overall survival (OS) were estimated by the Kaplan–Meier method. For OS the time from mastectomy until death from any cause was considered, whereas the first recurrence at any site, death without recurrence or occurrence of a new primary cancer were considered as events regarding RFS. The log-rank test was used to compare the treatment groups.

Possible interactions between prognostic factors and treatment (i.e. different effects of TAM in subgroups of the prognostic factors) were examined in multivariate Cox proportional hazards models. The multivariate analyses included tumour size, number of metastatic nodes, frequency of metastatic nodes in relation to total number of nodes removed, histological tumour type, grade of anaplasia, age, receptor status, menopausal status, and treatment. Due to lack of proportionality, the analyses were stratified for histological type. Patients with missing values, except for receptor status, were excluded from the multivariate analyses. Receptor status was only investigated in models including the subset of patients with known receptor status. Interactions between treatment and each of the prognostic variables except menopausal status were investigated. The level of statistical significance was set at 5%. All the estimated *P* values are those for a two-tailed test.

Analyses were performed according to the 'intention to treat-principle' irrespective of whether the patients did

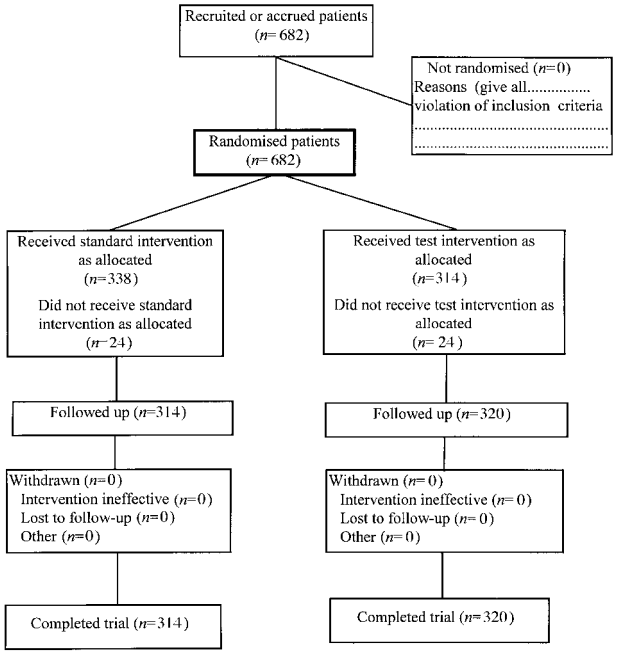

Figure 1. Flow chart of the progress of patients through the trial. (Adapted from Begg C, Cho M, Eastwood S, *et al.* Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996, 276, 637–639).

Table 1. *Characteristics of patients*

	Total	CMF + TAM	CMF
	n (%)	*n* (%)	*n* (%)
All	634 (100)	320 (100)	314 (100)
Age (years)			
<40	123 (19)	58 (18)	65 (21)
40–49	324 (51)	158 (49)	166 (53)
50–59	187 (29)	104 (33)	83 (26)
Tumour size			
<21 mm	250 (39)	131 (41)	119 (38)
21–50 mm	268 (42)	132 (41)	136 (43)
>50 mm	105 (17)	50 (16)	55 (18)
Unknown	11 (2)	7 (2)	4 (1)
Nodes removed			
0–3	123 (19)	60 (19)	63 (20)
4–9	371 (59)	186 (58)	185 (59)
10 +	139 (22)	74 (23)	65 (21)
Unknown	1	0	1
Positive nodes			
0	64 (10)	33 (10)	31 (10)
1–3	386 (61)	192 (60)	194 (62)
4 +	183 (29)	95 (30)	88 (28)
Unknown	1	0	1
Frequency of positive nodes			
<34%	258 (41)	134 (42)	124 (39)
34–67%	167 (26)	75 (23)	92 (29)
>67%	204 (32)	111 (35)	93 (30)
Unknown	5 (1)	0	5 (2)
Histopathology (WHO)			
Ductal	524 (83)	264 (83)	260 (83)
Lobular	75 (12)	39 (12)	36 (11)
Medullary	18 (3)	7 (2)	11 (4)
Unknown, others	17 (3)	10 (3)	7 (2)
Anaplasia (ductal carcinoma only)			
Grade I	125 (24)	60 (23)	65 (25)
Grade II	267 (51)	140 (53)	127 (49)
Grade III	118 (23)	58 (22)	60 (23)
Unknown	14 (3)	6 (2)	8 (3)
Oestrogen and/or progesterone receptor			
Positive	252 (40)	123 (38)	129 (41)
Negative	76 (12)	38 (12)	38 (12)
Unknown	306 (48)	159 (50)	147 (47)

*$P > 0.05$ for all comparisons between the treatment arms.

Table 2. *Nature of first event* within* 10 *years after randomisation*

	Total	CMF + TAM	CMF
	n (%)	*n* (%)	*n* (%)
All patients	634 (100)	320 (100)	314 (100)
Distant recurrence	159 (25)	76 (24)	83 (26)
Loco-regional recurrence	165 (26)	86 (27)	79 (25)
Distant and loco-regional	54 (9)	31 (10)	23 (7)
Death without recurrence, or other malignant disease	21 (3)	6 (2)	15 (5)
No event	235 (37)	121 (38)	114 (36)

*Recurrence, death without recurrence, or other malignant disease.

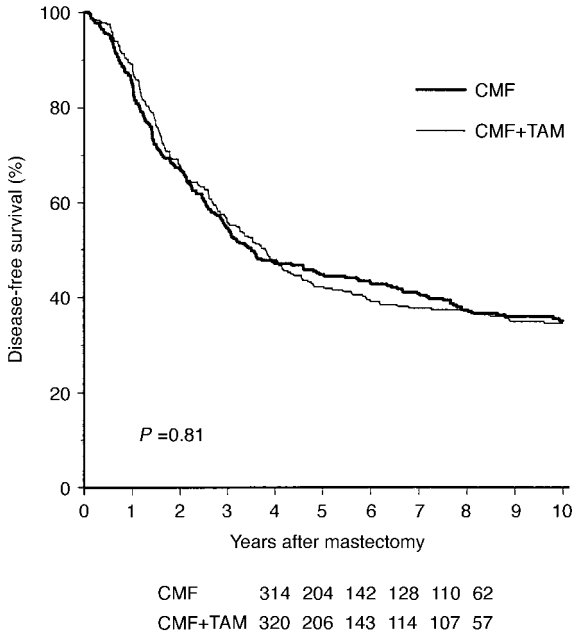

Figure 2. Proportion of patients alive without recurrence or other malignancy. Kaplan–Meier estimates with the number of patients at risk indicated.

complete the planned treatment or not. Patients who were randomised but found to be ineligible before start of the treatment were excluded. The univariate analysis of OS was, however, also carried out with the inclusion of randomised non-eligible patients.

The study was a priori designed to accrue 50 patients in each treatment arm per year for 5 years as this number of patients would assure detection of a 15% difference in 5-year OS (75% versus 60%) with 95% confidence. The study was monitored regularly by the DBCG data centre for excess mortality, and 3 years and 7 months from start of recruitment a significantly higher mortality was noted in the CMF + TAM group compared with the CMF + radiotherapy group. Accordingly, randomisation to the CMF + TAM arm was stopped [2]. The present analysis only includes patients in the CMF + TAM and the CMF groups randomised until the CMF + TAM arm was closed. Thus, the CMF alone group in this report is a subgroup of the CMF alone group in the recent report describing the comparison between CMF + radiotherapy versus CMF [10]. It should be noted that the rate of randomisation exceeded the expected, and the actual number of patients in the study meets the original statistical goal even though the randomisation was stopped prematurely.

Table 3. Recurrence-free and overall survival

	% 10-years recurrence-free survival (95% CI)		% 10-years overall survival (95% CI)	
	CMF + TAM	CMF	CMF + TAM	CMF
All	34 (29–40)	35 (30–40)	45 (40–51)	46 (41–52)
Age (years)				
<40	22 (11–33)	28 (17–39)	36 (24–49)	37 (25–49)
40–49	37 (29–45)	41 (34–49)	47 (40–55)	52 (45–60)
50–59	37 (27–47)	28 (18–38)	47 (38–57)	42 (32–53)
Tumor size				
<21 mm	52 (43–61)	47 (38–57)	61 (53–69)	61 (52–69
21–50 mm	25 (17–32)	32 (24–40)	39 (31–48)	43 (35–52)
>50 mm	18 (8–29)	16 (6–26)	22 (11–33)	24 (12–35)
Nodes removed				
0–3	28 (16–40)	38 (26–51)	45 (32–58)	48 (35–60)
4–9	37 (30–44)	35 (28–43)	49 (42–56)	48 (40–55)
10 +	33 (22–44)	29 (18–41)	36 (26–47)	42 (30–54)
Positive nodes				
0	55 (37–72)	62 (44–79)	70 (54–85)	71 (55–87)
1–3	41 (34–49)	39 (32–46)	51 (44–58)	53 (46–60)
4 +	13 (6–20)	17 (9–25)	25 (17–34)	24 (15–33)
Frequency of positive nodes				
<34%	52 (43–61)	47 (38–56)	61 (53–69)	64 (55–72)
34–67%	34 (23–45)	35 (25–46)	44 (33–55)	48 (38–58)
>67%	13 (7–20)	19 (11–27)	27 (19–35)	23 (14–31)
Histopathology (WHO)				
Ductal	32 (26–38)	33 (27–39)	44 (38–50)	44 (38–50)
Lobular	49 (32–65)	43 (26–59)	54 (38–69)	56 (39–72)
Medullary	43 (6–80)	55 (25–84)	43 (6–80)	73 (46–99)
Anaplasia (ductal carcinoma only)				
Grade I	50 (36–63)	39 (26–51)	63 (51–76)	55 (43–67)
Grade II	32 (25-40)	34 (26–43)	45 (37–53)	46 (38–55)
Grade III	17 (8–27)	22 (11–32)	24 (13–35)	25 (14–36)
Oestrogen and/or progesterone receptor				
Positive	40 (31–49)	36 (28–45)	48 (39–57)	47 (38–55)
Negative	24 (10–38)	24 (10–39)	32 (17–46)	34 (19–49)

*Numbers of patients are given in Table 1. Patients with unknown status for a given variable are not included. CI, confidence interval.

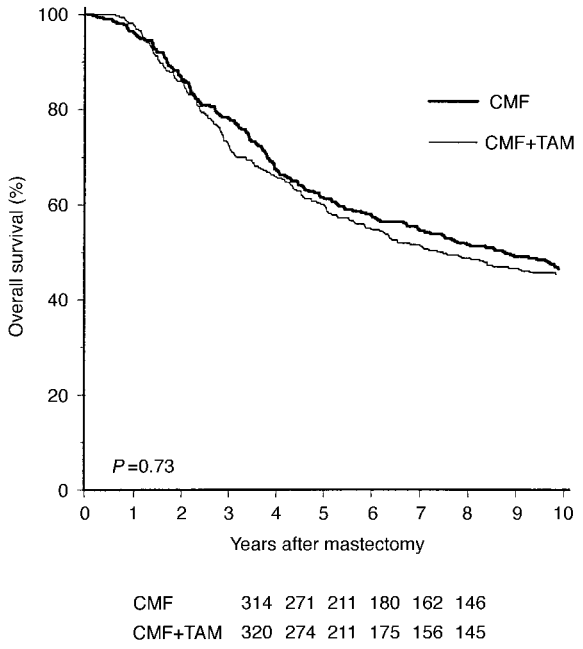

Figure 3. Proportion of patients alive. Kaplan–Meier estimates with the number of patients at risk below.

RESULTS

From November 1982 to June 1986 a total of 344 and 338 patients were randomised to treatment with CMF + TAM versus CMF, respectively. However, 24 patients in each arm were ineligible (due to patient refusal, metastatic disease, or concurrent other malignancy) leaving 320 and 314 eligible patients, respectively (Figure 1). The two groups were well balanced with regard to prognostic variables (Table 1). Receptor status was known for 52% of the patients. Among patients with known receptor status, 77% had receptor positive tumours. Median follow-up time, defined as the median time between the primary operation and the date of evaluation, was in the present analysis 12.2 years.

Ten years after mastectomy, 38% of those treated with CMF + TAM and 36% treated with CMF were still alive, free from recurrence and from other cancers (Table 2). The frequency of distant metastases, loco-regional recurrence and combined loco-regional and distant recurrence as first recurrence was similar in the two groups ($P = 0.22$). Ten-year RFS was similar in the two treatment regimens: CMF + TAM, 34% (95% confidence interval (95% CI), 29%–40%) versus CMF, 35% (95% CI, 30%–40%), $P = 0.81$ (Figure 2, Table 3). Ten-year OS was also similar: CMF + TAM 45% (95% CI, 40%–51%) versus CMF, 46% (95% CI, 41%–52%), $P = 0.73$ (Figure 3, Table 3). Inclusion of randomised but non-eligible patients in the analysis of OS did not appreciably change the OS: CMF + TAM 45% (95% CI, 40%–50%) versus CMF 45% (95% CI, 40%–51%).

The Cox proportional hazards model demonstrated that tumour size, number of metastatic nodes, frequency of metastatic nodes in relation to total number of nodes removed and grade of anaplasia were independent significant prognostic factors for OS, and the same factors plus age for RFS, whilst treatment with TAM had no significant impact (Table 4). No significant interactions between single prognostic factors and treatment were demonstrated. When only considering patients with known receptor status virtually the same results were seen. Receptor status did not quite reach statistical significance as an independent prognostic factor (Table 4). In the subset with known receptor status and using RFS and OS as endpoints, a non-significant tendency towards an interaction between receptor status and treatment was noted with TAM reducing the risk ratio in patients with receptor-positive tumours and increasing the ratio in patients with receptor-negative tumours (Table 4).

At the start of the trial, menostasia was recorded in 19% of the patients in the CMF + TAM group and in 14% in the CMF group ($P = 0.07$). Of the remaining patients, menostasia was recorded during weeks 4–48 in 71% versus 57% of patients ($P < 0.01$) (Table 5). When including menopausal status in the multivariate analyses (no menostasia versus menostasia at start versus menostasia during the first year) as a time-dependent variable, menostasia became an independent prognostic factor for both RFS and OS ($P < 0.01$) (Table 4). This indicates that developing menostasia during treatment predicts a prolonged RFS and OS, while menostasia at entry on trial had a negative impact on RFS and OS.

A total of 15 secondary cancers was diagnosed from entry into the trial until end of follow-up or death, 4 in the CMF + TAM and 11 in the CMF-group. No increased incidence of endometrial carcinoma among TAM-treated patients was demonstrated (Table 6).

DISCUSSION

In patients with early breast cancer adjuvant chemotherapy improves RFS and OS. Based on indirect comparisons, the effect is most significant in patients younger than 50 years of age [5]. Similarly, adjuvant TAM improved RFS and OS in both postmenopausal and in premenopausal patients [17]. This is compatible with findings from studies examining the importance of ovarian ablation or suppression in premenopausal patients showing reductions in the odds of recurrence and of death in the same magnitude of what is achieved by adjuvant chemotherapy [18]. The TAM-effect seems to be highly dependent on the oestrogen or progesterone receptor content in the tumour. In tumours poor for both oestrogen and progesterone receptor the beneficial effect is negligible [17]. Based on indirect comparisons from the meta-analyses and supported by randomised studies [19, 20] the efficacy of TAM is dependent on the treatment duration, with 5 years being superior to 1 or 2 years.

The present study was designed in 1981. At that time adjuvant chemotherapy was most commonly administered as 'classical' CMF, i.e. oral cyclophosphamide days 1–14 and i.v. methotrexate and 5-fluorouracil days 1 and 8 every fourth week. It was, however, the impression that the toxicity of this regimen was considerable, and preliminary data from an ongoing EORTC study comparing 'classical' CMF with intravenous CMF in metastatic breast cancer suggested that the two regimens were equally effective. In addition, the Milan Group, who introduced the CMF regimen in the adjuvant setting, utilised i.v. CMF every third week in all new studies since 1981 with 1–2 weeks treatment delay rather than dose reductions in case of myelosuppression [21]. From preliminary data, the Milan group observed similar efficacy with this regimen as was also subsequently demonstrated by indirect comparisons [22, 23]. Accordingly, a less toxic i.v. 4-week schedule was chosen for this study. Subsequently, however, it was demonstrated that 'classical' CMF was in fact

more efficient in metastatic breast cancer [24] as it has now also been suggested to be in the adjuvant setting [25]. When the study was planned, it had not yet unequivocally been demonstrated that the beneficial effects of adjuvant tamoxifen were limited to patients with steroid hormone receptor-rich tumours. Furthermore, for logistic reasons, only a smaller fraction of the patients had receptor measurements performed. Accordingly, it was decided to include all patients in the trial irrespective of receptor status. The optimal duration of TAM treatment was also not settled at the time. From the preceding DBCG 77C trial, it was demonstrated that 1 year of treatment significantly increased RFS and OS in postmenopausal high risk patients [26]. No comparative studies had demonstrated that longer durations were beneficial and,

Table 4. *Cox proportional hazards models*

	Recurrence			Death from any cause		
	RR	(95% CI)	*P* value	RR	(95% CI)	*P* value
Basic model including 588 patients with known status						
Tumour size			<0.001			<0.001
<21 mm	1.00			1.00		
21–50 mm	1.69	(1.33–2.15)		1.59	(1.24–2.03)	
>50 mm	3.41	(2.50–4.67)		3.31	(2.43–4.53)	
Positive nodes			0.03			0.01
0	1.00			1.00		
1–3	1.77	(1.09–2.87)		2.13	(1.25–3.63)	
4+	2.14	(1.23–3.71)		2.55	(1.41–4.61)	
Frequency of positive nodes			<0.001			<0.001
<34%	1.00			1.00		
34%–67%	1.28	(0.95–1.73)		1.39	(1.02–1.89)	
>67%	2.25	(1.65–3.06)		2.25	(1.64–3.08)	
Anaplasia			0.04			<0.001
Grade I	1.00			1.00		
Grade II	1.26	(0.94–1.70)		1.32	(0.98–1.78)	
Grade III	1.57	(1.11–2.21)		1.91	(1.36–2.68)	
Age			0.01			n.s.
<40 years	1.00					
40+ years	0.71	(0.55–0.92)				
Treatment			0.52			0.67
CMF	1.00			1.00		
CMF+TAM	0.93	(0.76–1.15)		1.05	(0.85–1.30)	
Receptor model including 311 patients with known receptor status*						
Oestrogen and/or progesteron receptor			0.06			0.06
Negative	1.00			1.00		
Positive	0.84	(0.60–1.17)		0.88	(0.63–1.23)	
Receptor model with interaction terms*						
Receptor positive						
CMF	1.00			1.00		
CMF + TAM	0.84	(0.60–1.17)		0.88	(0.63–1.23)	
Receptor negative						
CMF	1.00			1.00		
CMF + TAM	1.18	(0.67–2.09)		1.34	(0.75–2.39)	
Test of differential effect of TAM according to receptor status:			0.31			0.22
Menopausal model including 574 patients with known status†						
Menopausal status			0.01			0.01
No menostasia	1.00			1.00		
Menostasia at start	1.27	(0.91–1.77)		1.27	(0.93–1.74)	
Menostasia during first year	0.81	(0.62–1.06)		0.77	(0.60–1.00)	

The Cox analyses were stratified for histopathological type. *Significant factors from the basic model are included although not shown. †Factors from the basic model included, all but treatment being significant, although not shown. CI, confidence interval; RR, relative risk; n.s., not significant.

Table 5. *Number of patients according to menopausal status*

	Total	CMF + TAM	CMF
	n (%)	*n* (%)	*n* (%)
All	634 (100)	320 (100)	314 (100)
Menostasia			
Week 0	104 (16)	61 (19)	43 (14)
Week 4–48	340 (54)	185 (58)	155 (49)
No menostasia	176 (28)	66 (21)	110 (35)
Unknown	14 (2)	8 (3)	6 (2)

therefore, 1 year of treatment was chosen for this study. Treatment duration for TAM was subsequently examined in a randomised manner in the DBCG 89-programme (1 versus 2 years) [27] and by the Swedish Breast Cancer Co-operative Group (2 versus 5 years) [20].

The aim of the present study was to examine whether TAM + CMF was superior to CMF alone in the adjuvant setting in pre/perimenopausal high risk patients. Theoretically, combined endocrine and cytotoxic treatment may be advantageous compared with single modality treatment. The supposed modes of action are not identical and therefore the combined approach might prevent development of resistance in tumour cells. Data from several randomised studies in advanced breast cancer support this view, as combined modality treatment is in fact superior, at least with respect to response rate [6–10]. Despite the large number of patients and the very long follow-up, the study could not demonstrate any beneficial or untoward effects of the addition of TAM. This is in accordance with most other studies posing the same question as they generally fail to demonstrate any significant advantage of adjuvant TAM combined with chemotherapy in premenopausal patients. Most studies have, however, demonstrated a trend towards a prolonged DFS and OS among TAM-treated patients [28–35] particularly in the receptor-positive group, and one of the studies even showed a significant improvement of RFS and OS among receptor-positive premenopausal patients treated with TAM for 5 years in addition to chemotherapy [35]. In accordance, the meta-analysis of adjuvant TAM demonstrates receptor-positive or unknown patients to have a significant survival advantage if treated with TAM in addition to adjuvant chemotherapy [17]. Notably, this advantage is only seen in studies with longer than 1 year treatment with TAM, and is most pronounced in studies using approximately 5 years of TAM.

There is experimental evidence to suggest that TAM antagonises the effect of 5-fluorouracil (but not of cyclophosphamide) perhaps by inducing a reversible G_1 transition-delay. Consequently, tumour cells accumulate in G_1 rendering them less sensitive to the cytotoxic effect of cell cycle-specific chemotherapeutic drugs [36]. The finding of a (non-significant) trend towards a possible detrimental effect of tamoxifen concurrent with chemotherapy in patients with receptor-negative tumours in the present study (Table 4) could reflect this antagonism. Similar indications of detrimental effects of concurrent chemotherapy and tamoxifen in receptor-negative patients were made in other studies [31, 37].

In the present study, the occurence of menostasia during treatment was identified as an independent prognostic factor. This has also been found in other trials [2, 38, 39], although some retrospective studies failed to do so [40–42], adding to the evidence that even in premenopausal patients given adjuvant chemotherapy, endocrine effects are of some importance.

Thus, much evidence indicates that TAM in addition to chemotherapy may be beneficial in premenopausal patients. The fact that adjuvant TAM had no impact on RFS and OS in the present study may be due to either the short duration of TAM treatment (1 year), to the heterogeneity of the patient population with regard to receptor status (60% had unknown or negative receptor status), and to the concurrent administration of TAM and chemotherapy, which at least from theoretical reasoning may be inferior to the sequential administration of chemotherapy followed by TAM.

Table 6. *Number of secondary cancers reported to the Danish cancer registry from time of randomisation to death or* 1 *January,* 1995

	CMF	CMF + TAM
Person-years at risk	2187	2132
Pancreas	1	0
Lung	1	0
Endometrium	0	1
Ovary	4	0
Kidney	0	1
Bladder	1	1
Malignant melanoma	1	1
Thyroid	1	0
Multiple myeloma	1	0
Colon	1	0

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