

## 30 years' follow up of randomised studies of adjuvant CMF in operable breast cancer: cohort study

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### Abstract

**Objective** To assess the long term effectiveness of adjuvant treatment with cyclophosphamide, methotrexate, and fluorouracil (CMF) in patients with operable breast cancer at risk of relapse, on the basis of three successive randomised trials and one observational study conducted from June 1973 to December 1980.

**Design** Cohort study.

**Setting** Istituto Nazionale Tumori in Milan, Italy.

**Main outcome measures** Relapse free and overall survival, measured by univariate and multivariate analyses.

**Results** After a median follow up of 28.5 years for the initial study, adjuvant CMF was found to reduce the relative risk of relapse significantly (hazard ratio 0.71, 95% confidence interval 0.56 to 0.91,  $P=0.005$ ) and death (0.79, 0.63 to 0.98,  $P=0.04$ ). Administration of CMF for 12 cycles does not seem superior to a shorter administration of six cycles. In the node negative and oestrogen receptor negative trial, intravenous CMF significantly reduced the relative risk of relapse of disease (0.65, 0.47 to 0.90,  $P=0.009$ ) and death (0.65, 0.47 to 0.92,  $P=0.01$ ) at a median follow up of 20 years.

**Conclusions** When delivered optimally, CMF benefits patients at risk of relapse of distant disease without evidence of detrimental effects in any of the examined subgroups.

### Introduction

In 1975 we presented our first report on the efficacy of cyclophosphamide, methotrexate, and fluorouracil (CMF) as adjuvant treatment for node positive breast cancer.<sup>1</sup> A worldwide overview of chemotherapy for breast cancer confirmed that when the long term benefits of treatment are balanced against its risks, adjuvant chemotherapy can be worth while in many patients.<sup>2</sup> Questions have been raised in the past years concerning the true effectiveness of adjuvant CMF for specific subgroups of patients.<sup>3,4</sup> We report the results of 30 years of experience with adjuvant CMF in a series of successive clinical trials.

### Methods

The study designs of the randomised trials were reported earlier (see [bmj.com](http://bmj.com))<sup>1,5-7</sup> and are summarised in table 1. The study populations consisted of patients admitted to the Istituto Nazionale Tumori in Milan, Italy. All women who had had surgery (radical mastectomy or conservative surgery and full axillary clearance) for unilateral breast cancer were considered for inclusion in the studies if they had histological evidence that one or more axillary nodes were affected (first three studies) or if they had histologically negative axillary nodes and oestrogen receptor negative tumours (fourth study).

Patients with locally advanced or metastatic disease, those with a history of previous cancer, and those with concomitant severe non-malignant systemic disease were not eligible.

With the exception of the fourth study, assessment of the hormone receptors was not mandatory and was done retrospectively.

### Adjuvant treatment

In patients with node positive breast cancer, CMF consisted of cyclophosphamide (100 mg/m<sup>2</sup> orally from day 1 to 14), methotrexate (40 mg/m<sup>2</sup> intravenously on days 1 and 8), and fluorouracil (600 mg/m<sup>2</sup> intravenously on days 1 and 8), repeated every four weeks for either six or 12 cycles.<sup>1</sup> In this subset of patients, women older than 60 were to receive reduced doses of methotrexate (30 mg/m<sup>2</sup>) and fluorouracil (400 mg/m<sup>2</sup>).

In the fourth study, 12 cycles of cyclophosphamide (600 mg/m<sup>2</sup>), methotrexate (40 mg/m<sup>2</sup>), and fluorouracil (600 mg/m<sup>2</sup>) were given intravenously on day 1 and repeated three weeks later. No dose reductions for older patients were planned.<sup>7</sup>

In all studies, treatment with CMF was started two to four weeks after surgery. No other adjuvant treatments, in particular no endocrine treatment, were allowed, with the exception of breast irradiation for patients who had had conservative surgery. Breast irradiation had to be initiated within six to eight weeks

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**Table 1** CMF studies carried out at the Istituto Nazionale Tumori in Milan

Enrolment period	Study design	Eligible patients	Intervention	No of patients
June 1973 to September 1975	Randomised controlled trial	Node positive, premenopausal, and postmenopausal	Surgery v CMF for 12 cycles	179 v 207
September 1975 to May 1978	Randomised controlled trial	Node positive, premenopausal	CMF for 12 cycles v CMF for 6 cycles	160 v 164
May 1978 to October 1980	Observational study	Node positive, premenopausal	CMF for 12 cycles	220
December 1980 to October 1985	Randomised controlled trial	Node negative and oestrogen receptor negative, premenopausal, and postmenopausal	Surgery v intravenous CMF for 12 cycles	45 v 45

from surgery and was administered alongside CMF in women allocated to receive adjuvant chemotherapy.

**Study variables**

Details on baseline studies and follow up programmes are reported elsewhere (see *bmj.com*).<sup>1-5-7</sup> We considered treatment to have failed when the first evidence of new manifestations of disease in locoregional areas (including ipsilateral supraclavicular adenopathy), distant sites, the contralateral breast, or any combination of these sites was documented. We considered neither second primary cancers nor deaths owing to causes other than breast cancer treatment failures.

**Statistical analysis**

We calculated relapse free survival from the date of surgery to the first documented evidence of treatment failure. We used death from all causes as the end point for overall survival, which we also measured from the date of surgery. We analysed whether drug induced amenorrhoea in women menstruating at study entry was able to influence the outcome of treatment, excluding all patients who had a relapse within the first nine months after surgery. We tested the null hypothesis concerning the differential effects of treatment or of some prognostic factors in univariate analyses. We used a Cox regression model to

investigate the joint effects of treatment and of prognostic indicators. We estimated the relative risks as hazard ratios and calculated the rate of the sites of disease relapse as first event. We analysed the data that were available as of 28 February 2003. Only two patients in complete clinical remission were lost to follow up (see *bmj.com*).

**Results**

**First CMF study**

In the first study, after a median follow up of 28.5 years and a minimal follow up of 25.4 years, both relapse free survival and overall survival remained significantly superior in women receiving adjuvant CMF than in women treated with surgery alone (figure). Patients who received optimal doses of CMF ( $\geq 85\%$  of the planned doses) showed a longlasting, superior benefit (relapse free survival 42%, 95% confidence interval 26% to 59%; overall survival 40%, 26% to 55%) compared with patients who received lower doses (26%, 19% to 33%; 21%, 14% to 26%). See *bmj.com* for details of rates of relapse free and overall survival relative to main characteristics. Further investigation using regression analyses of the joint effects of treatment and prognostic indicators confirmed the significant benefit of adjuvant chemotherapy (table 2).

As reported in table 2, CMF contributed to reducing the relative risk of disease relapse by 34% and of death from all causes by 22%. The extent of nodal involvement remained a significant prognostic factor; patients with three or more positive nodes were also at an increased risk of relapse and death in this long term analysis. Neither age group nor menopausal status, oestrogen receptor status, or tumour size influenced relapse free survival significantly. As far as overall survival is concerned, patients aged 50 or more years at study entry had a significantly higher risk of dying than younger women. The lower rates of overall survival in these older women can be explained by deaths not due to progression of breast cancer or new primary malignancies.

The cumulative incidence of first relapse according to anatomical sites showed that the main therapeutic effect of adjuvant CMF was to reduce the incidence of distant metastases (an absolute difference of 11% between patients who received CMF and those who did not).

New malignancies other than contralateral breast cancers were documented in 12 patients with no prevailing distinctive pattern in either treatment group.

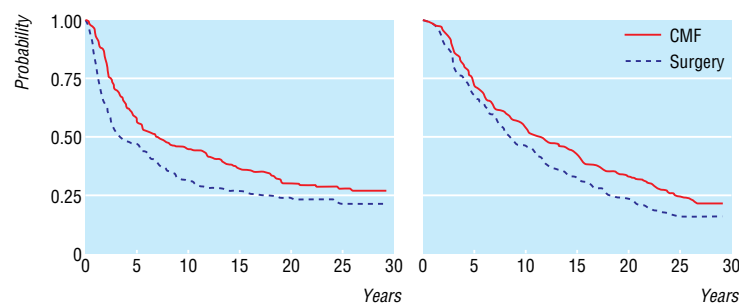
**CMF for six cycles compared with 12 cycles in premenopausal patients**

After a median follow up of 25 years, the outcome of treatment was not improved with a longer duration of adjuvant CMF. The estimated relapse free survival rates

**Table 2** Multivariate analysis of the first CMF study in 337 patients with known oestrogen receptor status. Final model

	Hazard ratio*	95% CI	P value (Wald test)
Relapse free survival:			
CMF v surgery alone	0.66	0.51 to 0.85	0.002
>3 affected lymph nodes v 1-3 affected lymph nodes	1.67	1.28 to 2.18	0.0001
Overall survival:			
CMF v surgery alone	0.78	0.61 to 0.98	0.04
>3 affected lymph nodes v 1-3 affected lymph nodes	1.40	1.09 to 1.80	0.009
Age $\geq 50$ v <50 years	1.43	1.12 to 1.82	0.004

\*A ratio of <1.0 favours CMF.



Treatment outcome in the first randomised CMF study after a median observation of 28.5 years. Left: Relapse free survival after surgery alone (179 patients) v CMF (207 patients). Univariate analysis: hazard ratio 0.71 (95% confidence interval 0.56 to 0.91; P=0.005). Right: Overall survival after surgery alone (179 patients) v CMF (207 patients). Univariate analysis: hazard ratio 0.79 (0.63 to 0.98; P=0.04)

were 39% after 12 cycles and 38% after six cycles of CMF. At 25 years, the overall survival rates were 40% in both treatment arms. In the multivariate analysis, the only variable able to influence treatment outcome was the extent to which axillary nodes were affected; patients with three or more affected nodes had a significantly higher risk of disease relapse and death (hazard ratio 2.3, 95% confidence interval 1.61 to 3.16,  $P=0.0001$ ).

### CMF and amenorrhoea

Grouping together all patients given CMF, a total of 397 women had monthly periods before starting the 12 cycle regimen, and 145 had monthly periods before starting the six cycle regimen. Overall, drug induced amenorrhoea was reported more often in the longer regimen (75% *v* 62%) than in the shorter one. However, in women aged 45 or older the incidence of amenorrhoea was unrelated to the duration of treatment (97% *v* 96%).

We assessed whether amenorrhoea induced by CMF could influence the outcome of treatment. We looked at relapse free survival in patients who had monthly periods before starting 12 cycles of CMF and found only a modest and non-significant advantage favouring patients with CMF induced amenorrhoea ( $P=0.2$ ). A multivariate analysis including amenorrhoea, extent of nodal involvement, oestrogen receptor status, and age group confirmed that ovarian suppression induced by adjuvant CMF had no significant role in treatment outcome (hazard ratio 1.13, 95% confidence interval 0.69 to 1.57,  $P=0.6$ ); the only significant prognostic indicator remained the extent of nodal involvement. See [bmj.com](http://bmj.com).

### Intravenous CMF in node negative tumours

When we looked at treatment outcome in patients with node negative and oestrogen receptor negative tumours, after a median follow up of 19.2 years, we found that CMF reduced the relative risk of both disease relapse and death by 35%. Premenopausal and postmenopausal women benefited equally from adjuvant CMF, and small ( $\leq 2.0$  cm) and large tumours ( $> 2.0$  cm) were equally affected. CMF had the greatest effect on highly undifferentiated tumours (relapse free survival 32% after surgery alone *v* 63% after intravenous CMF), but it also affected differentiated tumours (57% *v* 64%) (see [bmj.com](http://bmj.com)).

## Discussion

Our long term analysis of the trials we started three decades ago shows that the significant advantage in both relapse free and overall survival has persisted throughout the years and that adjuvant chemotherapy can suppress micrometastases to a moderate but worthwhile extent, regardless of their anatomical sites.

### Benefit of CMF and menopausal status

The magnitude of benefit of adjuvant CMF as given in our studies was apparently different between premenopausal and postmenopausal women. Although this different effect may be, at least in part, attributable to the lower doses of CMF delivered in women older than 60 years,<sup>1-5</sup> many investigators believed that the predominant effect of chemotherapy was chemical castration. Data from two randomised studies compar-

## What is already known on this topic

At a median follow up of about 15 years, adjuvant systemic therapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) can benefit patients with operable breast cancer

## What this study adds

Adjuvant systemic therapy has longlasting effects even after 30 years, and these are achieved at the cost of minimal long term sequelae

The poor prognosis associated with unfavourable indicators in patients treated locoregionally alone was improved by administration of adjuvant CMF

ing the effects of CMF with endocrine manipulations in premenopausal women reinforce this interpretation.<sup>3-8,9</sup> Our analysis of the influence of drug induced amenorrhoea, supported by many individual trials and the worldwide overview,<sup>2</sup> shows that adjuvant chemotherapy benefits hormone responsive and hormone unresponsive tumours. Endocrine therapy has no worthwhile benefit in oestrogen receptor negative subpopulations.<sup>10</sup> Our findings indicate that adjuvant chemotherapy has cytotoxic effects regardless of the putative hormone dependency of the tumour cells. The worldwide overview indicated that in hormone responsive tumours, the delivery of chemotherapy and endocrine therapy further reduces the relative risk of disease relapse and death compared with either modality alone.<sup>2-10</sup>

### Benefit of CMF and prognostic subsets

The goal to tailor adjuvant treatment to characteristics of individual tumours, the subject of current trials, was inconceivable at the time when we designed our studies. The role of new biological variables, including c-erb-b2 expression, was retrospectively assessed in the first randomised trial.<sup>11</sup> The poor prognosis associated with unfavourable indicators in the untreated group was overcome by adjuvant CMF, and our analysis confirms these results.

### Conclusion

New drugs available today include anthracyclines and taxanes, and these have improved outcomes of treatment over the CMF regimen.<sup>2</sup> Although technological advances will further improve our understanding of breast cancer and will contribute to tailoring treatment to the individual patient, our experience with adjuvant CMF over 30 years confirms that the effects of such a regimen are long lasting and may benefit patients with favourable and unfavourable prognostic indicators, at the cost of minimal long term sequelae.

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## Breast cancer mortality in Copenhagen after introduction of mammography screening: cohort study

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### Abstract

**Objectives** To evaluate the effect on breast cancer mortality during the first 10 years of the mammography service screening programme that was introduced in Copenhagen in 1991.

**Design** Cohort study.

**Setting** The mammography service screening programme in Copenhagen, Denmark.

**Participants** All women ever invited to mammography screening in the first 10 years of the programme. Historical, national, and historical national control groups were used.

**Main outcome measures** The main outcome measure was breast cancer mortality. We compared breast cancer mortality in the study group with rates in the control groups, adjusting for age, time period, and region.

**Results** Breast cancer mortality in the screening period was reduced by 25% (relative risk 0.75, 95% confidence interval 0.63 to 0.89) compared with what we would expect in the absence of screening. For women actually participating in screening, breast cancer mortality was reduced by 37%.

**Conclusions** In the Copenhagen programme, breast cancer mortality was reduced without severe negative side effects for the participants.

### Introduction

Organised, population based, mammography screening was introduced in Copenhagen in 1991. Since then the validity of the trial results and the justification of mammography screening have been debated intensively.<sup>1-3</sup> Mammography screening was introduced in only three out of 16 administrative regions, so the regions without a programme provide a natural

control group during the full period of follow up. In addition, opportunistic screening has been limited.<sup>3</sup> Taking advantage of this “natural experiment,” and using the nationwide population and health registers in Denmark, we developed a method to determine the effect of mammography screening on breast cancer mortality.<sup>4</sup> We present here the results of the first 10 years of screening in Copenhagen.

### Methods

#### Model

We used a regression model with a study group, a historical control group, a national control group, and a historical national control group (table). We studied the effect of invitation to, as well as participation in, screening. The end point was mortality due to breast cancer.

The study group included women invited for screening in Copenhagen during the first five invitation rounds from 1 April 1991 to 31 March 2001. The screening interval was two years. The target group included about 40 000 women aged 50-69 at the start of each invitation round. Only the second invitation round included women aged 50-71. Women moving to Copenhagen received their invitation shortly after their arrival, unless their date of birth was scheduled for invitation later in the round. Invitations did not go to women if they moved out of Copenhagen before their scheduled date for invitation. Women invited for screening remained in the study group even if they moved to another region. We followed up all women from their first date of invitation until death,



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