Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

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See **Comment**

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Summary

Background Quinquennial overviews (1985–2000) of the randomised trials in early breast cancer have assessed the 5-year and 10-year effects of various systemic adjuvant therapies on breast cancer recurrence and survival. Here, we report the 10-year and 15-year effects.

Methods Collaborative meta-analyses were undertaken of 194 unconfounded randomised trials of adjuvant chemotherapy or hormonal therapy that began by 1995. Many trials involved CMF (cyclophosphamide, methotrexate, fluorouracil), anthracycline-based combinations such as FAC (fluorouracil, doxorubicin, cyclophosphamide) or FEC (fluorouracil, epirubicin, cyclophosphamide), tamoxifen, or ovarian suppression: none involved taxanes, trastuzumab, raloxifene, or modern aromatase inhibitors.

Findings Allocation to about 6 months of anthracycline-based polychemotherapy (eg, with FAC or FEC) reduces the annual breast cancer death rate by about 38% (SE 5) for women younger than 50 years of age when diagnosed and by about 20% (SE 4) for those of age 50–69 years when diagnosed, largely irrespective of the use of tamoxifen and of oestrogen receptor (ER) status, nodal status, or other tumour characteristics. Such regimens are significantly ($2p=0{\cdot}0001$ for recurrence, $2p<0{\cdot}00001$ for breast cancer mortality) more effective than CMF chemotherapy. Few women of age 70 years or older entered these chemotherapy trials.

For ER-positive disease only, allocation to about 5 years of adjuvant tamoxifen reduces the annual breast cancer death rate by 31% (SE 3), largely irrespective of the use of chemotherapy and of age (<50, 50–69, ≥70 years), progesterone receptor status, or other tumour characteristics. 5 years is significantly ($2p<0{\cdot}00001$ for recurrence, $2p=0{\cdot}01$ for breast cancer mortality) more effective than just 1–2 years of tamoxifen. For ER-positive tumours, the annual breast cancer mortality rates are similar during years 0–4 and 5–14, as are the proportional reductions in them by 5 years of tamoxifen, so the cumulative reduction in mortality is more than twice as big at 15 years as at 5 years after diagnosis.

These results combine six meta-analyses: anthracycline-based versus no chemotherapy (8000 women); CMF-based versus no chemotherapy (14 000); anthracycline-based versus CMF-based chemotherapy (14 000); about 5 years of tamoxifen versus none (15 000); about 1–2 years of tamoxifen versus none (33 000); and about 5 years versus 1–2 years of tamoxifen (18 000). Finally, allocation to ovarian ablation or suppression (8000 women) also significantly reduces breast cancer mortality, but appears to do so only in the absence of other systemic treatments.

For middle-aged women with ER-positive disease (the commonest type of breast cancer), the breast cancer mortality rate throughout the next 15 years would be approximately halved by 6 months of anthracycline-based chemotherapy (with a combination such as FAC or FEC) followed by 5 years of adjuvant tamoxifen. For, if mortality reductions of 38% (age <50 years) and 20% (age 50–69 years) from such chemotherapy were followed by a further reduction of 31% from tamoxifen in the risks that remain, the final mortality reductions would be 57% and 45%, respectively (and, the trial results could well have been somewhat stronger if there had been full compliance with the allocated treatments). Overall survival would be comparably improved, since these treatments have relatively small effects on mortality from the aggregate of all other causes.

Interpretation Some of the widely practicable adjuvant drug treatments that were being tested in the 1980s, which substantially reduced 5-year recurrence rates (but had somewhat less effect on 5-year mortality rates), also substantially reduce 15-year mortality rates. Further improvements in long-term survival could well be available from newer drugs, or better use of older drugs.

Introduction

In early breast cancer, disease is detected only in the breast or, in the case of women with node-positive disease, the breast and locoregional lymph nodes, and all detected disease can be removed surgically. However, undetected deposits of disease may remain either locally or at distant sites that, if untreated, could over the next 5, 10, 15, or more years develop into a life-threatening

clinical recurrence. Breast cancer is unusual in that although the risk of distant recurrence is greatest during the first decade, it may still be substantial during the second decade after diagnosis. The main aim of systemic adjuvant treatment is to control any remaining deposits of disease, reduce the recurrence rate, and improve long-term survival.

Over the past few decades, many randomised trials have been undertaken of various treatments for early breast cancer, but the duration of follow-up differs greatly between different trials and between different patients in the same trial. Hence, meta-analyses of the effects of such treatments on long-term outcome (during and, where possible, after the first decade) in various types of patient should ideally involve central review of data on time to recurrence, death, or end of follow-up from every individual patient in every trial. Moreover, as the numbers randomised continue to increase, and follow-up on those already randomised continues to accumulate in many trials, such meta-analyses should ideally be updated every few years.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) was, therefore, set up in 1984–85[1] to coordinate quinquennial worldwide meta-analyses[2–10] of centrally collected data from every woman in all randomised trials of the treatment of early breast cancer that had, at the time of the analysis, already been running for at least 5 years. The present report is of the final results from the year 2000 EBCTCG meta-analyses of the trials of systemic adjuvant treatments (chemotherapy, endocrine therapy, or chemoendocrine therapy) that had begun in or before 1995. The corresponding meta-analyses of the trials of local treatments (surgery or radiotherapy) will be reported separately.

This is the fourth quinquennial cycle of this worldwide collaboration. It addresses many of the same questions as the previous cycles, but with more trials, more patients, better ascertainment of causes of death, and, particularly, longer follow-up. Hence, there is now substantially more evidence than before[8–10] comparing the effects on 10-year survival of different adjuvant regimens (eg, anthracycline-based *vs* other chemotherapy regimens; longer *vs* shorter tamoxifen regimens; ovarian ablation or suppression in addition to chemotherapy *vs* chemotherapy alone).

From the older trials of adjuvant treatment versus not, where the 10-year survival differences were already definite,[7,8] the 15-year differences between treatment and control are now stable enough to be compared usefully with the 10-year differences. Thus, from the first and second decades of follow-up in various types of trial, a clearer picture is now emerging of what the lifelong risks and benefits could eventually be.

Methods

Trial identification and data handling procedures have been described previously.[3,4] Information was sought from all randomised trials that had started by 1995. This report describes all the trials of more than 1 month[9] of systemic adjuvant therapy in which two treatment arms provided an unconfounded comparison of: (a) single-agent chemotherapy versus no adjuvant chemotherapy; (b) polychemotherapy versus no adjuvant chemotherapy; (c) anthracycline-based polychemotherapy versus standard polychemotherapy with CMF (cyclophosphamide, methotrexate, fluorouracil); (d) longer versus shorter polychemotherapy; (e) tamoxifen versus no adjuvant tamoxifen; (f) longer versus shorter tamoxifen; or (g) ovarian ablation or suppression (in women of age <50 years) versus no adjuvant ovarian treatment. Throughout, chemotherapy (CT) means cytotoxic chemotherapy. Table 1 shows the numbers available.

Data for every individual patient

As before,[3–6] information was sought for every woman in every eligible randomised trial on her allocated treatment, date of randomisation, age, menopausal status, whether or not there had been evidence of tumour spread to the locoregional lymph nodes (node-positive or node-negative), and on the results of any oestrogen receptor (ER) or progesterone receptor (PR) measurements. If measured, the receptor status of the primary tumour was described as positive if there was 10 fmol or more of receptor protein per mg cytosol protein or if there was any immunohistochemical evidence of receptor protein, and as ER-poor or PR-poor otherwise. (If unmeasured or unavailable, it was described as ER-unknown or PR-unknown.)

Information was sought on the dates of first local recurrence (which could include regional nodes), distant recurrence, contralateral breast cancer, other second primary cancer, and death (with the cause of death being sought only if distant recurrence had not been recorded). Where possible, follow-up was extended to the year 2000. The preliminary analyses were presented and discussed at a meeting in September, 2000, of the trial investigators. Since then, the data have been extensively checked for internal consistency and completeness and amended or updated through correspondence with the relevant trialists. The revised analyses were made available for comments by the collaborating trialists during 2004 through a password-protected website. Following their feedback, a draft of this report was prepared, circulated to the members of the EBCTCG for comment, revised, and recirculated.

Averaging treatment effects by meta-analyses

When several different trials have all addressed a similar question (eg, comparing the effects of polychemotherapy *vs* no adjuvant chemotherapy on the recurrence rate, or on some other event rate), the real effects of treatment may well differ somewhat from one trial to another, because the types of patient and the follow-up durations might differ. Moreover, even if two treatment protocols appear similar, they might have been applied differently.

Hence, the first step in the meta-analysis of treatment versus control in such a set of trials has been to analyse the event rates in every trial separately (stratified for nodal status, age, and year of follow-up), yielding a logrank statistic (the observed minus the expected number in the treatment group who had the relevant event) and its variance.[11] These statistics, one per trial, are then simply added together, yielding a grand total (O–E) and its variance (V) that can be used to determine whether, on average in those trials, treatment had any material effect on the time to first event for the outcome being analysed. Thus, women in one trial are compared directly only with other women of similar age and nodal status within that same trial, and not with women in another trial.

The overall logrank statistics (O–E and V) are used not only to calculate significance levels (p values) but also to help describe the average of the effects of treatment in the various different trials. For, it can be shown that (O–E)/V provides an appropriately weighted average of the log of R, the ratio (treatment *vs* control) of the annual rates of whatever category of events (eg, recurrence, mortality) is being analysed (see Formulae, below).[3]

Interpretation of weighted averages of effects in different trials

If the event rate ratios (treatment *vs* control) would, but for the play of chance in the randomisation process, be fairly similar in all the trials that make an appreciable contribution to the overall average, and do not differ greatly between the early and the later years of follow-up in those trials, then these relatively simple statistical methods would be of high statistical sensitivity—indeed, no other methods would be appreciably more sensitive.[3,11] Such methods do not, however, implicitly assume that the event rate ratio really does remain constant or that the treatment effects in different trials really are similar (so, it is inappropriate to refer to them as fixed-effect methods, or to make the combination of different trial results unduly dependent on heterogeneity tests).[3] There will often be appreciable differences between the real treatment effects in different trials (as, for example, in a meta-analysis that includes both the trials of just 1–2 years of tamoxifen and the trials of about 5 years of tamoxifen)[8] or in the earlier and the later years of follow-up (as, for example, in trials of chemotherapy regimens that produce much greater proportional reductions in early than in later recurrence rates).[9] But, (O–E)/V still provides an appropriately weighted average of the effects of the treatment allocation on early and on later event rates in the various different trials.

All analyses are based as far as possible on the intention-to-treat principle, so they compare all women allocated one treatment versus all those allocated the other, irrespective of compliance. Hence, their results may well slightly underestimate the effects on the event rate ratio that stricter compliance could have achieved.[12]

Outcomes

The main outcomes analysed were first recurrence (at any site), breast cancer mortality, overall mortality, cause-specific mortality before recurrence, and the incidence of other types of cancer before breast cancer recurrence. Recurrence was defined as the first reappearance of breast cancer at any site, and so included second primary breast cancers and local or distant recurrences of the original cancer. Deaths from unknown causes were included with deaths from breast cancer, unless it was stated explicitly that the death was not due to breast cancer. Where no recurrence was recorded before a breast-cancer-attributed death, it was assumed that a distant recurrence had just preceded it (13% of all deaths, since mortality may be monitored for longer than recurrence is).

Because causes are not reliably available for many deaths after recurrence, the analyses of time to death from causes other than breast cancer (and of the incidence of other types of cancer) were censored at the time of first recurrence. Almost all trials reported on contralateral breast cancer, but some did not otherwise separate local from distant recurrence: in those that did, isolated local recurrence is any ipsilateral local or regional recurrence without contralateral or distant recurrence.

Different statistical methods for different outcomes

All-cause mortality is analysed by the standard logrank methods (and the associated survival curve methods) for meta-analyses,[11] yielding not only the logrank statistics O–E and V but also (for plotting survival curves) the all-cause death rates in each treatment group, calculated separately in every year of follow-up.[3] Non-breast-cancer mortality is analysed by similar methods, but with

	Available*		Unavailable† (%)	
	Trials	Deaths/women by year 2000	Trials	Women randomised by year 2000
Cytotoxic chemotherapy (CT)‡				
Single-agent CT *vs* Not	14	2114/3994	0	0
PolyCT *vs* Not	60	10 173/28 764	7	1862 (6%)
Longer *vs* shorter polyCT	11	2567/6125	2	426 (7%)
Anthracycline *vs* CMF-based CT	17	4044/14 470	6	1269 (8%)
Tamoxifen (Tam)‡				
1–2 years of Tam *vs* Not	44	13 914/33 209	6	~1600 (5%)
About 5 years of Tam *vs* Not	12	4071/15 017	6	~5000 (25%)
Longer *vs* shorter Tam	15	5984/32 047	0	0
Ovarian ablation/suppression‡				
Ablation *vs* Not	15	3006/6506	2	158 (2%)
Suppression *vs* Not	6	832/4807	5	3247 (40%)
Total in present report	194	46 705/144 939	34	~13 000 (9%)

*Trials with more than two treatment arms may appear as more than one trial (with, for balance, controls counted more than once to adjust for this). †Numbers of trials known to be unavailable. In such trials, the numbers randomised by the year 2000 may be uncertain (or wholly unavailable, in which case they are taken as 100, since such studies may well be small). ‡Not indicates no adjuvant therapy of the type indicated in the bold heading (but, such treatment could well be given after recurrence). Trials of short chemotherapy (≤1 month) are not included. For each type of comparison, forest plots in webappendix 1 (appendix to table 1) give, for each contributory trial, year started, treatments compared, numbers randomised, and analyses (and meta-analyses) of recurrence and mortality.

Table 1: **Availability of relevant trials that began by 1995**

***Panel:* Format of figures, and selection of particular outcomes for emphasis**

Figures (eg, figure 1) that illustrate the ratios (treatment *vs* control) of recurrence rates (left) and of breast cancer death rates (right) use black squares to plot these ratios, each with area proportional to the amount of information that contributed to it, and a 99% confidence interval (CI). The illustrations of recurrence rate ratios are accompanied by tabulations of the corresponding numbers (treatment and control) of women who had a recurrence, of woman-years before recurrence, and of the corresponding annual recurrence rate (%/year). The illustrations of breast cancer death rate ratios are, however, accompanied by tabulations of all deaths after recurrence (irrespective of their actual causes) as a percentage of all women originally randomised (irrespective of follow-up duration and of how many had a recurrence). Since most women in these trials have been followed up for some years, the number of woman-years on the left is always much larger than the number of women on the right.

The treatments in these trials had relatively little effect on overall non-breast-cancer mortality, so analyses of breast cancer mortality, together with analyses of any particular life-threatening side-effects, may provide a more stable (and generalisable) guide to the net effects of these treatments on long-term survival than direct analyses of overall mortality would do. The latter are therefore given only in webappendix 1 and on the study website.

Figures that give results in other formats (eg, figures 2 and 3) illustrate either 15-year probabilities of recurrence (left) and 15-year probabilities of death from breast cancer (right), or just 5-year probabilities of recurrence (with 10-year probabilities of recurrence, breast cancer mortality, and overall mortality available in webappendix 1 and on the study website).

Even in meta-analyses of the worldwide evidence, subgroup analyses can be subject to substantial statistical instabilities, but such instabilities may be relatively less important for 5-year recurrence probabilities because systemic adjuvant treatments may well have a clearer effect on early recurrence rates than on other outcomes. Hence, for statistical stability, 5-year probabilities are generally used in the main Results to illustrate any variation between subgroups in the absolute reductions in recurrence produced by treatment. The p values in all figures that illustrate subgroup-specific absolute risk reductions are, however, from logrank analyses of events both during and after the first 5 years (as is the case in all figures that illustrate subgroup-specific proportional risk reductions).

For every numbered figure there is a correspondingly numbered (1–14) annex-figure (in webappendix 1) that provides extensive additional analyses. Likewise, for every numbered table there is a correspondingly numbered (1–4) appendix (also in webappendix 1). The first three of these give details of every separate trial contributing to that table, plus appropriate meta-analyses of them (eg, the appendix to table 1 gives in its various forest plots analyses of recurrence and mortality in each of the 194 separate trials in table 1), and the appendix to table 4 gives the 15-year prognosis of untreated control patients, by ER and nodal status.

censoring at the time of first recurrence, yielding another logrank O–E and V, together with the death rates from causes other than breast cancer in each treatment group in every separate year of follow-up.

Since breast cancer mortality plus other mortality equals all-cause mortality, the breast cancer mortality rate in each treatment group in every separate year since randomisation can be estimated by subtracting the estimated non-breast-cancer mortality rate in that year from the all-cause mortality rate in that year. This means that even though it is not known which deaths after recurrence were actually due to breast cancer, it is still possible to estimate what the pattern of mortality from breast cancer would have been if all other causes of death could have been eliminated (and vice versa). Likewise, logrank subtraction (ie, subtraction of the logrank statistics O–E and V for non-breast-cancer mortality from those for all-cause mortality) yields logrank statistics that can be used to assess without bias the effects of treatment just on breast cancer mortality.[10]

Proportional and absolute benefits

Throughout this report, the effects of treatment are described either as proportional benefits (eg, a breast cancer death rate ratio of 0·75, which is equivalent to a 25% proportional reduction in the annual death rate) or as absolute benefits (eg, reducing the 15-year risk of death from breast cancer down to 40% in the treated group from 50% in the control group, which would correspond to an absolute 15-year benefit of 10%). If the proportional benefits are similar in different types of patient, the absolute benefits should appear greater in medium-risk than in low-risk patients. For example, a treatment that consistently produces a death rate ratio of 0·75 might produce an absolute 15-year benefit of 10% (about 40% *vs* 50% risk) for women with node-positive disease and of 5% (about 20% *vs* 25% risk) for those with node-negative disease in these trials. (The absolute benefit of treatment could, in principle, be smaller in those known to be at such very high risk that nearly everybody, irrespective of their allocated treatment, dies within a few years, but in practice these adjuvant trials did not generally involve many such patients.)

Relating death rate ratios to risks of death

It may be that R, the ratio of the annual death rates (treatment *vs* control), is about the same in the early and later years of follow-up. If so, then it can be shown that treatment would simply raise to the power R the survival probability in the control group (at a given number of years after randomisation).[4,5] For example, 0·5 to the power 0·75 yields 0·6, so a death rate ratio of 0·75 would yield a survival probability of 0·6 instead of 0·5, corresponding to 40% versus 50% mortality, as above. In general, the death rate ratio tends to be slightly more extreme than the ratio of the probabilities of death, as in the above example, where 0·75 is slightly more extreme than the ratio of 40% to 50%.

Formulae for calculations from logrank O–E and V

It can be shown that V represents the amount of information underlying the analysis, and is usually about a quarter of the total number (treatment plus control) of women who have had a relevant event. (When calculating the weighted average of the treatment durations in several different trials, or when averaging any other design characteristics, the weights used are the values of V from analyses of the effects of treatment on recurrence rates.) It can also be shown that O–E is usually about minus half

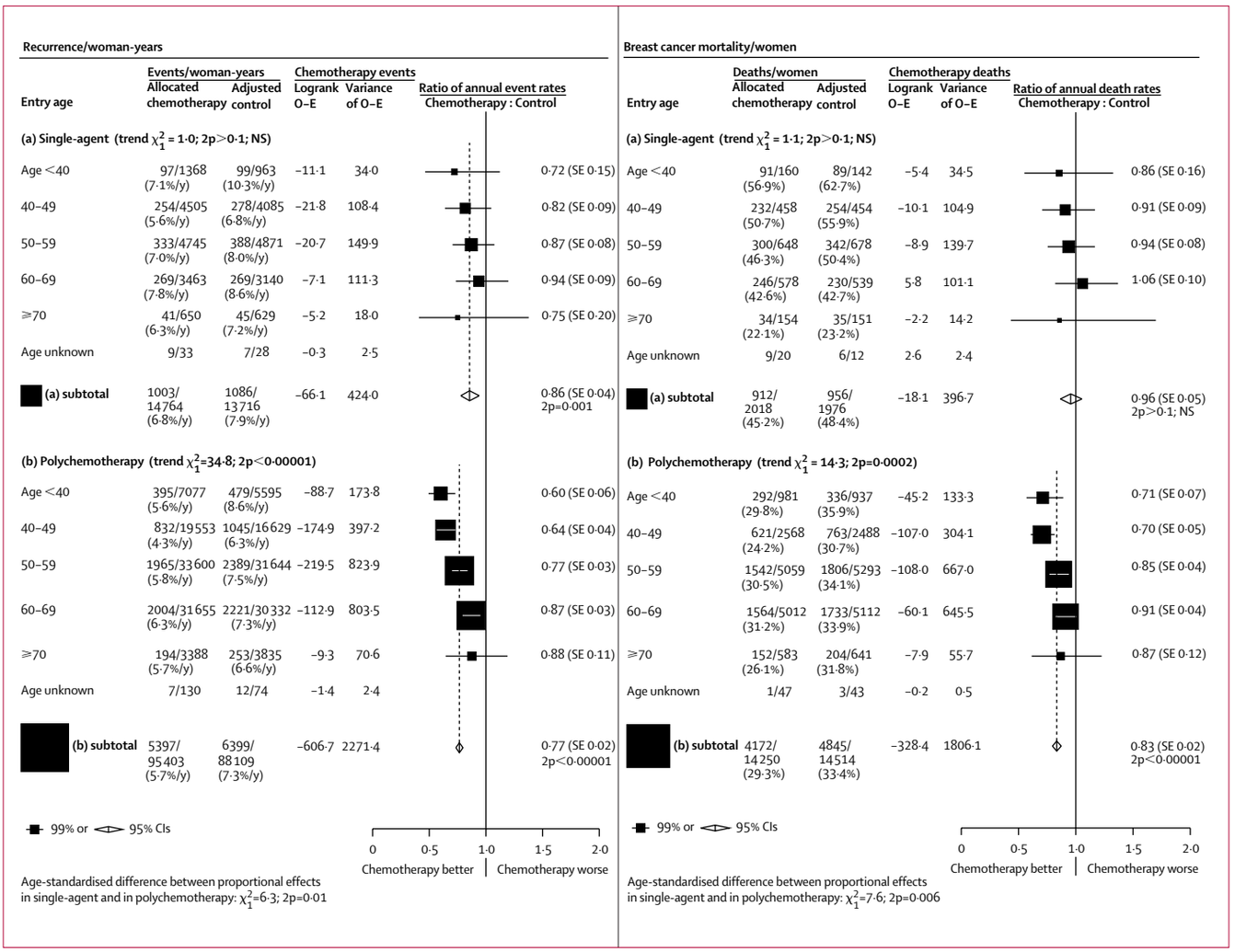


Figure 1: **Single-agent chemotherapy versus not and polychemotherapy versus not, by 10-year age groups: annual event rate ratios (treatment *vs* control) for recurrence and for breast cancer mortality**

the number of events prevented. This latter approximation is used chiefly to help describe any effects of treatment on rare events, such as the incidence of second cancers.

To describe effects of treatment on major outcomes, such as recurrence or breast cancer death, O–E and V are combined to calculate R, the event rate ratio.[3–5] Let b denote (O–E)/V, the log of the event rate ratio, and let s^2 denote the variance of b (which can be shown to be 1/V). The 95% confidence limits for b are then $b \pm 1{\cdot}96s$. Hence, those for exp(b), the event rate ratio itself, are exp($b \pm 1{\cdot}96s$). The SE attributed to an event rate ratio of R is calculated to make (R–1)/SE equal to b/s.

If two independent event rate ratios, exp($b1$) and exp($b2$), are to be multiplied together, yielding exp($b1+b2$), then S^2, the variance of $b1+b2$, is the sum of the separate variances of $b1$ and $b2$, so the 95% confidence limits for the product are exp($b1+b2 \pm 1{\cdot}96S$).

To test whether there are any significant differences between the proportional effects of treatment in two categories (eg, node-negative and node-positive) of patients in which the log event rate ratios are $b1$=(O1–E1)/V1 and $b2$=(O2–E2)/V2, respectively, the weight w of the evidence as to whether or not such an interaction exists is first defined as V1×V2/(V1+V2). The test is then based on the weighted difference $d=w(b1-b2)$, which can be shown to have variance w. (If d were to be calculated separately within each age-group then the sum of these weighted differences would provide an age-standardised test of interaction, with variance equal to the sum of the weights.)

Tests of heterogeneity and of trend

Suppose that information on the effects of treatment is to be combined from several different strata (eg, trials).

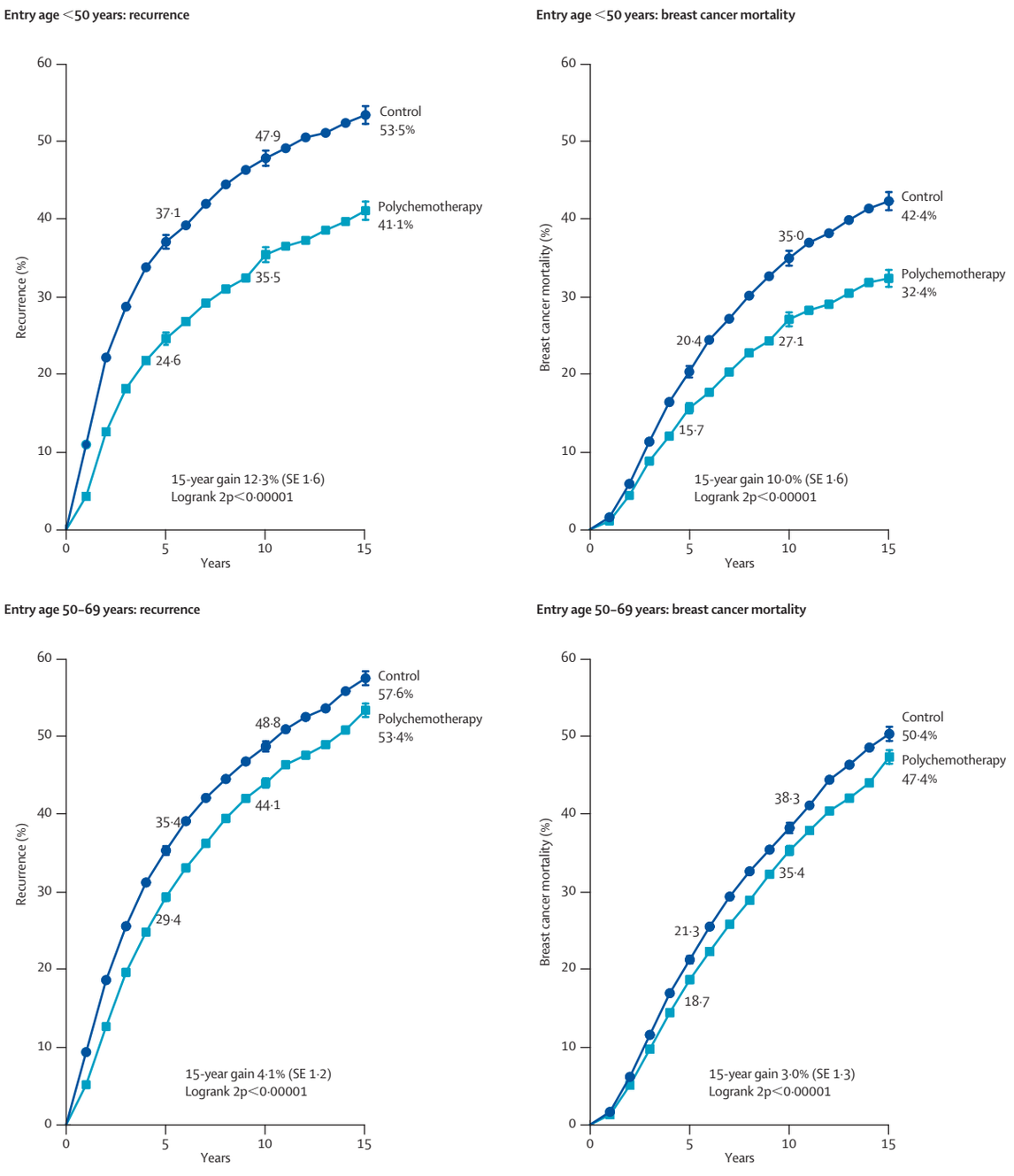


***Figure 2*: Polychemotherapy versus not, by entry age <50 or 50–69 years: 15-year probabilities of recurrence and of breast cancer mortality**
Younger women, 35% node-positive; older women, 70% node-positive. Error bars are ±1SE.

First calculate the logrank statistic (o–e) and its variance v in each separate stratum, and add these up to get the overall logrank (O–E) and its variance V (ie, the sum of the separate variances). Delete any uninformative strata (ie, those for which v is zero), and number the remaining strata from 1 to n. A χ^2 test (on n–1 degrees of freedom) for heterogeneity between the treatment effects in different strata can be obtained by subtracting

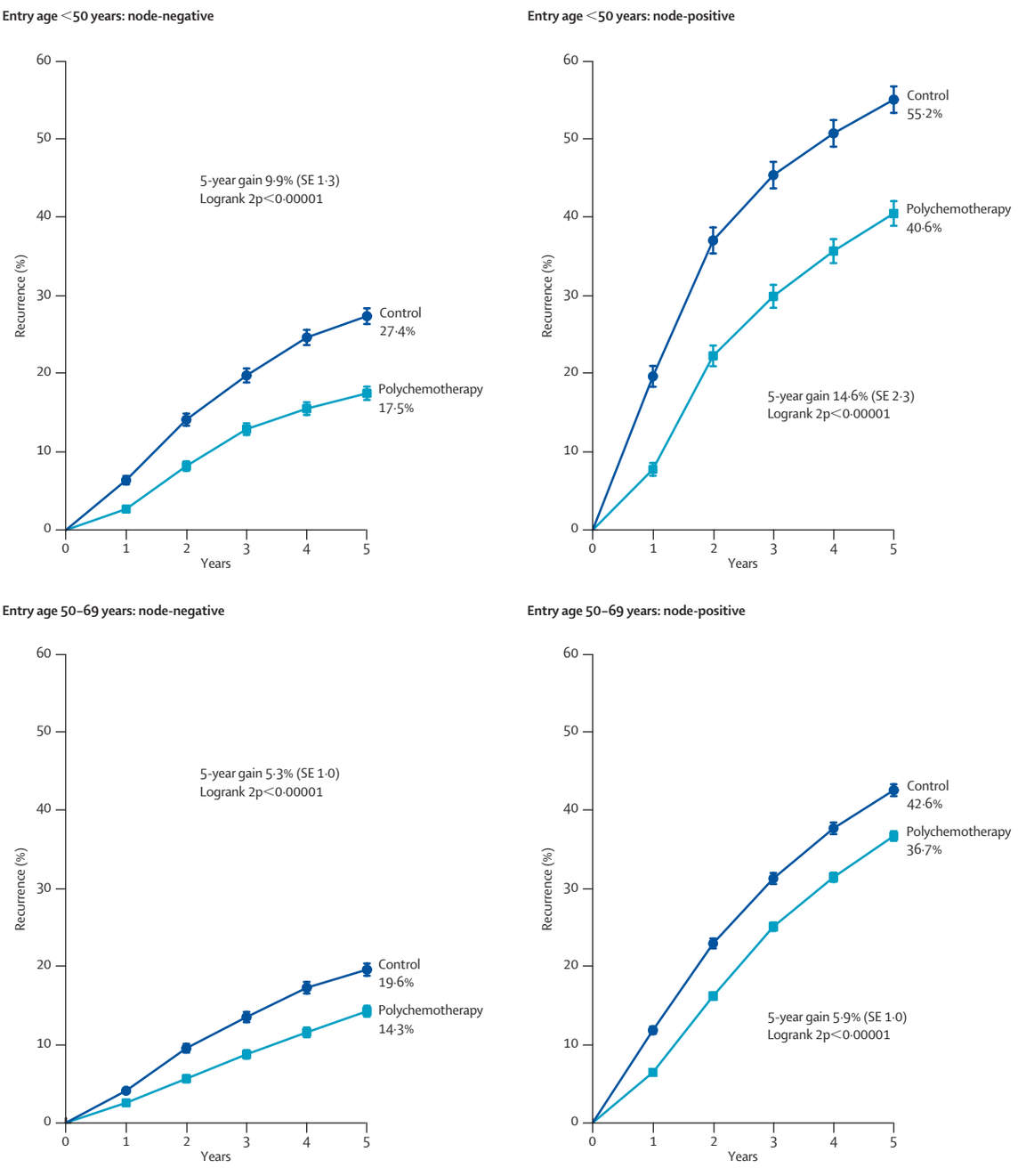


Figure 3: **Polychemotherapy versus not, by nodal status and entry age: 5-year probabilities of recurrence**
Error bars are ±1SE.

$(O–E)^2/V$ from the sum of the separate values, one per stratum, of $(o–e)^2/v$.

Alternatively, a χ^2 test for trend (ie, for whether the treatment effect changes progressively from one stratum to the next) can be obtained as follows: if the stratum numbered s has logrank statistics (o–e) and v then define m, the mean stratum number, to be the sum, one term per stratum, of sv/V and define T to be the sum, one

term per stratum, of (s–m)(o–e). The variance of T, var(T), is then the sum, one term per stratum, of $(s–m)^2v$, and the χ^2 test (on 1 degree of freedom) for trend is $T^2/var(T)$. If there are only two strata then the tests for trend and heterogeneity are identical.

Terminology

For a meta-analysis of many trials (just as for a standard analysis of a single trial) the CIs, standard errors (SEs), and significance levels (p values) are to help assess the extent to which the play of chance just in the randomisation process could have affected the calculated result. All p values are two-sided (and, for consistency with previous reports,[2–10] are described as 2p). Because of the number of hypotheses being tested, 2p is not given in tabulations of multiple possible side-effects if it exceeds 0·1. For balance, in three-way trials with two active treatment groups, the controls are counted twice in the adjusted control totals: other calculations are not affected.

Role of the funding source

This collaboration is funded from the general long-term financial support of the CTSU by organisations that had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The EBCTCG secretariat (see Contributors) had full access to all the data and analyses and had final responsibility for the decision to submit for publication.

Results

The panel describes the format of figures and tables in this report. The study website provides supplementary information to every figure and table in the form of annex-figures and table appendices, which are also available in webappendix 1 (with explanations of what they are in webappendix 2). A list describing every trial separately can be found in webappendix 3.

See http://www.ctsu.ox.ac.uk/~ebctcg/

See Lancet Online for webappendix 1, webappendix 2, and webappendix 3

Results are given first for chemotherapy, then for tamoxifen, and then for ovarian ablation or suppression. Table 1 shows the numbers of trials providing data and of women in the relevant categories of randomised comparison. It is restricted to women randomised by the year 2000 in trials that began by 1995. Information is unavailable for about 9% of women, mainly in trials that were still randomising patients in the late 1990s. Hence, most such women would have contributed only a few years of follow-up, and their unavailability will have relatively little effect, particularly on the analyses of event rates more than 5 years after diagnosis. None of the available trials involved taxanes, trastuzumab, raloxifene, or modern aromatase inhibitors.

Chemotherapy

Single-agent chemotherapy or polychemotherapy versus no adjuvant chemotherapy

Drugs tested—There were only 4000 women in the trials of single-agent chemotherapy, compared with 29 000 in the trials of polychemotherapy, so the latter yield much more definite results. The polychemotherapy regimens chiefly involved 6 or 12 months of CMF-based treatment or about 6 months of anthracycline-based treatment with combinations such as FAC (fluorouracil, doxorubicin [synonym: adriamycin], cyclophosphamide) or FEC (fluorouracil, epirubicin, cyclophosphamide), although some involved other agents (eg, vincristine, melphalan). In the trials of single-agent chemotherapy, only 13% of the information was from trials of 6 months of an anthracycline, which is too little to be separately informative: almost all the rest was from the single-agent trials of 6 or 12 months of older agents such as cyclophosphamide, melphalan, or fluorouracil.

Age-specific results—Figure 1 summarises the proportional risk reductions from single-agent chemotherapy and from polychemotherapy in the trials that compared more than 1 month of such treatment versus no adjuvant chemotherapy. The data have been subdivided into 10-year bands of age at entry (starting at <40 years and going up to ⩾70 years), because of the previously established relevance of age at diagnosis.[9] Few women older than 70 years of age, and very few older than 80, were randomised into these chemotherapy trials. (Finer age divisions, with 5-year age groups from <30, 30–35, to ⩾70, are available in webappendix 1 [annex-figure 1], along with a subdivision of figure 1 by ER status.)

There is clear evidence that these single-agent chemotherapy regimens reduce recurrence rates and that these polychemotherapy regimens reduce not only recurrence but also mortality from breast cancer (and hence overall mortality; webappendix 1 [annex-figure 1]). Taking all ages together, for single-agent chemotherapy the ratios (treatment *vs* control) of the annual event rates are 0·86 (SE 0·04, logrank 2p=0·001) for recurrence and 0·96 (0·05, 2p=0·4) for breast cancer mortality, while for polychemotherapy they are 0·77 (0·02, 2p<0·00001) and 0·83 (0·02, 2p<0·00001), respectively.

Indirect comparison of single-agent and polychemotherapy—With both single-agent and polychemotherapy, there is a trend towards greater benefits among younger women, but both for recurrence and for mortality the age-standardised effects of the single-agent regimens in these trials were significantly less favourable than those of the polychemotherapy regimens (figure 1). Polychemotherapy has come to be used widely,[13] and most subsequent chemotherapy analyses are restricted to polychemotherapy and to women younger than 50 years of age (younger), or 50–69 (older), when randomised into trials of it.

Polychemotherapy versus no adjuvant chemotherapy in younger and older women

Figure 2 shows the 15-year recurrence (left) and breast cancer mortality (right) probabilities for these younger (upper) and older (lower) groups of women. In all four

analyses the differences are highly significant (all $2p<0\cdot00001$), but the absolute benefits at 10 or 15 years appear to be about three times as great for younger than for older women, and to be somewhat greater for recurrence than for mortality.

In many of these trials, women in the control group who had recurrence could then be offered cytotoxic treatment. To the extent to which this was the case, any differences in mortality compare a policy of immediate adjuvant treatment (exposing to cytotoxic therapy even those who never were going to relapse) with one of treating patients only when recurrence is detected, and show that it is not always safe to defer treatment.

In figure 2, most of the effect of adjuvant chemotherapy on the risk of recurrence is seen within the first 5 years after randomisation, and figure 3 subdivides this effect on the 5-year recurrence risks both by age and by nodal status. (Among the younger women in these trials only 35% had node-positive disease, whereas 70% of the older women did so.) Although the absolute 5-year gains for women with node-negative disease appear to be smaller than those for women with node-positive disease, they are not significantly smaller (but, see Discussion).

Selected subgroups—Figure 4 describes the proportional risk reductions produced in various different circumstances, and annex-figure 4 in webappendix 1 gives further such subgroup analyses. The event rate ratios (treatment *vs* control) for recurrence and for breast cancer mortality are given separately for younger and for older women according to (a) the type of polychemotherapy regimen, (b) the presence or absence of tamoxifen in both treatment groups, (c) both ER status and tamoxifen use, (d) nodal status, and (e) period of follow-up.

The effects of treatment are greater in younger than in older women, and are greater for recurrence than for mortality. Hence, any heterogeneity between the proportional risk reductions produced by treatment in different subgroups of the trials or patients may best be detected by the logrank analyses of recurrence rates among younger women, even though there are only 7000 younger women in these trials.

Indirect comparisons between CMF-based and anthracycline-based polychemotherapy—About half the available evidence is from trials of CMF-based regimens, and about a third is from trials of anthracycline-based regimens. In the CMF-based regimens, 84% of the information was from trials of 6, 9, or 12 months of treatment (with no significant trend towards greater benefit with longer treatment) and 90% was from trials that involved no cytotoxic drugs other than CMF (the remainder involving these three drugs and vincristine). In the anthracycline-based trials the mean duration was 6 months, and the anthracycline used was always doxorubicin (66%) or epirubicin (34%).

Both among younger and among older women there are no significant differences between the proportional risk reductions (in recurrence or in breast cancer mortality) that were produced by the CMF-based and the anthracycline-based chemotherapy regimens in these particular trials (figure 4a). But, although this indirect comparison indicates that there are, on average, no large differences in efficacy, there could still be moderate but worthwhile differences in efficacy between these two types of regimen (as is indicated by the directly randomised comparisons of anthracycline-based regimens versus CMF; see below).

Presence or absence of tamoxifen—Some trials were of chemotherapy given with tamoxifen (concurrent chemoendocrine treatment) versus tamoxifen alone, some were of chemotherapy followed by tamoxifen (sequential chemoendocrine treatment) versus tamoxifen alone, and some were of chemotherapy alone (with no tamoxifen in either group). There was, however, no significant heterogeneity between the proportional risk reductions produced by chemotherapy in these three different settings (figure 4b).

Nearly all the evidence on sequential chemoendocrine therapy involved older women, among whom it appeared somewhat more effective than concurrent chemoendocrine treatment, but this comparison is indirect and the difference is not significant. No large, directly randomised comparisons of concurrent versus sequential chemoendocrine therapy are available in the present dataset, although an intergroup study favouring sequential therapy has recently been published.[14]

ER status and tamoxifen—In ER-poor disease, the trials of tamoxifen versus not show that even 5 years of tamoxifen has little effect on recurrence or breast cancer mortality.[8] Hence, the effects of chemotherapy in ER-poor disease should be similar in the presence or the absence of tamoxifen, and may best be estimated by combining the evidence from parts i and iv of figure 4c (ie, by adding together the relevant logrank statistics and calculating $\exp[(O-E)/V]$). Such calculations show that chemotherapy is effective both for younger and for older women with ER-poor disease: recurrence rate ratios 0·61 (SE 0·07) for younger and 0·72 (0·05) for older women (both $2p<0\cdot00001$); breast cancer death rate ratios 0·68 (0·08) for younger and 0·81 (0·05) for older women ($2p=0\cdot0002$ and $2p=0\cdot0004$, respectively). These four event rate ratios are not materially altered (0·64, 0·72, 0·71, and 0·80, respectively) by further restriction to ER-poor, PR-poor disease (webappendix 1 [annex-figure 4]).

In ER-positive disease, tamoxifen is highly effective,[8] but again there is no good evidence that it modifies the proportional risk reduction produced by chemotherapy (parts ii and v of figure 4c). In particular, both for younger and for older women with ER-positive disease, chemoendocrine therapy is significantly better than

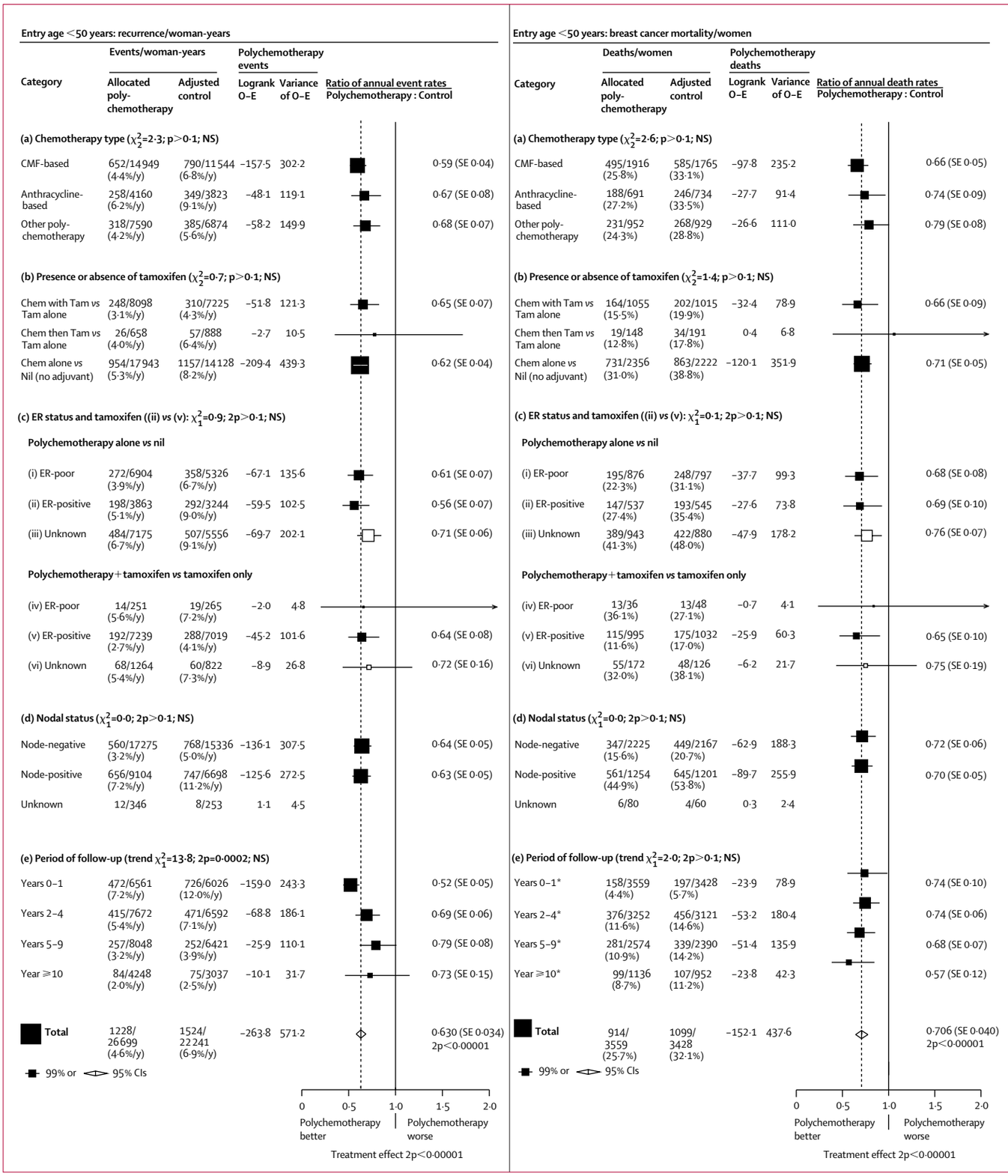
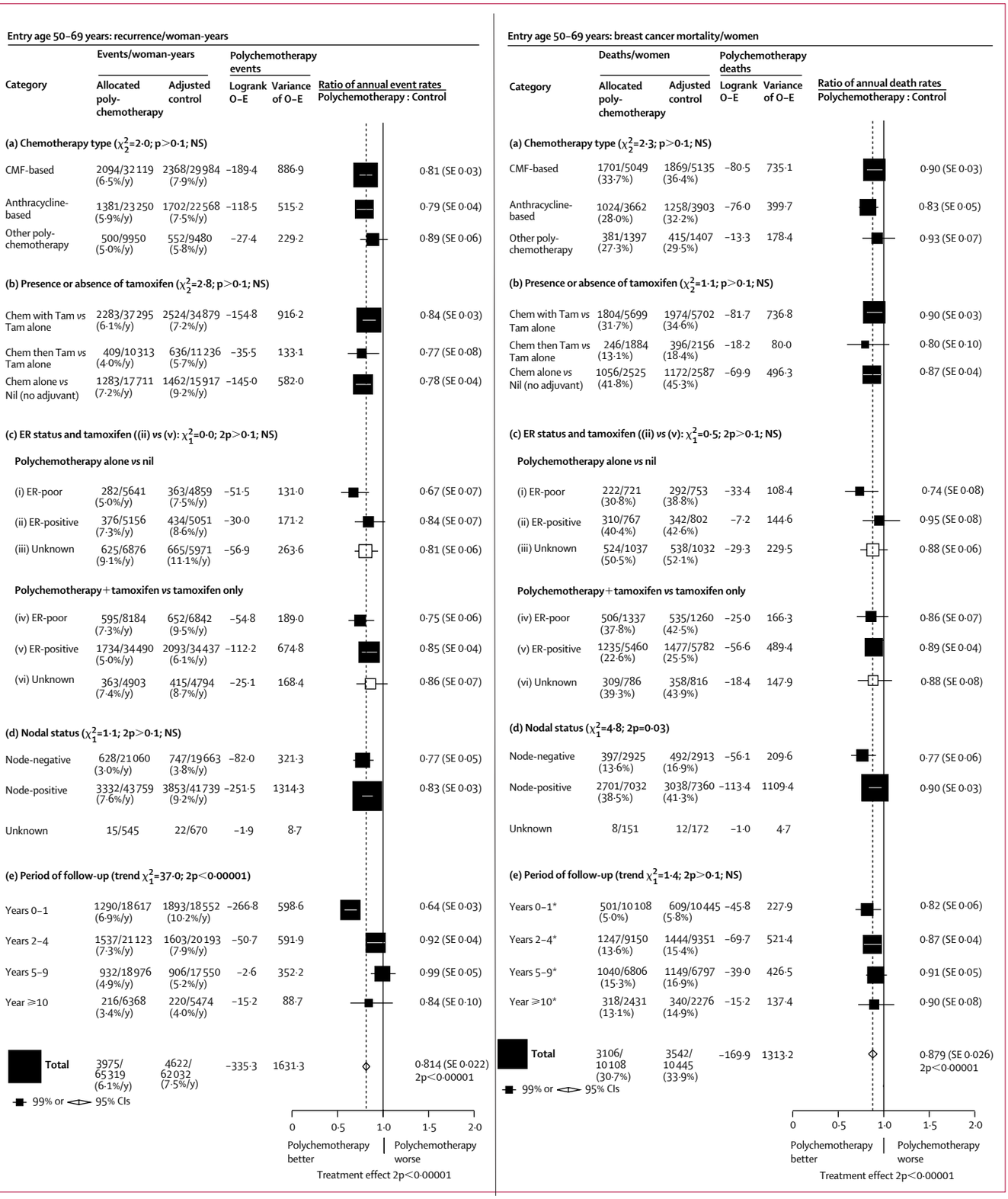


Figure 4: Polychemotherapy versus not, by type of chemotherapy, use of tamoxifen, ER status, nodal status, or period of follow-up: event rate ratios (continued on facing page)



The four parts give analyses of recurrence and of breast cancer mortality separately by entry age <50 (on facing page) and 50–69 years. *Denominator is the number entering that period.

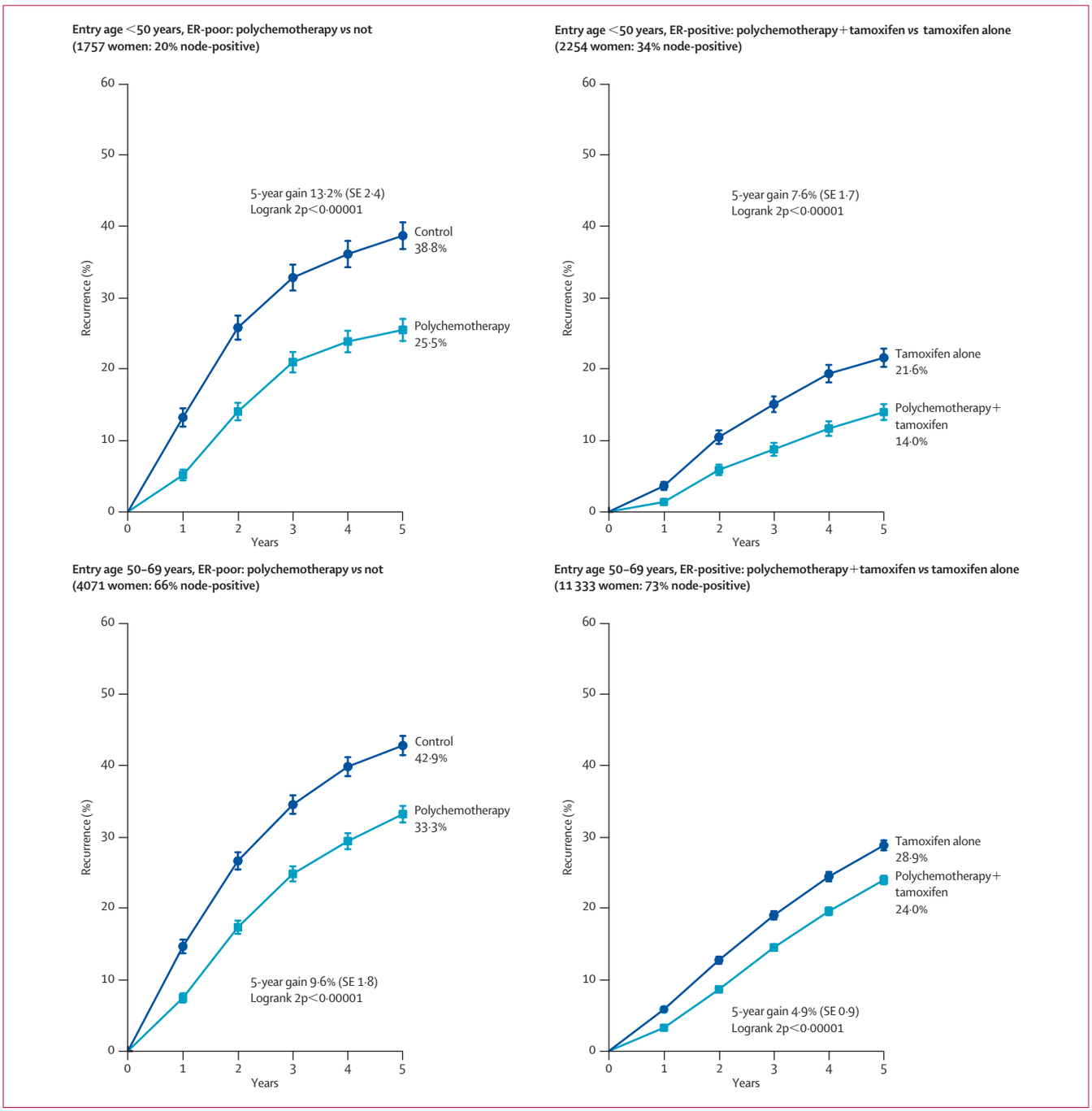


Figure 5: **Polychemotherapy versus not in ER-poor disease or in tamoxifen-treated ER-positive disease: 5-year probabilities of recurrence**
ER-poor disease includes some treated with tamoxifen. ER-positive includes 12% ER-unknown. Error bars are ±1SE.

endocrine therapy alone (recurrence rate ratios 0·64 [SE 0·08] for younger women and 0·85 [0·04] for older women; both 2p<0·00001).

A finer subdivision by age of the effects of chemotherapy in ER-poor disease and in ER-positive disease is given in webappendix 1 (annex-figure 1). Most of these trials involved CMF-based regimens; separate estimates of the effects of anthracycline-based regimens in ER-poor and ER-positive disease are given below, indicating somewhat greater benefit than with CMF.

Even if the proportional risk reductions were the same for ER-poor as for ER-positive disease, the 5-year gains from chemotherapy would be about twice as great for ER-poor disease as for tamoxifen-treated ER-positive disease. For, in the absence of chemotherapy, the 5-year risks for women of similar nodal status are about twice as great for ER-poor disease as for such ER-positive disease (see Discussion). Figure 5 shows the absolute 5-year benefits of chemotherapy in ER-poor disease (left) and in tamoxifen-treated ER-positive disease (right). Despite a smaller proportion of the ER-poor disease in these trials involving nodal spread, the 5-year gains produced by chemotherapy appear to be about twice as great in ER-poor as in tamoxifen-treated ER-positive disease. The 15-year gains are, however, less strongly dependent on ER status (see Discussion).

Nodal status—Among younger women, the proportional reductions in recurrence and in breast cancer mortality that are produced by chemotherapy appear to be about the same in node-negative as in node-positive disease (figure 4d, entry age <50 years), and among older women nodal status appears to be of little relevance to the proportional reduction in recurrence (figure 4d, entry age 50–69 years). Hence, nodal status may well be of little relevance to the proportional reduction in breast cancer mortality in either age-group. If so, the best estimate of the breast cancer death rate ratio (treatment *vs* control) among older women would be about 0·88 (ie, the overall risk ratio for all older women) both for node-negative and for node-positive disease, and the absolute benefit would be appreciably greater for node-positive disease, despite appearances to the contrary in figure 3. Nodal status is not strongly related to ER status (figure 5).

Period of follow-up—Among younger women the main divergence in recurrence takes place just during the first 5 years, when the absolute recurrence rate is high and the recurrence rate ratio is most favourable. This produces an absolute difference of 12% (37% *vs* 25%) in the 5-year recurrence probability, and this absolute difference of about 12% then persists after year 5 (figure 2, upper left, and figure 4e, entry age <50 years; here and elsewhere, the period-specific woman-years are slightly affected by rounding). By contrast, the probabilities of death from breast cancer continue to diverge not only in the first 5 years but also in later years. Hence, the absolute difference between them is about twice as great at year 15 as at year 5 (figure 2, upper right). This corresponds to a highly significantly favourable breast cancer death rate ratio among younger women not only during the first 5 years but also, separately, during years 5–9 and during later years (≥10) (figure 4e, entry age <50 years).

Among older women, the main divergence in recurrence takes place just within the first 2 years of starting chemotherapy (figure 2, lower left). Correspondingly, the ratio of recurrence rates (figure 4e, entry age 50–69 years) is highly favourable (0·64 [SE 0·03], 2p<0·00001) during years 0–1, but thereafter appears to be only slightly favourable (0·92 [0·04] during years 2–4; 0·96 [0·05] during years ≥5). The difference in breast cancer mortality among older women is too small for the analyses of the mortality rates in each separate period to be separately reliable. But, as is the case among younger women, the death rate ratio does appear to be persistently somewhat less than unity during years 0–1, 2–4, 5–9, and 10 or more (figure 4e, entry age 50–69 years). These consistent death rate ratios suggest that the slight convergence in breast cancer mortality after year 14 in figure 2 was just chance instability, but even if it were

	Poly-chemotherapy (n=14 250)	Adjusted control (n=14 514)	Polychemotherapy		
			Logrank O–E	Variance of O–E	2p
Mortality					
All-cause mortality	4769	5403	−327·6	2035·3	<0·00001
Breast cancer mortality (ie, death after recurrence or with wholly unknown cause)	4172	4844	−329·1	1806·2	<0·00001
Non-breast-cancer mortality (ie, deaths/years without recurrence) in trials that provided causes	597/92 592 (0·7%/year)	559/85 599 (0·7%/year)	1·4	229·3	..
Non-breast-cancer mortality (as above); anthracycline-based regimens only*	207/27 675 (0·7%/year)	168/25 805 (0·6%/year)	10·2	59·0	..
Vascular	202	183	10·2	75·2	..
Stroke	41	47	−1·9	17·2	..
Thromboembolic	15	13	1·9	5·3	..
Heart, etc (ie, other vascular)	146	123	10·2	53·0	..
Anthracycline-based regimens only*	47	31	6·7	11·6	0·05
Neoplastic	166	161	−5·2	65·8	..
Haemopoietic	17	16	−1·1	7·5	..
Anthracycline-based regimens only*	8	2	1·3	2·1	..
Lung cancer	30	16	3·1	10·3	..
Other neoplastic	119	129	−7·3	48·1	..
Other or unknown (but not breast cancer)	229	215	−3·6	89·9	..
Non-breast-cancer mortality in years 0–1 only/ years at risk	96/24 838 (0·4%/year)	76/24 440 (0·3%/year)	10·1	34·9	0·09
Entry age <50 years	5/6061	6/5570	−0·8	2·3	..
Entry age 50–59 years	22/8909	18/8906	2·1	8·9	..
Entry age 60–69 years	52/8872	44/8821	6·3	19·1	..
Entry age ≥70 years	17/996	8/1143	2·4	4·7	..
Second cancer incidence					
Any second primary† (without prior recurrence)	835	783	−10·4	337·3	..
Contralateral breast (before any other recurrence)	312	333	−23·5	140·4	0·05
Entry age <50 years	89	116	−20·8	49·1	0·003
Entry age ≥50 years	223	217	−4·7	94·1	..
Other site† (without prior such event)	528	466	9·0	203·2	..
Uterus (cervix, corpus, or unspecified site)	99	96	−1·6	39·1	..
Ovary	38	28	1·5	13·8	..
Liver	3	0	1·0	0·7	..
Lung	57	33	4·7	20·3	..
Colon or rectum	66	66	−1·6	25·5	..
Haemopoietic	34	32	−1·2	13·7	..
Anthracycline-based regimens only*	13	7	1·3	3·5	..
Other second primary	235	213	7·1	92·8	..

*Results just for the trials of anthracycline-based versus no chemotherapy. Corresponding results for trials of anthracycline-based versus CMF chemotherapy: all-cause mortality 1914/7228 versus 2133/7243 deaths/women (p<0·00001), non-breast-cancer mortality 105/40 750 versus 96/39 114 deaths/woman-years without recurrence (0·26 *vs* 0·25%/year), including heart, etc, nine versus seven deaths and haemopoietic neoplasms seven versus three deaths (of 17 *vs* nine incident cases). In trials of longer versus shorter anthracycline duration there were only 1/360 versus 2/360 cardiac or haemopoietic deaths (webappendix 1 [appendix to table 1 and annex-figure 6]). †Women found to have two different second primaries at the same time contribute to the analyses of both, but only once to these totals. Trial-specific results for each outcome are in webappendix 1 (appendix to table 2).

Table 2: **Mortality and second cancer incidence before any recurrence of the original breast cancer (women of any age) for polychemotherapy versus not: numbers with such events, and logrank analyses**

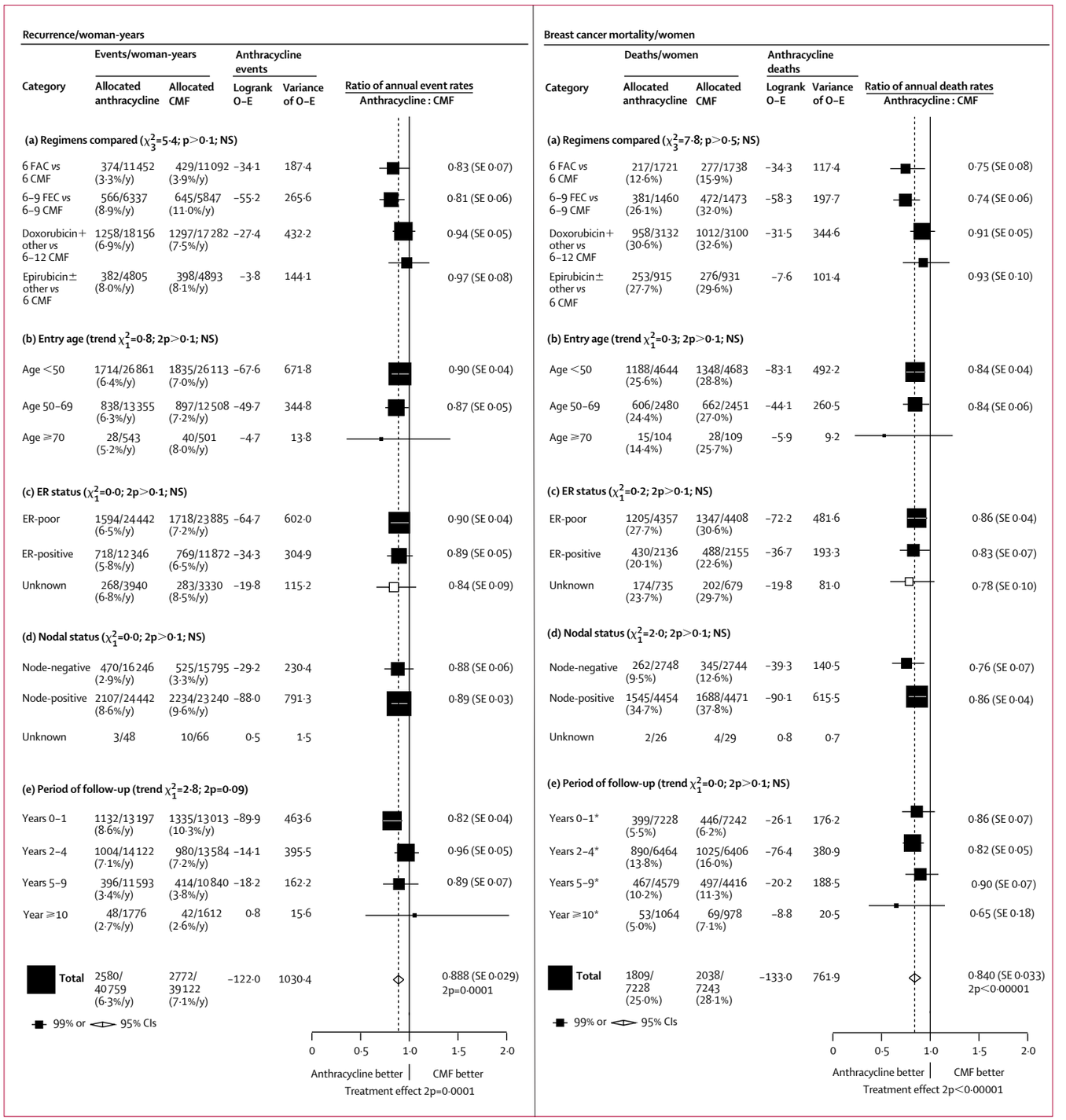


Figure 6: **Anthracycline-based regimen versus CMF, by type of regimen, entry age, nodal status, or period of follow-up: event rate ratios**
Trials of either doxorubicin or epirubicin, usually with other cytotoxic drugs (eg, as FAC or FEC), versus 6–12 (mean 6·5) cycles of CMF. *Denominator is the number entering that period.

ignored the 15-year gain would still be less than 4% among older women from these (largely CMF-based) regimens.

Other features, and site of first recurrence—PR status was available from 85% of those with known ER status (but was closely correlated with it). Histology was available

from 44% of all tumours (16% good, 53% moderate, 31% poor differentiation), and diameter was available for 83% of node-negative tumours (57% <2 cm, 40% 2–5 cm, 3% >5 cm). But, given age, there was no significant heterogeneity with respect to these features (or with respect to menopausal status) in the proportional risk reductions produced by chemotherapy (webappendix 1 [annex-figure 4]). Both among older and among younger women, chemotherapy produced significant reductions not only in distant recurrence but also in isolated (ipsilateral) local recurrence.

Other outcomes—Table 2 shows the effects of polychemotherapy on cause-specific mortality and on the incidence of second cancers during the time before any recurrence of the original breast cancer. Taking all polychemotherapy regimens together, the average non-breast-cancer death rate is 0·7%/year both in the treatment and the control group, with no significant excess in any particular cause or period. There is, however, a non-significant excess of such deaths during the first 2 years among women of age 60–69 years or 70 and older, suggesting early hazards of 0·2% (twice the difference between the annual mortality rates in years 0–1; table 2) and 2%, respectively. Anthracycline-based regimens are considered separately below, after the trials that compare them directly against other regimens (figure 6).

There is a marginal reduction in the incidence of contralateral breast cancers before any other recurrence (0·5 *vs* 0·6%/year, 2p=0·05), which appears to be more definite in younger than in older women, but this has already been included in the foregoing analyses of recurrence rates. There is no significant effect on the incidence of leukaemias and lymphomas or of any other category of neoplastic disease (table 2), although different regimens might involve different such hazards.

Directly randomised chemotherapy comparisons

Longer versus shorter chemotherapy—Only 6000 women are included in trials that directly compared longer versus shorter polychemotherapy (weighted mean treatment duration 10·7 *vs* 5·0 months, mostly with CMF-based regimens; webappendix 1 [appendix to table 1]). Almost all had node-positive disease and half had a recurrence, most of whom died. Although the recurrence rate during the first 2 years was significantly lower with longer treatment (11·2 *vs* 13·0%/year, ratio 0·84 [SE 0·05], 2p=0·003), the overall findings indicate little long-term gain from longer treatment with these largely CMF-based regimens (recurrence rates 8·3 *vs* 8·7%/year, ratio 0·95 [SE 0·04, 95% CI 0·88–1·02]; breast cancer death rate ratio 0·98 [0·04, 0·90–1·06]; deaths without recurrence 77/3054 *vs* 77/3071; webappendix 1 [annex-figure 6]).

Of these 6000 women, only 720 were in trials that compared longer versus shorter anthracycline-based regimens (mean treatment duration 7·2 *vs* 3·5 months), so the CIs for this treatment comparison were uninformatively wide (recurrence rate ratio 0·83 [95% CI 0·69–1·01]; breast cancer death rate ratio 0·95 [0·76–1·19]; deaths from heart disease or leukaemia 1/360 *vs* 2/360; webappendix 1 [appendix to table 1]).

Anthracycline-based regimens versus CMF—Although the indirect comparisons of anthracycline-based and CMF-based regimens did not suggest any substantial difference in efficacy (figure 4a), the directly randomised comparisons involve smaller SEs for the comparison between the two treatment effects, particularly at younger ages, and favour anthracyclines (figure 6). A total of 14 000 women (9000 younger, 5000 older) were included in trials that compare anthracycline-based versus CMF-based regimens.

The anthracyclines tested were doxorubicin (60%) or epirubicin (40%), usually given for about 6 months in combination with other cytotoxic drugs (eg, as FAC or FEC, which were the most widely studied combinations). The CMF-based regimens used in the control groups all involved CMF with no other cytotoxic drugs, and were mostly given for about 6 (mean 6·5) months. The overall findings show a moderate but highly significant advantage of anthracyclines over CMF (recurrence rate ratio 0·89 [SE 0·03], 2p=0·001; breast cancer death rate ratio 0·84 [0·03], 2p<0·00001). The corresponding 10-year probabilities of recurrence, breast cancer mortality, and overall mortality are plotted in webappendix 1 (annex-figure 6); in each case the absolute difference between anthracycline-based and CMF chemotherapy is about 3% at 5 years and 4% (SE 1) at 10 years.

The proportional risk reductions just among the 5000 older women have relatively wide CIs (as do those just in ER-positive disease, in node-negative disease, or in particular periods; figure 6). Nevertheless, the superiority of the anthracycline-based regimens does appear to be about as great for older as for younger women.

Combination of direct and indirect evidence to estimate the effects of anthracycline-based regimens on mortality

Breast cancer mortality reduction, by age—The directly randomised comparisons of anthracycline-based versus no chemotherapy in figure 4a suggest breast cancer death rate ratios of 0·74 (SE 0·09) for younger and 0·83 (0·05) for older women. But, combination of the results for CMF-based versus no chemotherapy in figure 4a with those for anthracycline-based versus CMF chemotherapy in figure 6 provides indirect, but independent, evidence that anthracycline-based regimens could be somewhat more effective than this (suggesting breast cancer death rate ratios of 0·55 [0·66×0·84] for younger and 0·76 [0·90×0·84] for older women). An inverse-variance-weighted average of these direct and indirect estimates suggests that such anthracycline-

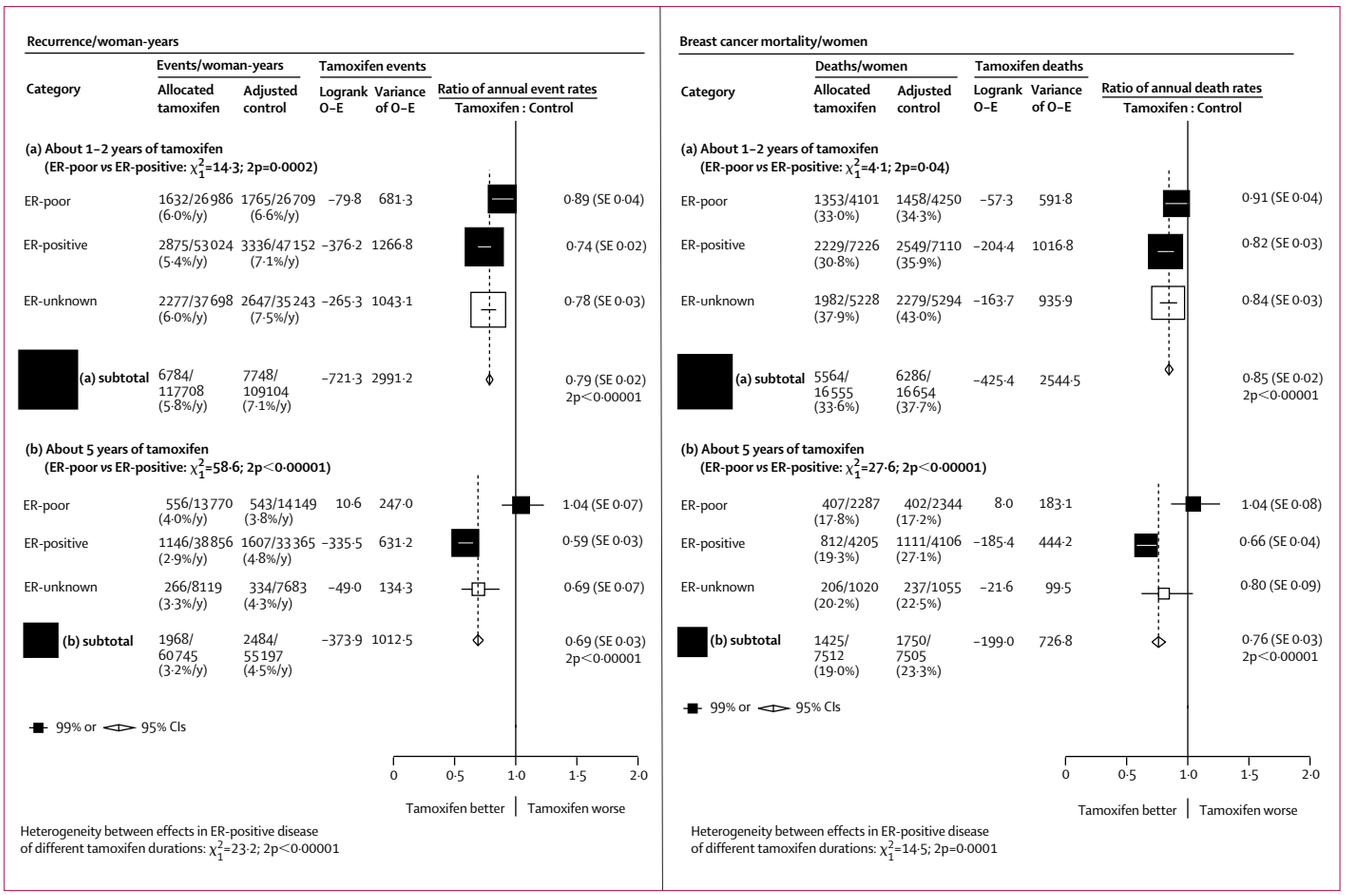


Figure 7: **Tamoxifen versus not, by ER status and treatment duration (about 1–2 years or about 5 years of tamoxifen): event rate ratios**

based regimens would yield breast cancer death rate ratios of about 0·62 (SE 0·05) for younger and 0·80 (0·04) for older women.

Breast cancer mortality reduction, by age and ER status—Both among younger and among older women, the proportional effects on breast cancer mortality of these anthracycline-based regimens are not significantly related to ER status. The appendix to table 1 in webappendix 1 includes detailed meta-analyses of the chemotherapy trials, subdivided by age, ER status, and treatment regimen. Appropriate combination of the direct and the indirect evidence from these trials (the inverse-variance-weighted average, as above) yields the best estimate of the breast cancer death rate ratio produced by such anthracycline-based regimens.

Among younger women with ER-poor and ER-positive disease, the best estimates of the breast cancer death rate ratio are 0·61 (SE 0·10) and 0·64 (0·09), respectively (difference 2p=0·7), whereas among older women with ER-poor and ER-positive disease, the best estimates are 0·76 (0·06) and 0·81 (0·05), respectively (difference 2p=0·5). After standardising for age (in two groups), the best estimate of the breast cancer death rate ratio does not depend significantly on ER status (difference 2p=0·2), but after standardising for ER status (in three groups: ER-poor, ER-unknown, or ER-positive) it does still depend significantly (2p=0·0001) on age.

Cardiotoxicity and leukaemogenicity of anthracycline-based regimens—In the trials of CMF-based versus no chemotherapy there is no apparent excess of vascular deaths or haemopoietic neoplasms (webappendix 1 [appendix to table 2]). But, in the aggregate of all the trials of anthracycline-based versus no chemotherapy (figure 4) and of anthracycline-based versus CMF chemotherapy (figure 6), a total of 11 581 women were allocated anthracyclines and 11 880 were not. During the period before any recurrence their death rates are 0·46 versus 0·40%/year from all causes (logrank 2p=0·2), 0·08 versus 0·06%/year from heart disease, etc (2p=0·4), and 0·02 versus 0·01%/year from haemopoietic neoplasms (2p=0·10, with corresponding incidences of 0·04 *vs* 0·02%/year, 2p=0·16; table 2).

These differences in vascular and neoplastic mortality are not significant, and thus far indicate a hazard of only a few per 1000 per decade from the anthracycline-based regimens in these trials, which is much smaller than an absolute reduction of a few percent in breast cancer mortality. But, any such hazards could be greater with longer follow-up (into old age) or with different anthracycline-based regimens.

Indirect comparisons between different anthracycline-based regimens

FAC or FEC—The results from every separate trial of anthracycline-based chemotherapy versus no chemotherapy, or versus CMF, are given in webappendix 1 (appendix to table 1), and there is no significant heterogeneity between the anthracycline-based regimens. But, two of the most widely studied such regimens were 6 months (or, in one trial, 8 months) of FAC and 6 months (or, in one trial, 9 months) of FEC. These appear to be of comparable efficacy, and, on average, confer definite benefits.

The trials of FAC or FEC versus no adjuvant chemotherapy yield breast cancer death rate ratios of 0·69 (SE 0·16) for younger and 0·79 (0·07) for older women; the trials of FAC or FEC versus CMF for 6–9 months (mean 7) yield ratios of 0·74 (0·06) for younger and 0·78 (0·08) for older women; and the trials of CMF alone for no more than 9 months (mean 7) versus no adjuvant chemotherapy yield ratios of 0·64 (SE 0·12) for younger and 0·93 (0·05) for older women. Combining these three meta-analyses, as before, yields the weighted averages of the breast cancer death rate ratios produced by FEC or FAC: 0·56 (SE 0·10, $2p<0·00001$) for younger and 0·76 (0·06, $2p<0·0001$) for older women. These results for about 6 months of FAC or FEC are statistically definite, and appear about as promising as the averaged results for all anthracycline-based regimens (of which the FAC or FEC results are a large part).

Various other ways of subclassifying the trials of anthracycline-based versus no adjuvant chemotherapy were considered (eg, treatment duration, use of doxorubicin or of epirubicin) without finding any significant heterogeneity of benefit (data not shown). The same was true of various ways of subclassifying the trials of anthracycline-based regimens versus CMF. But, the numbers of events are too small for either type of trial to provide statistically reliable evidence as to whether there really is any important heterogeneity.

Tamoxifen

Tamoxifen versus no tamoxifen

Figure 7 summarises the effects of 1–2 years of tamoxifen and of about 5 years of tamoxifen in the trials that compared tamoxifen versus no adjuvant tamoxifen. Because of the established relevance of the hormone receptor status of the primary tumour, the analyses are subdivided by ER status, classified as ER-poor, ER-positive, and ER-unknown. Procedures for measuring receptor status continue to evolve, so current and future measurements could well be more predictive of response. But, even though it may be difficult to characterise exactly the receptor assays used many years ago in these trials, at least the ER measurements were, on average, highly significantly predictive of the response to 5 years of adjuvant tamoxifen (figure 7).

Tamoxifen duration and ER status—Among women with ER-positive disease, the reduction in the recurrence rate and in the breast cancer death rate are highly significant both in the trials of 1–2 years of tamoxifen and in those of about 5 years of tamoxifen, but are greater in the latter. This indirect evidence that 1–2 years is less effective than 5 years of tamoxifen in ER-positive disease is highly significant ($2p<0·00001$ for recurrence, $2p=0·0001$ for breast cancer mortality), and is supported by the directly randomised comparisons of different tamoxifen durations that are presented below.

Among women with ER-poor disease, there did appear to be some benefit in the trials of 1–2 years of tamoxifen, but there did not in the trials of about 5 years of treatment, so the apparent benefit might have been due largely or wholly to false-negative ER measurements in some of the early trials of 1–2 years of tamoxifen, perhaps aggravated by the play of chance. As expected, the results for women with tumours of unknown ER status (most of which would, if measured, probably have been classified as ER-positive) are slightly weaker than those for women with ER-positive disease.

In webappendix 1 (annex-figure 7), women are subdivided by both ER and PR status. Where both are available, it is the ER and not the PR status (as measured in these trials) that chiefly determines the effect of tamoxifen on the ratio of recurrence rates.

5 years of tamoxifen in ER-positive disease

Among women with ER-positive disease in the trials that sought to assess the effects of about 5 years of tamoxifen, which is a commonly used duration of such treatment,[13] the annual recurrence rate was almost halved (recurrence rate ratio 0·59 [SE 0·03]) and the breast cancer mortality rate was reduced by a third (death rate ratio 0·66 [0·04]; figure 7) by being allocated active treatment. Most subsequent analyses of these trials are restricted to women with ER-positive (or ER-unknown) disease, irrespective of their measured PR status. Figure 8 shows the 15-year recurrence and breast cancer mortality probabilities among such women in the trials of about 5 years of tamoxifen. The benefits of being allocated active treatment are substantial, and persistent.

Most of the effect on recurrence is seen during the first 5 years, while tamoxifen was generally still continuing to be given, but most of the effect on breast cancer mortality comes after this period (figures 8 and 9e).

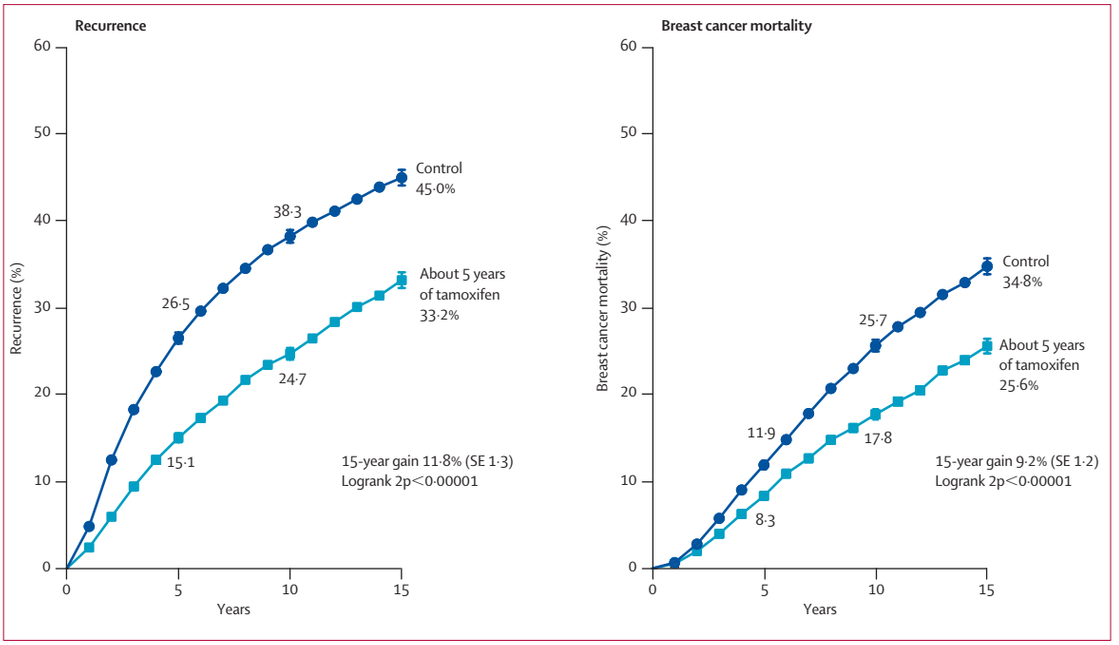


Figure 8: **About 5 years of tamoxifen versus not in ER-positive (or ER-unknown) disease: 15-year probabilities of recurrence and of breast cancer mortality**
10 386 women: 20% ER-unknown, 30% node-positive. Error bars are ±1SE.

Indeed, the difference in the 15-year probability of death from breast cancer is about three times as great as that in the 5-year probability. Since tamoxifen has little net effect on the aggregate of all other causes of death (see below), its absolute effects on all-cause mortality are similar to its absolute effects just on breast cancer mortality (webappendix 1 [annex-figure 8]).

Figure 8 may slightly underestimate the effects of actually using 5 years of tamoxifen in ER-positive disease, since 20% of women had ER-unknown disease, so a few percent must actually have had ER-poor disease. Moreover, in these trials of long-term daily treatment there may well have been some non-compliance with the treatment allocation. Furthermore, 18% of the recurrences at least 2 years after allocation to tamoxifen were in women reallocated to stop at 2 years[15] or at 3 years (*vs* continuing) who had reached their stopping point, whereas only 10% were in women reallocated to continue after 5 years (*vs* stopping).

In many of these trials, women in the control group who had recurrence could then be offered treatment. To the extent to which this was the case, the effects on mortality show that for tamoxifen, as for chemotherapy, deferral of treatment is not always safe.

Relevance to tamoxifen of dose and of chemotherapy—Figure 9 describes the proportional risk reductions produced by about 5 years of adjuvant tamoxifen in various different circumstances (and webappendix 1 [annex-figure 9] describes further such subgroup analyses). The proportional risk reductions produced by tamoxifen appear to be about the same in trials of 20 mg/day as in trials of 30–40 mg/day (figure 9a). They also appear to be about the same in trials of chemoendocrine therapy (concurrent or sequential) versus the same chemotherapy alone as they are in the trials of tamoxifen alone, without any chemotherapy (figure 9b).

The comparisons in figures 9 and 4 show that for women with ER-positive disease, chemoendocrine therapy is better than chemotherapy alone or endocrine therapy alone, but do not provide reliable evidence as to whether there is any material difference in long-term outcome between concurrent and sequential chemo-endocrine therapy, and no large trials of concurrent versus sequential treatment are available in the present dataset. (Results from an intergroup trial published since 2000,[14] however, favour sequential treatment.)

The effects of about 5 years of tamoxifen on the 5-year probabilities of recurrence in selected subgroups are plotted in figure 10. The recurrence probabilities in the chemoendocrine trials do not diverge much during the first year. Apart from this, however, allocation to about 5 years of tamoxifen approximately halves the annual recurrence rate throughout those first 5 years, largely irrespective of any chemotherapy.

Age and nodal status—The proportional risk reductions produced by tamoxifen are little affected by entry age (figure 9c) or by nodal status (figure 9d). In particular, the reduction in recurrence is substantial, and highly significant ($2p<0{\cdot}00001$), both for women younger than 40 years of age when randomised and for those

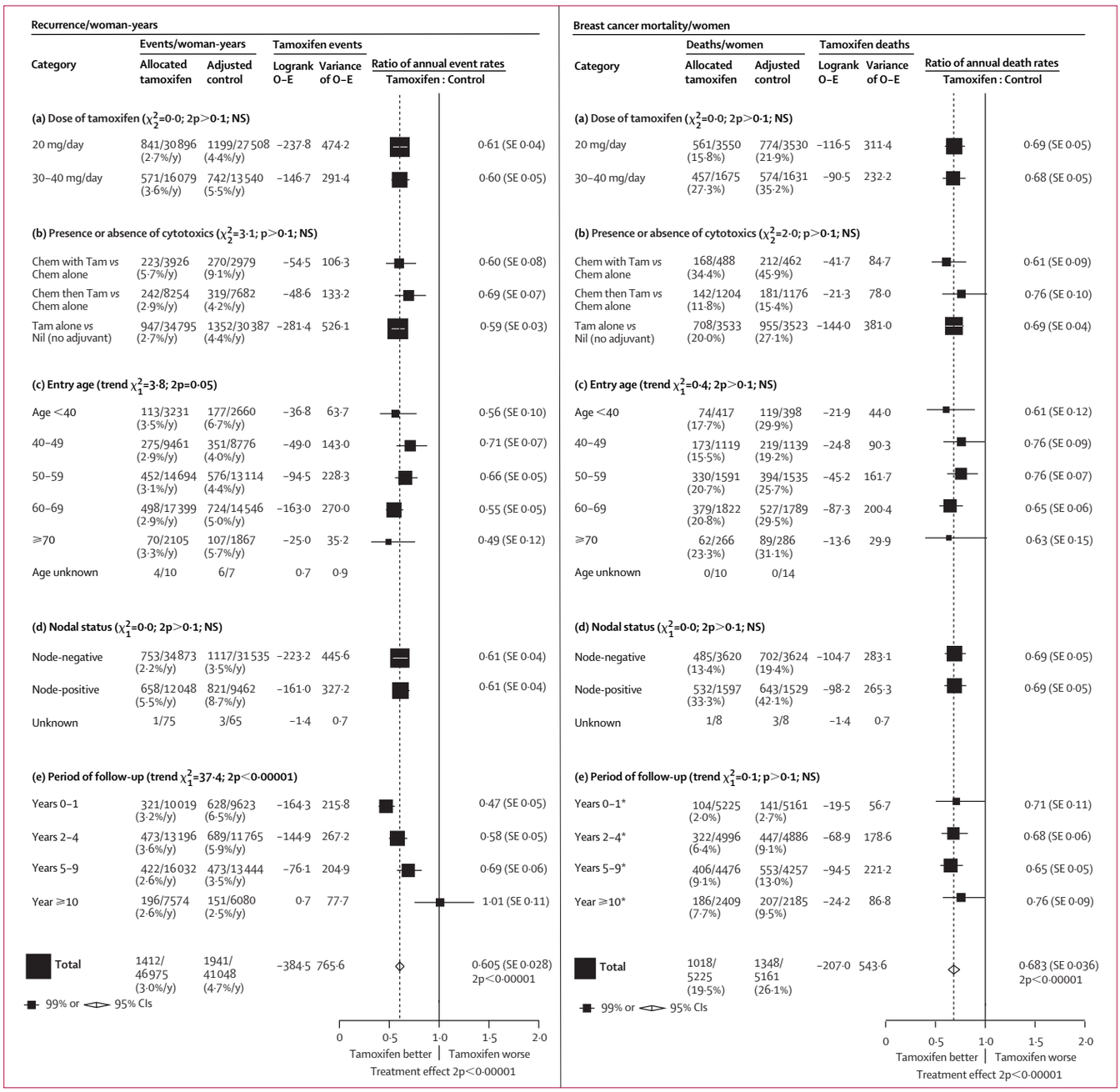


Figure 9: **About 5 years of tamoxifen versus not in ER-positive (or ER-unknown) disease, by tamoxifen dose, use of chemotherapy, age, nodal status, or period of follow-up: event rate ratios**
*Denominator is the number entering that period.

older than 70. Hence, the absolute risk reduction after 5 years of tamoxifen is similar for younger and for older women, but is significantly greater for those with node-positive than node-negative disease (figure 10).

The 10-year probabilities are given in webappendix 1 (annex-figure 10). For breast cancer mortality, the 10-year gains were substantial and definite not only for women with node-positive disease (32·0% *vs* 44·5%, 10-year gain 12·6% [SE 2·0], 2p<0·00001) but also for those with node-negative disease (12·2% *vs* 17·5%, 10-year gain 5·3% [0·9], 2p<0·00001).

Period of follow-up—In figure 9e the event rate ratios in years 0–1, 2–4, 5–9, and later (≥10) are analysed

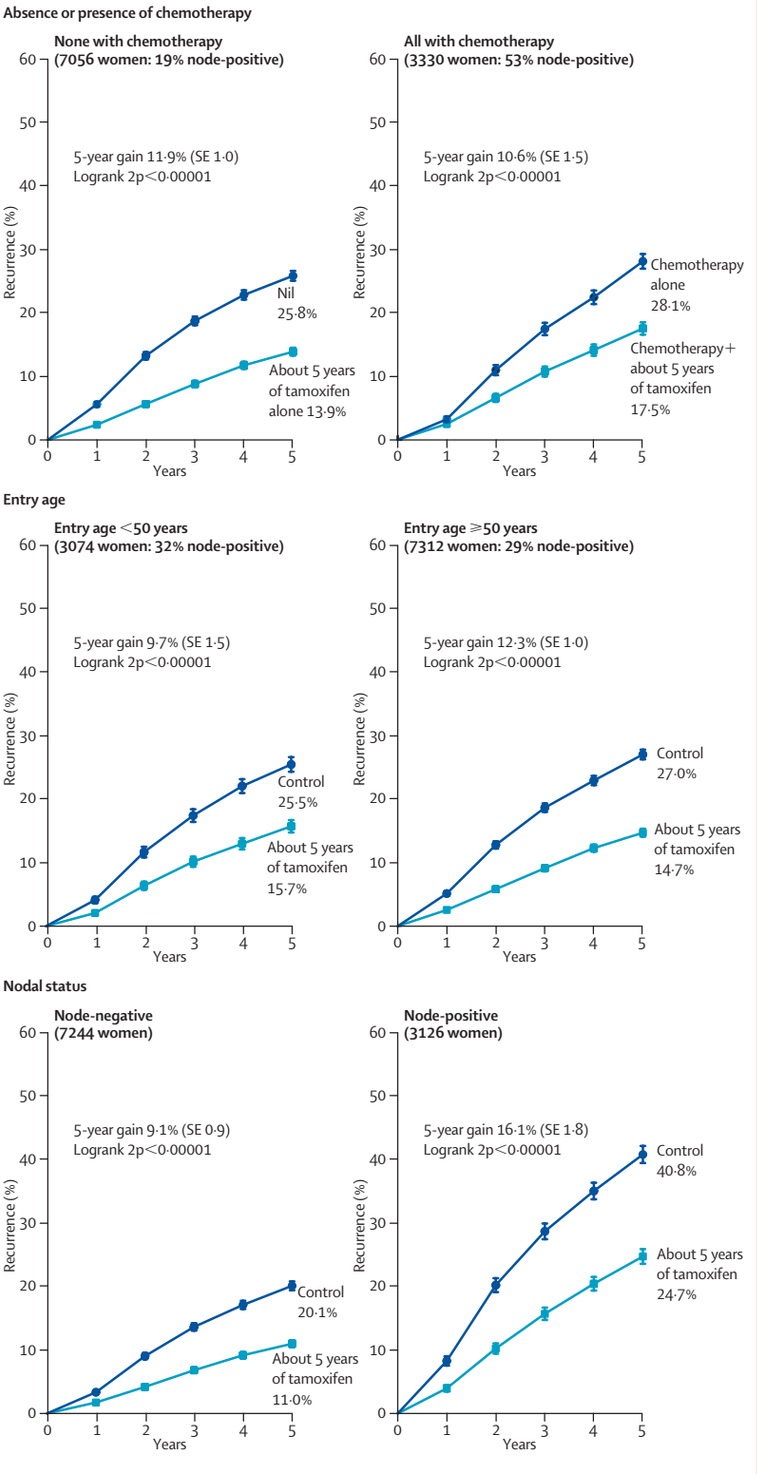


Figure 10: **About 5 years of tamoxifen versus not in ER-positive (or ER-unknown) disease, by use of chemotherapy, entry age, or nodal status: 5-year probabilities of recurrence**
Error bars are ±1SE.

separately (see also the 15-year probabilities in figure 8). Most of the tamoxifen-allocated women whose disease recurred during years 5–9 would have stopped taking the drug some time earlier (although some had been re-randomised at year 5 to continue), but the ratio (treatment *vs* control) of recurrence rates in years 5–9 was still 0·69 with a narrow CI.

This persistent reduction of about a third in the annual recurrence rate indicates that if women who have been on tamoxifen for some time stop taking it then the earlier gains are not quickly lost and, in addition, there is a protective carryover effect that substantially reduces the risk of recurrence over the next few years. The recurrence rates after year 10 were, however, similar in the treatment and control groups, indicating no further gain in recurrence (but no net loss of the earlier gains).

For breast cancer mortality the persistence of the effects of about 5 years of treatment is even more remarkable. The overall death rate ratio continues to be about 0·7 not only during years 0–4 ($2p<0·00001$) but also during years 5–9 ($2p<0·00001$) and during later years (≥10; $2p=0·01$), resulting in steady divergence between treatment and control throughout the first 15 years in breast cancer mortality (figure 8) and overall mortality (webappendix 1 [annex-figure 8]).

Other features, and site of first recurrence—Further subgroup analyses are given in webappendix 1 (annex-figure 9), indicating no significant heterogeneity in the proportional risk reduction with menopausal status, tumour size, PR status (as measured in these trials), or site of first recurrence. The ratio of recurrence rates was 0·47 (SE 0·08, $2p<0·00001$) for isolated (ipsilateral) local recurrence and 0·64 (0·05, $2p<0·00001$) for distant recurrence.

Other outcomes—Table 3 shows the effects of about 5 years of tamoxifen on cause-specific mortality, and on the incidence of second cancers, during the period before any recurrence of the original cancer. It includes all 15 000 women in such trials, irrespective of ER status (figure 7b), since ER status might well be of little relevance to any life-threatening side effects. Overall, there is no significant excess of deaths from any particular cause, and the average non-breast-cancer death rate was 0·8%/year both in the treatment and in the control groups.

Because tamoxifen can delay or prevent recurrence, the treatment groups spent more time than the controls at risk of death before recurrence (61 000 woman-years *vs* 55 000 woman-years), so the absolute numbers of deaths before recurrence from particular causes cannot be compared directly. The logrank statistics correct for this, however, and the overall O–E value of 3·4 suggests a non-significant excess of only about seven non-breast cancer deaths (ie, double the logrank O–E). This overall excess can be accounted for by the small excesses of

deaths from thromboembolic disease (O–E 2·7) and from uterine cancer (O–E 2·5). Both are non-significant, but both may well reflect real hazards, given the effects of tamoxifen on the incidence of non-fatal pulmonary emboli and of uterine cancer.[16]

If there is a real excess of about five deaths (as indicated by doubling the logrank O–E values) from each of these two diseases in about 60 000 woman-years then the two together would represent an absolute risk of about 0·2% per decade among women allocated about 5 years of tamoxifen. This is small by comparison with the absolute 10-year reductions in breast cancer mortality (5·3% and 12·2%, respectively, for node-negative and node-positive disease). Because there are so few deaths from these two side-effects it is not possible just from these trials to assess separately the risks in the first and second decades after randomisation, or to assess the dependence of risk on age, or on other factors.

Overall mortality from vascular disease is non-significantly lower with tamoxifen than with control, since a non-significant excess of stroke (which was not apparent during the first 5 years, when tamoxifen was generally being taken) and thromboembolic disease are outweighed by a non-significant deficit in other vascular mortality, most of which involves heart disease. This apparent reduction is compatible with a real protective effect against heart disease, perhaps from the favourable lipid changes produced by tamoxifen,[17] but could also be due to the play of chance.

There is a definite decrease of about a third in the incidence of contralateral breast cancer (4·0 *vs* 6·0 per 1000 per year), which has already been included in the foregoing analyses of overall recurrence rates, a definite increase by a factor of about 3 in the incidence of uterine cancer (1·9 *vs* 0·6 per 1000 per year), and no significant effect on the incidence of any other type of cancer. Hence, the overall incidence of second cancers is non-significantly lower in the tamoxifen than in the control groups.

The effect on contralateral breast cancer is definite, and highly significant, only for women who had originally had ER-positive or ER-unknown disease, which is the population in which the effects of tamoxifen are particularly relevant (incidence rate ratio 0·61 [95% CI 0·50–0·73]). There appears to be little effect on contralateral breast cancer among women who had originally had ER-poor disease (ratio 0·99 [95% CI 0·70–1·36]; χ^2_1 for heterogeneity of effect by ER status 6·0, 2p=0·014), although the 95% CI includes the possibility of a reduction of almost a third.

	About 5 years of tamoxifen (n=7512)	Adjusted control (n=7505)	Tamoxifen		
			Logrank O–E	Variance of O–E	2p
Mortality					
All-cause mortality	1905	2166	−195·8	940·1	<0·00001
Breast cancer mortality (ie, death after recurrence or with wholly unknown cause)	1425	1750	−199·1	726·8	<0·00001
Non-breast-cancer mortality (ie, deaths/years without recurrence) in trials that provided causes	480/61 111 (0·8%/year)	416/55 422 (0·8%/year)	3·4	213·5	..
Vascular	189	169	−3·9	85·7	..
Stroke	54	29	8·0	19·3	0·07
Thromboembolic	15	8	2·7	5·7	..
Heart, etc (ie, other vascular)	120	132	−14·5	61·0	0·06
Neoplastic (not breast)	126	105	4·6	54·9	..
Uterus (cervix, corpus, or unspecified site)	9	2	2·5	2·6	..
Ovary	5	9	−2·2	3·5	..
Liver	3	2	0·6	1·2	..
Lung	26	26	−0·6	12·1	..
Colon or rectum	18	12	2·3	7·0	..
Haemopoietic	14	8	1·8	5·2	..
Other neoplastic	51	46	0·2	23·5	..
Other/unknown (but not breast cancer)	165	142	2·6	74·8	..
Second cancer incidence*					
Any second primary (without prior recurrence)	709	666	−7·8	328·7	..
Contralateral breast (before any other recurrence)	244 (0·4%/year)	331 (0·6%/year)	−53·1	139·6	<0·00001
ER-poor original breast cancer	69	75	−0·8	35·3	..
ER-positive or ER-unknown	175	256	−52·3	104·3	<0·00001
Uterus (cervix, corpus, or unspecified site)	118 (0·19%/year)	32 (0·06%/year)	38·4	36·5	<0·00001
Other site (without prior such event)	347	304	6·2	155·7	..
Ovary	25	22	0·6	11·7	..
Liver	7	3	2·1	2·4	..
Lung	52	41	3·8	22·0	..
Colon or rectum	62	62	−2·9	29·8	..
Haemopoietic	26	19	2·5	11·1	..
Other second primary	176	158	0·2	80·1	..

*See note to table 2 on slight sub-additivity of tabulated numbers. Trial-specific results for each outcome are in webappendix 1 (appendix to table 3).

Table 3: **Mortality and second cancer incidence before any recurrence of the original breast cancer (all women, irrespective of ER status) for about 5 years of tamoxifen versus not: numbers with such events, and logrank analyses**

Directly randomised tamoxifen comparisons

Longer versus shorter durations of tamoxifen—Trials of tamoxifen duration generally seek to randomise women with potentially hormone-sensitive disease who have already completed some years of adjuvant tamoxifen between stopping and continuing, but some randomisations were generated earlier, before the follow-up at which treatment might be stopped. The present analyses therefore exclude the few women with ER-poor disease, and the few woman-years (or women who had an event) after randomisation was issued but before the treatment options would differ.

By the year 2000, some 29 000 of the remaining women had been randomised between longer and shorter tamoxifen. Of these, 18 000 (with mean follow-up 5 woman-years) were in trials comparing about 5 versus 1–2 years of tamoxifen, and 8000 (with mean follow-up only 2 woman-years) were in trials comparing about 10 versus 5 years of tamoxifen[18] (figure 11). Since then, at least another 10 000 have been randomised (mostly comparing about 10 versus 5 years of tamoxifen), but no information from them is yet available.

Overall, longer treatment appears to be more effective at controlling breast cancer than shorter treatment is, although the event rate ratio (after those allocated to stop tamoxifen should have done so) is more extreme for

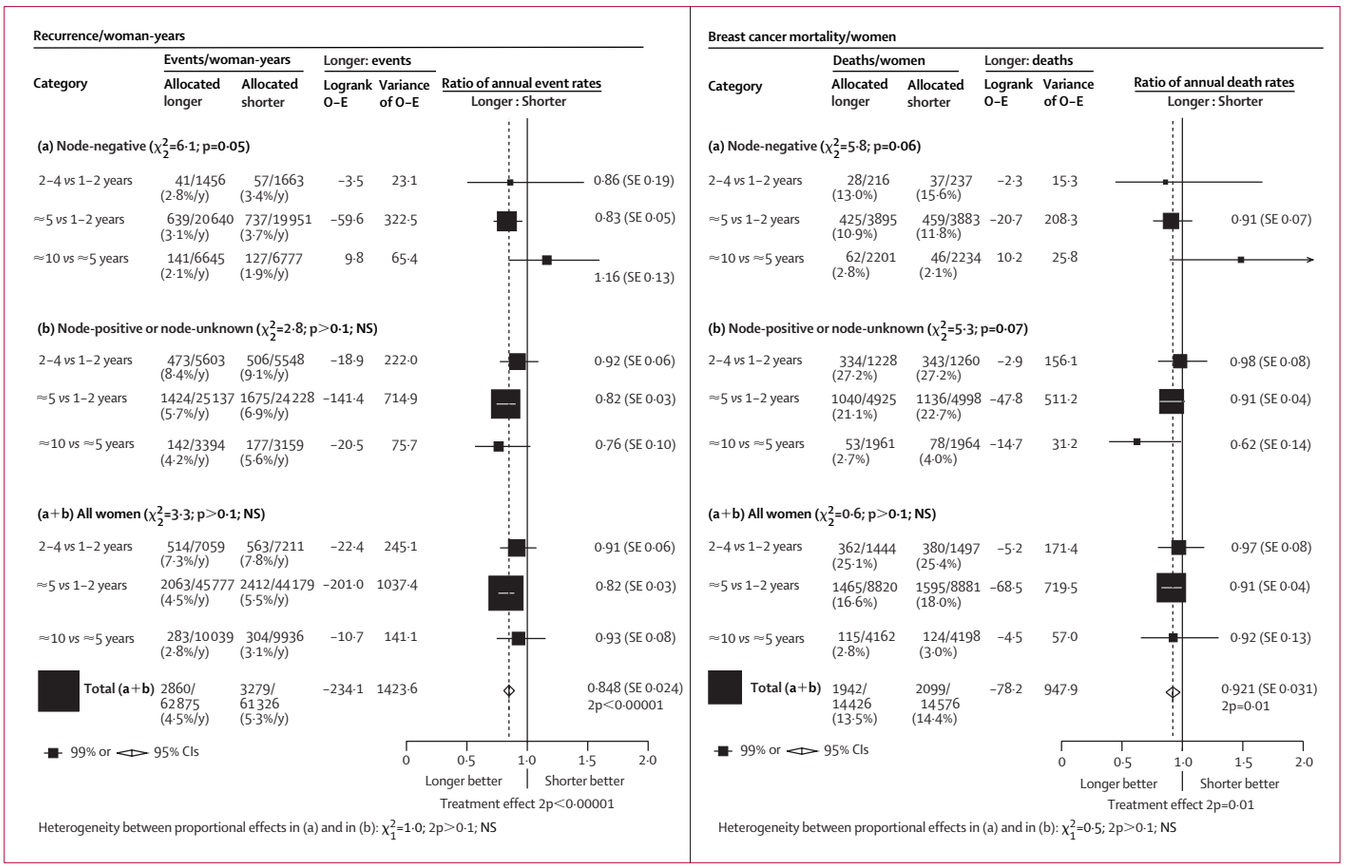


Figure 11: **Longer versus shorter tamoxifen duration in ER-positive (or ER-unknown) disease, by treatment type and nodal status: event rate ratios**

recurrence (ratio 0·85 [SE 0·02], 2p<0·00001) than for breast cancer mortality (ratio 0·92 [0·03], 2p=0·01), perhaps because retreatment on recurrence was generally allowed. With longer treatment there is, however, a slight and non-significant excess mortality rate from other causes (0·98 *vs* 0·94%/year; 619/62 875 *vs* 578/61 326 deaths/woman-years, 2p=0·5). This includes excesses of 0·01%/year from each of thromboembolism (0·017 *vs* 0·005%/year; 11 *vs* 3 deaths, 2p=0·07), stroke (0·08 *vs* 0·07%/year; 51 *vs* 45 deaths, 2p=0·5), other vascular causes (0·20 *vs* 0·21%/year; 128 *vs* 118 deaths, 2p=0·6), and non-vascular causes (0·66 *vs* 0·65%/year). Although these differences are not significant, some (eg, the excess of thromboembolic deaths) may well reflect real hazards.

With longer treatment there is no apparent excess mortality from uterine cancer (13 *vs* 15 deaths), but the incidence of uterine cancer is significantly increased (0·21 *vs* 0·11%/year; 130 *vs* 70 cases, 2p=0·00002). As in the trials of 5 years of tamoxifen versus no tamoxifen (table 3), the increase in uterine cancer is outweighed by a somewhat larger decrease in contralateral breast cancer (0·28 *vs* 0·45%/year; 177 *vs* 277 cases, 2p<0·00001), and no other cancer incidence rates are significantly affected. Overall, therefore, the incidence of second cancers is non-significantly lower with longer tamoxifen treatment.

About 5 versus 1–2 years of tamoxifen—The trials of tamoxifen versus no tamoxifen in figure 7 provide indirect evidence that 5 years is substantially more effective than only 1–2 years of tamoxifen. Most of the information in figure 11 relates to this particular comparison, providing directly randomised confirmation that about 5 years of treatment is better than 1–2 years (recurrence rate ratio 0·82 [SE 0·03], 2p<0·00001; breast cancer death rate ratio 0·91 [0·04], 2p=0·01).

These results can be subdivided by time since those allocated to stop tamoxifen should have done so (webappendix 1 [annex-figure 11]), finding only a little effect on recurrence, and none on breast cancer mortality, during the first 2 years after randomisation (years 0–1). This may be because of some carryover of the effects of the previous year or two of tamoxifen, before randomisation. Both for recurrence and mortality, the main protective effect of the extra few years of treatment is seen during years 2–4 and 5–9 (with, as yet, little information on years ⩾10). The

significant reductions during years 5–9 both in recurrence rates (ratio 0·79 [SE 0·06]) and in breast cancer mortality rates (ratio 0·83 [0·06]) again represent a carryover benefit, since the few extra years of tamoxifen treatment after randomisation would have ended some time before this period began.

In these trials of about 5 versus 1–2 years of tamoxifen (webappendix 1 [annex-figure 11]), there is little overall effect of longer treatment on non-breast-cancer mortality (0·97 *vs* 0·96%/year, death rate ratio 1·01 [SE 0·07]), or in the numbers of deaths attributed to uterine cancer (8 *vs* 10), stroke (26 *vs* 28), thromboembolism (5 *vs* 3), other vascular causes (74 *vs* 79), or other causes (0·72 *vs* 0·69%/year, death rate ratio 1·04 [SE 0·08]). Hence, the difference in overall survival is also significant.

About 10 versus 5 years of tamoxifen—As of the year 2000, there were only a few hundred recurrences in the trials of about 10 versus 5 years of tamoxifen, so although longer treatment appears to involve slightly lower recurrence and breast cancer mortality rates the findings are not yet reliably informative. A clinical alert for the use of tamoxifen in node-negative disease was issued in the USA in 1996[19] (suggesting that for women with node-negative, ER-positive disease, continuation of adjuvant tamoxifen beyond 5 years was appropriate only in trials), and figure 11 is subdivided by nodal status. The apparently unfavourable results for women with node-negative disease are, however, not significantly different from the apparently favourable results for women with node-positive disease.

In these trials of about 10 versus 5 years of tamoxifen, non-breast-cancer mortality appears to be somewhat greater among those allocated longer treatment, but the difference is not clearly significant either overall (1·2 *vs* 0·9%/year, death rate ratio 1·31 [SE 0·16], 2p=0·06) or in the numbers of deaths attributed to uterine cancer (4 *vs* 4, 2p=1·0), stroke (20 *vs* 13, 2p=0·2), thromboembolism (5 *vs* 0, 2p=0·06), other vascular causes (32 *vs* 26, 2p=0·4), or other causes (0·6 *vs* 0·5%/year, death rate ratio 1·22 [SE 0·20], 2p=0·3).

Both for recurrence and, particularly, for mortality, much larger numbers of events will have to accrue in the trials of 10 versus 5 years of tamoxifen before statistically reliable evidence emerges.

Combination of direct and indirect evidence to estimate the effects in ER-positive disease of 5 years of tamoxifen on breast cancer mortality

Among women with ER-positive disease, the directly randomised comparison of about 5 years of tamoxifen versus no adjuvant tamoxifen in figure 7 indicates a breast cancer death rate ratio of 0·66 (SE 0·04). A similar conclusion can be obtained indirectly, by combining the results for 1–2 years of tamoxifen versus no tamoxifen in figure 7 with those for 5 versus 1–2 years of tamoxifen in webappendix 1 (annex-figure 9). This suggests that in ER-positive disease, 5 years of tamoxifen would produce a breast cancer death rate ratio of 0·74 (SE 0·05 [0·82×0·90]).

The direct estimate of 0·66 and the indirect estimate of 0·74 are both readily compatible with a breast cancer death rate ratio of about 0·7, and the inverse-variance-weighted average of them is 0·69 (SE 0·03). (If the direct estimate had been 0·62 [SE 0·06], as in the trials of exactly 5 years of tamoxifen, the weighted average would still have been 0·69, but with SE 0·04.)

Ovarian ablation or suppression

Almost 8000 women younger than 50 years of age with ER-positive or ER-unknown disease have been randomised into trials of ovarian ablation by surgery or irradiation (4317 women, 63% ER-untested, mean follow-up 8 woman-years) or of ovarian suppression by some years of treatment with a luteinising-hormone-releasing-hormone inhibitor (LHRHI; 3408 women, 26% ER-untested, mean follow-up 5 years; figure 12).

Overall, there is a definite effect of ovarian ablation or suppression both on recurrence ($2p<0·00001$) and on breast cancer mortality (2p=0·004), but it is not as extreme as it seemed to be in earlier meta-analyses of these trials, when ovarian ablation was not generally being tested against a background of effective systemic therapy.[7]

The absolute effects on 15-year outcome are shown in figure 13. For recurrence, the main divergence between treatment and control appears to take place during just the first few years, but with no indication of any loss of this early gain in later years. This early difference in recurrence seems to correspond to a somewhat later difference in mortality, although the numbers of events in later years are too small for such apparent patterns in the results to be reliable. Nevertheless, for breast cancer mortality there appears to be little difference between treatment and control during the first few years, but a moderate difference at 10 years and (as for recurrence) there is no indication that any benefits that accrue during the first decade of follow-up are lost during the second decade.

Because these women were all younger than 50 years of age when randomised, there have, as yet, been relatively few deaths attributed to causes other than breast cancer, and these other deaths do not appear to be increased by treatment during either the first or the second decade (webappendix 1 [annex-figure 13]; death rate ratio 0·94 [SE 0·18], 2p=0·7).

Addition of ovarian treatment to other treatments—There is no indication that the effects of ovarian ablation differ from those of ovarian suppression, or that the risk reductions for women younger than 40 years of age at entry differ from those for women of age 40–49 (figure 12). But, in

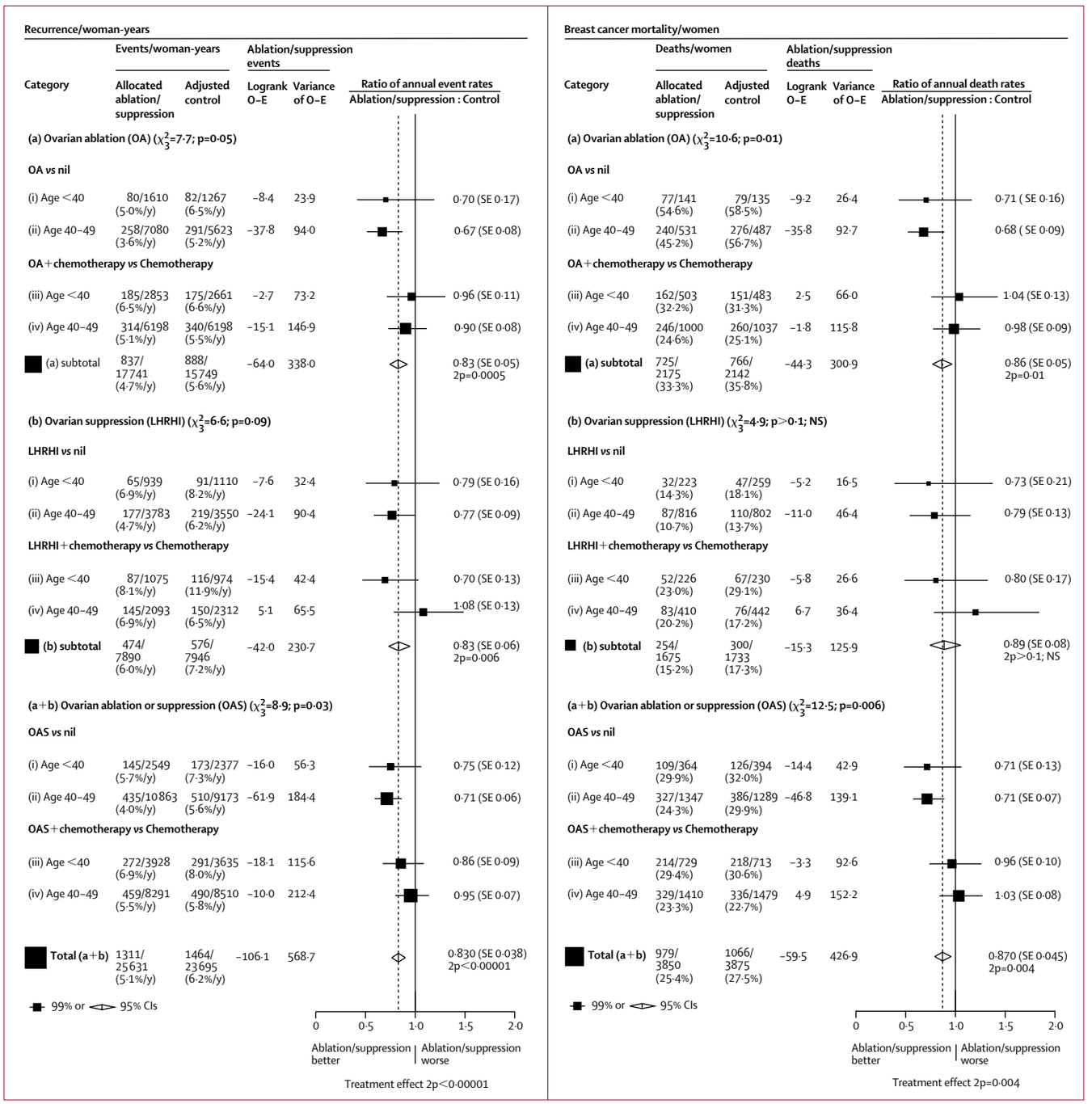


Figure 12: **Ovarian ablation or suppression versus not in ER-positive (or ER-unknown) disease, by treatment type and 10-year entry age-groups (<40 or 40–49 years only): event rate ratios**

both age ranges the effects of ovarian treatment appear to be smaller in the trials where both groups got chemotherapy than in the trials where neither did. This could be because concurrent hormonal treatment interferes with the cytotoxic effects of chemotherapy or because chemotherapy can permanently reduce ovarian activity, limiting the benefits that other ovarian treatments can offer.

When, however, such weak overall results are divided both by age and by chemotherapy into four subgroups the CIs for some of the subgroup results (and, in particular, for comparisons between different subgroup

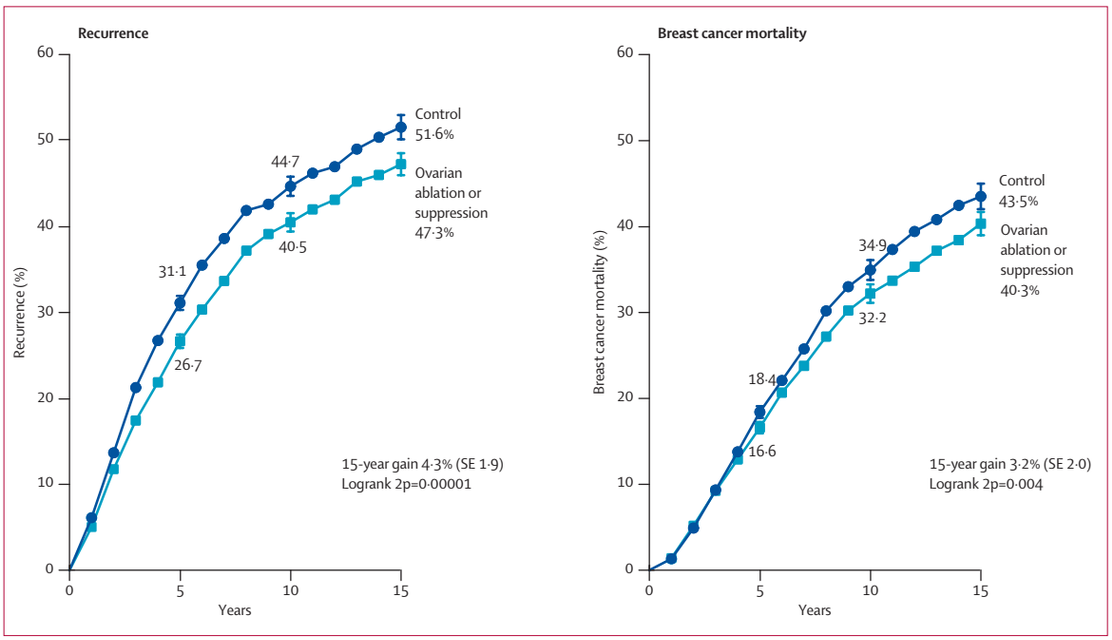


***Figure 13*: Ovarian ablation or suppression versus not in ER-positive (or ER-unknown) disease: 15-year probabilities of recurrence and of breast cancer mortality**
7601 women, all with entry age <50 years: 47% ER-unknown, 61% node-positive. Error bars are ±1SE.

results) are wide. So, any real heterogeneity in the efficacy of ovarian treatment between these four subgroups may be appreciably less, or more, extreme than figure 12 suggests.

Discussion

15-year survival

The present analyses of systemic adjuvant treatment for early breast cancer involve a total of almost 150 000 women in 200 randomised trials, many with long-term follow-up. This collaboration, which could at first assess only short-term survival differences, has now continued for 20 years, providing increasingly reliable evidence about the 15-year risks and benefits of various treatments that were being tested in the 1980s (eg, about 6 months of treatment with anthracycline-based combinations such as FAC or FEC, or about 5 years of tamoxifen-based hormonal therapy).

Such regimens have been used widely, and were recommended in 2001 by a US National Institute of Health consensus development conference,[13] although other regimens are now gaining favour. At least in terms of breast cancer mortality, however, even these older adjuvant regimens involve substantial long-term benefits for some types of patient, and in combination they can approximately halve the annual breast cancer death rate among middle-aged women with ER-positive disease (see below).

The effects of these adjuvant treatments on breast cancer mortality are generally remarkably persistent, with some gain during years 0–4 and then additional gains during years 5–9 and 10–14. Indeed, for each of the main comparisons studied (polychemotherapy *vs* no chemotherapy, one type of chemotherapy *vs* another, 5 years of tamoxifen *vs* no tamoxifen) there is no significant trend between years 0–4, 5–9, and 10–14 in the ratio (treatment *vs* control) of the annual death rates from breast cancer (figures 4, 6, and 9). Hence, as the 15-year probability of death from breast cancer is generally more than twice the 5-year probability, at least in women with ER-positive disease, the absolute gain produced by treatment is generally at least twice as great for 15-year as for 5-year survival.

The approximate constancy of the breast cancer death rate ratio facilitates the assessment of what a combination of different treatments (eg, chemo-endocrine therapy) is likely to achieve, since the death rate ratios for chemotherapy and for the addition of hormonal therapy to chemotherapy can simply be multiplied together, irrespective of any differences in follow-up duration.

By contrast, combination of recurrence reductions in different trials (or comparisons between proportional recurrence reductions in newer and in older trials) should be period-specific. For, even if the early recurrence reductions from a particular type of treatment will never be lost, the proportional recurrence reductions may well be greater in the first few years than in later years (figures 4, 6, and 9). If so, the overall proportional reduction in recurrence will tend to be systematically greater in the early results from new trials than it will be when those same trials mature.

Generalisability of proportional reductions in breast cancer mortality

Trials involve a non-representative sample of countries, and generally include a non-representative sample of hospitals within those countries and of patients within those hospitals. Moreover, women in these long-term trials were all diagnosed in previous decades, making them systematically different from present or future patients (eg, in the proportions detected by screening, having mastectomy, having axillary dissection, investigated by immunohistochemistry, monitored by various new technologies, etc) in ways that may substantially change the stage-specific prognosis.

The absolute risk reductions now achievable by such treatments may therefore not be the same as in these trials, especially among any future patients who are known to be at very low risk (eg, those with small, well-circumscribed, screen-detected tumours of low histological grade) or at unusually high risk. But, the proportional risk reductions may well be similar. For, in the trials, the proportional reductions in recurrence and in breast cancer mortality did not seem to depend strongly on any factors other than age for chemotherapy and ER status for endocrine therapy (figures 4, 6 and 9; see also the corresponding annex-figures in webappendix 1). In particular, the response to tamoxifen appears to depend strongly on ER status, but not on PR status (at least as measured in these trials). Hence, these proportional risk reductions offer a reasonable way of generalising previous trial results to future patients (of given age and ER status) in different populations.

Even then, however, some approximate allowance should be made for the extent to which non-compliance with the allocated treatments systematically weakens the trial results, and for any improvements over time in stage-specific prognosis, and in the way nominally similar chemotherapy regimens are actually given. For example, there could well be ways of giving CMF-based or anthracycline-based regimens that are more effective than was the case, on average, in these trials.[20]

Absolute risks in untreated patients, by ER status and nodal status

Translation of the proportional risk reductions (or, more precisely, breast cancer death rate ratios) produced by chemotherapy, hormonal therapy, or both into absolute 15-year gains depends on having some estimate of the 15-year breast cancer mortality risks without either type of treatment. In the trials of polychemotherapy in the absence of tamoxifen (figure 4) or of tamoxifen (of any duration; figure 7) in the absence of chemotherapy, the 5-year, 10-year, and 15-year breast cancer mortality among the controls shows how the prognosis without either treatment used to depend on ER and nodal status.

With 74 000 years of follow-up among untreated women with breast cancer of known ER and nodal status in these trials (36 000 in ER-positive node-negative, 16 000 in ER-positive node-positive, 17 000 in ER-poor node-negative, and 5000 in ER-poor node-positive disease), the breast cancer mortality at 5, 10, and 15 years, respectively, is 7%, 20%, and 31% in ER-positive node-negative disease, and 23%, 51%, and 63% in ER-positive node-positive disease. Among untreated women of the same nodal status, the breast cancer death rate is about twice as great in ER-poor as in ER-positive disease during just the first 5 or 6 years, but it is substantially lower in ER-poor than in ER-positive disease over the next 10 years, so the 15-year breast cancer mortality of untreated women is largely independent of ER status (and of age; webappendix 1 [appendix to table 4]).

The women in both types of trial were, however, randomised many years ago. Trends since then towards earlier diagnosis, more sensitive tests of nodal or distant spread, and better control of any recurrent disease could well mean that, even without any adjuvant chemotherapy or endocrine therapy, current and future patients would have somewhat lower stage-specific 15-year risks (eg, about 25% and 50% for node-negative and node-positive disease). Indeed, for many women with small, screen-detected node-negative tumours the 15-year risks from untreated disease would probably be much less than 25%. Table 4 estimates the absolute risk reductions separately for women whose 15-year breast cancer mortality without such treatment would be 12·5%, 25%, and 50%. The results are subdivided by ER status and age.

Proportional and absolute breast cancer mortality reduction by ER status, age, and underlying risk

Chemotherapy only in ER-poor or ER-positive disease

On average, the anthracycline-based regimens tested in these trials produced breast cancer death rate ratios of about 0·62 and 0·80, respectively (ie, proportional mortality reductions of 38% [SE 5] and 20% [4]), in women younger than 50 and in those 50–69 years of age.

These proportional reductions are approximately independent of ER status. (For example, among women 50–69 years of age, the best estimates of the breast cancer death rate ratios produced by the anthracycline-based regimens tested in these trials are 0·80 [SE 0·04] for all women, including those with unknown ER status, and 0·76 [0·06] and 0·81 [0·05], respectively, for women with ER-poor and ER-positive disease.) The upper part of table 4 shows, for these proportional reductions, how their absolute effects on 15-year breast cancer mortality (in the absence of other causes of death) depend on the underlying risks without treatment.

The most extensively tested such regimens involved FAC or FEC, generally given for about 6 months, and the corresponding results from them (proportional mortality reductions of 44% [SE 10] and 24% [6]) were statistically definite in both age-ranges, and appeared about as promising as the overall average.

Chemotherapy, 70 years of age or older

These trials of chemotherapy involved too few women older than 70 years of age to be reliably informative (even if ER status is ignored) as to whether it confers any net survival benefit among them.

Endocrine therapy in ER-positive disease

For women of any age with ER-positive disease, 5 years of tamoxifen multiplies the breast cancer death rate by about 0·69 (ie, produces a proportional reduction of 31% [SE 3]). The lower part of table 4 first shows the absolute effects of this on breast cancer mortality, in the absence of other causes of death. Particularly among older women (≥70 years), however, these potential gains in long-term survival may be substantially curtailed by limitations on normal life expectancy that are due to the other causes of death in old age, unrelated to breast cancer or its treatment (see Non-breast cancer mortality, below).

Chemoendocrine therapy in ER-positive disease

In the particular case of middle-aged women with ER-positive disease, the anthracycline-based regimens studied in these trials reduce the annual breast cancer death rate by about 38% for women younger than 50 years of age and by about 20% for those of age 50–69 years. This remains approximately true even if hormonal therapy is to be given, and 5 years of tamoxifen can further reduce the annual breast cancer death rate by about 31%, even if chemotherapy has already been given. A further 31% reduction in the death rate ratios of about 0·62 or 0·80 that remain after chemotherapy would produce death rate ratios of about 0·43 or 0·55, indicating that a chemoendocrine combination of such treatments (perhaps given consecutively[14]) would approximately halve the average annual death rate from breast cancer during the first 15 years after diagnosis.

Exact multiplicativity would imply a 57% reduction for women younger than 50 years of age and a 45% reduction for those of age 50–69 years, but such apparent precision may be excessive. Even approximate multiplicativity of the death rate ratios produced by these treatments (figures 4 and 9) can, however, help provide reasonable estimates of the absolute extra benefit from adding such endocrine therapy to chemotherapy, or of adding such chemotherapy to endocrine therapy (lower part of table 4).

Since chemotherapy and tamoxifen are effective in postmenopausal women, they should also be effective after ovarian ablation or suppression. The converse, however, is not clearly shown by these trials (figure 12), perhaps because they lacked measurements of ER status or of residual ovarian function after chemotherapy. Although, for women younger than 50 years of age, ovarian ablation or suppression is of definite value in the absence of other systemic treatments, there is no direct evidence in figure 12 that it would add much to the effects of chemotherapy plus tamoxifen (or some other ER modulator).

Systemic adjuvant treatment and age at diagnosis (years)	Proportional effect on annual breast cancer mortality rate (treatment *vs* control)		15-year breast cancer mortality with treatment (risk [%] and absolute gain) versus corresponding risk without treatment (M)					
	Ratio of rates (R)	Proportional reduction	M=12·5 (eg, low-risk node-negative)		M=25 (eg, node-negative)		M=50 (eg, node-positive)	
			Risk	Gain	Risk	Gain	Risk	Gain
Chemotherapy only in ER-poor or ER-positive disease*								
None (any age)	1·0	..	12·5	..	25·0	..	50·0	..
Anthracycline (age <50 years)	0·62	38%	7·9	4·6	16·3	8·7	34·9	15·1
Anthracycline (50–69 years)	0·80	20%	10·1	2·4	20·6	4·4	42·6	7·4
Anthracycline (≥70 years)	?	?	?	?	?	?	?	?
Endocrine, or chemoendocrine, therapy in ER-positive disease*								
None (any age)	1·0	..	12·5	..	25·0	..	50·0	..
Tamoxifen (any age)	0·69	31%	8·8	3·7	18·0	7·0	38·0	12·0
Anthracycline+tamoxifen (age <50 years)	0·62×0·69	57%	5·6	6·9	11·6	13·4	25·7	24·3
Anthracycline+tamoxifen (50–69 years)	0·80×0·69	45%	7·1	5·4	14·7	10·3	31·8	18·2
Anthracycline+tamoxifen (≥70 years)	?×0·69	?	?	?	?	?	?	?

Anthracycline: about 6 months of anthracycline-based adjuvant chemotherapy with regimens such as FAC or FEC, as in the reviewed trials. Tamoxifen: about 5 years of adjuvant tamoxifen. The 15-year survival probability with treatment is calculated as (1–M/100) to the power R. The webappendix 1 (appendix to table 4) gives the 15-year prognosis of untreated control patients, subdivided by ER and nodal status. *For women of given nodal status the 5-year mortality is greater for ER-poor than for ER-positive disease, but the 15-year risks may be similar, as may the 15-year benefits of anthracycline-based chemotherapy (since the age-specific breast cancer mortality ratios for anthracycline-based *vs* no chemotherapy do not depend significantly on ER status). Combination of the direct and indirect randomised evidence yields breast cancer death rate ratios (treatment *vs* control) of 0·62 (SE 0·05) at younger than 50 years and 0·80 (SE 0·04) at age 50–69 years for allocation to anthracycline and 0·69 (SE 0·03) for allocation to tamoxifen. (Allowance for any inappropriate non-compliance with the treatment allocations in these trials would, in expectation, further reduce breast cancer mortality.)

Table 4: **Estimated effects of 6 months of anthracycline-based chemotherapy, 5 years of tamoxifen, or both on 15-year breast cancer mortality (%), in the absence of other causes of death: relevance of ER status, age, and underlying risk (10–15%, 25%, or 50%)**

Non-breast-cancer mortality

The trials of anthracycline-based chemotherapy versus no chemotherapy or versus CMF-based chemotherapy involved a non-significant excess mortality of about 0·2% from heart disease, leukaemia, or lymphoma during an average of 6 years of follow-up (table 2). The trials of 5 years of tamoxifen involved no net excess incidence of second cancers, but an excess mortality of about 0·2% from uterine cancer or pulmonary embolus during an average of 8 years of follow-up, and a non-significant increase in stroke deaths that was outweighed by a non-significant reduction in cardiac deaths (table 3).

Other non-breast-cancer mortality is largely or wholly unaffected by these treatments, but somewhat modifies the net long-term benefit of systemic adjuvant treatment (especially for tamoxifen in old age) by reducing, by a similar factor, the proportion of long-term survivors in both groups. Thus far, therefore (chiefly in just the first decade or so of follow-up), any fatal side-effects of these adjuvant treatments among women younger than 70 years of age appear, on average, to involve net mortality differences of at most a few per 1000 per decade, which are a small fraction of the absolute reductions in breast cancer mortality.

20-year survival

At least for middle-aged patients, a perspective of 20 or more years may often be appropriate in considering

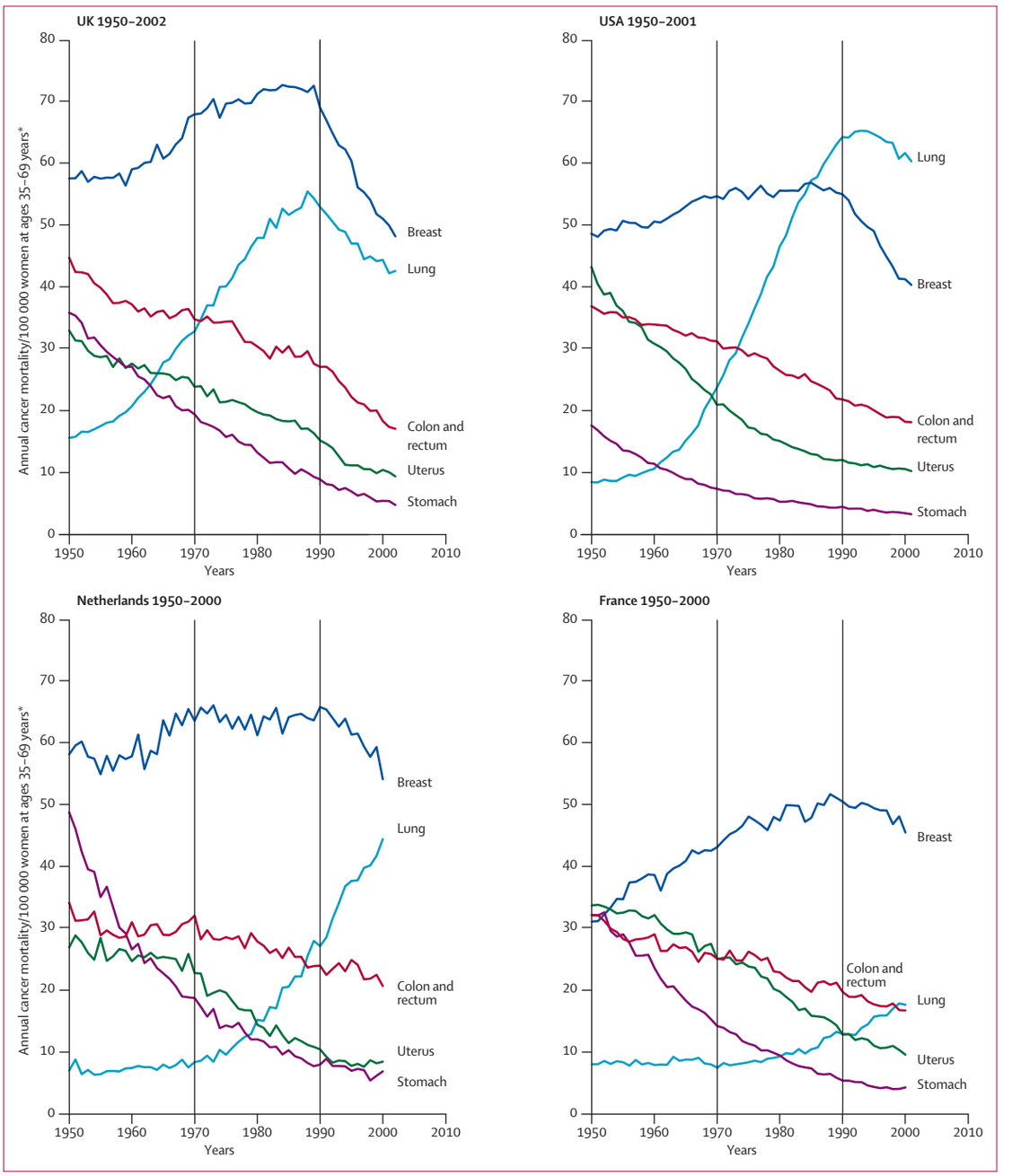


Figure 14: **Trends since 1950 in age-standardised (35–69 years) death rates,* comparing breast and selected other types of cancer, among women in the UK, the USA, Netherlands, and France**

*The age-standardised rate is the mean of the seven separate rates in the 5-year age ranges 35–39 up to 65–69. Data from WHO statistics on deaths and UN population estimates.

treatment options, because life expectancy without breast cancer could be long and treatment could affect cause-specific mortality not only in the first decade but also in the second decade after diagnosis. This indicates a need for the investigators of older trials (and, eventually, of current trials) to make suitable arrangements for at least 20-year follow-up of recurrence and cause-specific mortality, and for appropriate worldwide pooling of these 20-year results. For, some of the questions that these trials addressed (eg, active *vs* no adjuvant treatment) may never be revisited in future trials.

A long-term perspective may also help resolve some more general questions in early breast cancer, such as how differences in local control or chemotherapy soon after diagnosis would affect long-term outcome, and how 5 or 10 years of hormonal treatment would affect cause-specific mortality in both the first and the second decade after diagnosis.

Even if older adjuvant regimens such as about 6 months of FAC or FEC and about 5 years of tamoxifen, as recommended by a US National Institute of Health consensus development conference published in 2001,[13] can approximately halve the annual death rate from ER-positive breast cancer, significant risks of recurrence and death remain, especially if both the first and the second decade of follow-up are considered. Extrapolation of the 15-year results for the untreated women in the tamoxifen trials suggests that even if they had received a treatment that persistently halved their annual breast cancer mortality rate, at least a sixth of those with node-negative disease and a third of those with node-positive disease would still eventually die from breast cancer during the first, second, or third decade after diagnosis (in the absence of other causes of death during those decades).

Thus, there is ample room for better drugs (eg, newer hormonal treatments, newer treatments for particular subtypes of breast cancer, newer chemotherapeutic agents, etc) to demonstrate their value. There is also ample room for better use of existing drugs:[20] different combinations, or doses, or sequencing could well produce moderate but worthwhile additional benefits, and the appropriate duration of treatment with current chemotherapeutic and hormonal regimens remains uncertain, especially among patients at substantial risk of late recurrence.

Trends in national mortality rates

The demonstration over the past few decades of various ways of producing moderate improvements in short-term outcome (and now in long-term outcome) by adjuvant treatment of early breast cancer has been accompanied by corresponding changes in medical practice.[13] In the USA, for example, adjuvant treatment of node-negative breast cancer was uncommon in 1987, but it increased suddenly during 1988–91, and was in general use by 1992.[21] The present meta-analyses show that such changes must have contributed substantially to the recent decrease in national breast cancer mortality rates that began in the USA and several other countries during the 1990s, and is still continuing. Figure 14 illustrates this for the UK, the USA, Netherlands, and France, and webappendix 1 (annex-figure 14) gives similar illustrations for the 15 countries with a female population of more than 4 million for which the WHO provides data on long-term trends in mortality from breast cancer and other major neoplastic diseases (including lung cancer). In general, the trends in breast cancer mortality were more favourable in the 1990s than in previous decades (although in several countries this change in the breast cancer mortality trends was being offset by a continuing rise in female lung cancer mortality).

Because most of the improvement in 15-year breast cancer mortality produced by adjuvant chemotherapy and hormonal therapy (and by adjuvant radiotherapy[10]) occurs after the first 5 years, there may be a delay of a decade or so between any widespread changes in practice and the main effects that these will eventually have on national breast cancer mortality rates. Thus, for example, earlier diagnosis (partly because of screening), wider use of appropriate treatments, or both, during the 1980s, contributed substantially to the sudden decreases of 25–30% in the US and UK breast cancer mortality rates in middle age that took place during the 1990s[22] (despite rising incidence rates) and to the reductions that are now becoming apparent in several other countries (despite, in some cases, rising incidence rates and previously rising death rates).

Further moderate improvements during the 1990s involving better local disease control (partly because of more careful and more extensive screening) and better use of systemic treatments both for early and for advanced disease should in aggregate help these decreases in national mortality rates to continue throughout the present decade. Hence, accumulation of the effects of several small or moderate improvements in diagnosis and treatment over the past few decades may well mean that by 2010 the national breast cancer death rates in middle age will, in many countries, be only about half of what they would otherwise have been.

Contributors

The EBCTCG secretariat (M Clarke, R Collins, S Darby, C Davies, V Evans, J Godwin, R Gray, P McGale, R Peto, and Y Wang) accept full responsibility for the overall content of this report. C Davies and J Godwin accept responsibility for planning and editing the study website.

Conflict of interest statement

We declare that we have no conflict of interest.

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