Chemotherapy and hormonal therapy for early breast cancer:

Effects on recurrence and 15-year survival in an overview of the randomised trials

Early breast cancer trialists' collaborative group (EBCTCG)
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Text, 4 Tables, 14 Figures and website

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Abstract

Background — Quinquennial overviews (1985-2000) of the randomised trials in early breast cancer have assessed the 5, 10 and now 15-year effects of various systemic adjuvant therapies.

Methods — Collaborative meta-analyses of 145 000 women in 194 unconfounded trials of adjuvant chemotherapy or hormonal therapy that began by 1995. Many involved CMF (cyclophosphamide, methotrexate, fluorouracil), anthracyclines (A or E, adriamycin or epirubicin, in various drug combinations such as FAC or FEC), tamoxifen or ovarian suppression: none involved taxanes, herceptin or aromatase inhibitors.

Results — At ages <50 and 50-69, 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 0.05 and 20% SE 0.04 respectively,(with standard error 5) for those aged <50 and by about 20% (SE 4) for those aged 50-69 when diagnosed, largely irrespective of the use of tamoxifen, and of estrogen receptor (ER) status, nodal status or other tumour characteristics. Such regimens other characteristics, or use of tamoxifen. Such regimens (eg, CAF or CEF) are significantly more effective than CMF chemotherapy. Few women aged 70+ entered chemotherapy trials.

For ER+ disease only, aAllocation to about 5 years of adjuvant tamoxifen reduces the annual breast cancer death rate by 31% (SE 0.03) (but only in women with ER+ disease), , largely irrespective of the use of chemotherapy, and of age (<50, 50-69, 70+), progesterone receptor statuss , other characteristics or use of chemotherapyor other tumour characteristics. Five years is significantly ($p<0.01$) more effective than just 1-2 years of tamoxifen. For ER+ disease tumours the annual breast cancer mortality rates during years 0-4 and 5-14 are similar, as are the proportional reductions in them by 5 years of tamoxifen, so the cumulative gain in survivalreduction in mortality is more than twice as big at 15 as at 5 years.

These results combine 6 meta-analyses: anthracycline-based vs no chemotherapy (8000 women); CMF-based vs no chemotherapy (14 000); anthracycline vs CMF-based chemotherapy (14 000); ~5 years tamoxifen vs none (15 000); ~1-2 years tamoxifen vs none (33 000); and ~5 vs 1-2 years tamoxifen (18 000). Allocation to ovarian ablation or suppression (8000 women aged <50) also significantly reduces breast cancer mortality, but, apparently, only in the absence of other systemic treatments.

For women aged <70 with ER+ 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% and 20% from chemotherapy at ages <50 and 50-69 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 (before any allowance for trial results being weakened by non-compliance). Overall survival would be comparably improved, as these treatments have relatively small side-effects on mortality from the aggregate of all other causes.

Conclusion — Adjuvant treatments that were being tested in the 1980s, which substantially reduce 5-year recurrence rates, also substantially reduce 15-year overall 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 loco-regional 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 each individual patient in each 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 (in 1985, 1990, 1995, 2000 etc[2-9]) of centrally collected data from each 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 chemo-endocrine therapy) that had begun in or before 1995. The corresponding meta-analyses of the trials of local treatments (surgery and/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[7-9] comparing the effects on 10-year survival of different adjuvant regimens (eg, anthracycline-based versus CMF [cyclophosphamide, methotrexate, fluorouracil]-based chemotherapy regimens; longer versus shorter tamoxifen regimens; ovarian ablation or suppression in addition to chemotherapy versus chemotherapy alone).

From the older trials of adjuvant treatment versus not, where the 10-year survival differences were already definite, 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. Information was sought from all randomised trials that had started by 1995. This report describes all the trials of more than one month[8] 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; (d) longer versus shorter polychemotherapy; (e) tamoxifen versus no adjuvant tamoxifen; (f) longer versus shorter tamoxifen; or (g) ovarian ablation or suppression (in women aged <50) versus no adjuvant ovarian treatment. Throughout, chemotherapy means cytotoxic chemotherapy (CTX).

Data on each individual patient — As before,[3-5] information was sought for each woman in each 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 loco-regional lymph nodes (N+ or N-) and on the results of any oestrogen receptor or progesterone receptor (ER or PR) measurements. If measured, the receptor status of the primary tumour was described as positive (ER+ or PR+) if there was ≥10 fmol 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 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 and circulated to the members of the EBCTCG for comment.

Averaging treatment effects by meta-analyses — When several different trials have all addressed a similar question (eg, comparing the effects of polychemotherapy versus 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, as the types of patient might differ 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 several such trials has been to analyse the event rates in each 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 suffered the relevant event) and its variance.[10] 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 statistical 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[3] that (O-E)/V provides an appropriately weighted average of the log of R, the ratio (treatment versus control) of the annual rates of whatever category of events (eg, recurrence, mortality etc) is being analysed: see Calculations, below.

Interpretation of weighted averages of effects in different trials — If the event rate ratios (treatment versus 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.[3,10] 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 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[7]) 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[8]). 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 those allocated one treatment versus all those allocated the other, irrespective of compliance. Hence, their results may well slightly under-estimate the effects on the event rate ratio that stricter compliance could have achieved.[11]

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 as well as 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 prior to a breast-cancer-attributed death, it was assumed that a distant recurrence had just preceded it (13% of all deaths, as mortality may be monitored for longer than recurrence is).

As causes are not reliably available for many of the 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, "ipsilateral local recurrence" is any 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,[10] 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 each year of follow-up.[3] Non-breast-cancer mortality is analysed by similar methods, but with 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 each separate year of follow-up.

As breast cancer mortality plus other mortality equals all-cause mortality, the breast cancer mortality rate in each treatment group in each separate year since randomisation can then 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 unbiasedly the effects of treatment just on breast cancer mortality.[9]

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% versus 50%) for women with node-positive disease and of 5% (about 20% versus 25%) 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.)

Formulae relating death rate ratios to risks of death — It may be that R, the ratio of the annual death rates (treatment versus control), is about the same in the early and in the 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] 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, yielding 40% vs 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 suffer 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 logrank variances for the effects of treatment on recurrence rates.) It can also be shown that O-E is usually about minus half 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 used instead to calculate R, the event rate ratio.[3,4] 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, the confidence limits for exp(b), the event rate ratio itself, are exp($b \pm 1{\cdot}96s$). The standard error (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, N- and N+) 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). 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 chi-squared test (on n-1 degrees of freedom) for heterogeneity between the treatment effects in different strata can be obtained by subtracting $(O-E)^2/V$ from the sum of the separate values, one per stratum, of $(o-e)^2/v$.

Alternatively, a chi-squared test for trend (ie, for whether the treatment effect changes progressively from one stratum to the next) can be obtained as follows: if stratum number 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 chi-squared test (on 1 degree of freedom) for trend is $T^2/\text{var}(T)$. 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 confidence intervals, standard errors 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 2-sided (and, for consistency with previous reports,[2-9] 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 3-way trials with two active treatment groups, the controls are counted twice in the "adjusted control" totals: other calculations are not affected.

Website (http://www.ctsu.ox.ac.uk/~ebctcg/) — For each numbered figure there is a correspondingly numbered (1 to 14) website Annex-figure that provides extensive additional analyses. Likewise, for each numbered table there is a correspondingly numbered (1 to 4) website Appendix. The first three give details of each 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 final one gives the 15-year prognosis of untreated control patients, by ER and nodal status.

FORMAT OF FIGURES: OUTCOMES SELECTED FOR EMPHASIS

Figures (eg, figure 1) that illustrate the ratios, treatment versus 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. The illustrations of recurrence rate ratios are accompanied by tabulations of the corresponding numbers, treatment and control, of women who suffered 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 % of all women originally randomised (irrespective of follow-up duration and of how many suffered recurrence). As most women in these trials have been followed 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 on the website.

Figures that give results in other formats (eg, figures 2 and 3) illustrate either 15-year probabilities of recurrence (left) and 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 on the 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 in all figures that illustrate subgroup-specific proportional risk reductions).

Results

Availability of data — 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 the women, mainly in trials that were still randomising patients in the late 1990s. Hence, most 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. No trial with outcome data available involved newer classes of drug such as taxanes, HER-2 inhibitors, aromatase inhibitors or selective oestrogen receptor modulators (SERMs) that are more specific than tamoxifen. The website Appendix to table 1 gives the drugs in each trial.

Chemotherapy

Single-agent chemotherapy or polychemotherapy vs no adjuvant chemotherapy

Drugs tested — There were only 4000 women in the trials of single-agent chemotherapy, as against 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 chemotherapy (C, M, F: cyclophosphamide, methotrexate, 5-fluorouracil) or about 6 months of anthracycline-based regimens such as CAF or CEF (A, E: adriamycin, epirubicin), although some regimens involved other agents (eg, V, Mel: 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 of the rest was from trials of 6 or 12 months of older agents (C, Mel or F).

Age-specific results — Figure 1 summarises the proportional risk reductions from single-agent chemotherapy and from polychemotherapy in the trials that compared more than one month of such treatment versus no adjuvant chemotherapy. The data have been subdivided into 10-year bands of age at entry, starting at <40 and going up to 70+ years of age, because of the previously established relevance of age at diagnosis. Few women aged over 70, and very few aged over 80, were randomised into these chemotherapy trials. (Finer age divisions, with 5-year age groups from <30, 30-35 to 70+, are available in website 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: website Annex-figure 1). Taking all ages together, for single-agent chemotherapy the ratios, treatment versus control, of the annual event rates are 0·86 (standard error 0·04, logrank 2p=0·001) for recurrence and 0·96 (SE 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 effect of the

single-agent regimens in these trials was significantly less favourable than that of the polychemotherapy regimens (foot of figure 1). Because of this apparently greater overall effect for polychemotherapy and the more widespread use nowadays[12] of polychemotherapy regimens than of the main types of single-agent chemotherapy regimen that were tested in these trials (most of which began many years ago), subsequent chemotherapy analyses concentrate only on the trials of polychemotherapy. Owing to the paucity of data on women aged 70 or over, these subsequent analyses are restricted to women aged under 50 ("younger") or 50-69 ("older") when randomised.

Polychemotherapy vs 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 (each $2p<0{\cdot}00001$), 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 suffered 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) versus a policy of treating patients only when recurrence is detected, and indicate 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 five years after randomisation, and figure 3 subdivides these effects 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, while 70% of the older women did so.) Although the absolute 5-year gains for women with N- disease appear to be smaller than those for women with N+ disease, they are not significantly smaller, even among younger women, perhaps reflecting the statistical instability of subgroup analyses in general (whether based on absolute 5-year gains as in figure 3, on absolute 10-year gains as in website Annex-figure 3, or on proportional risk reductions over all follow-up periods, as in figure 4 below).

Selected subgroups — Figure 4 describes the proportional risk reductions produced in various different circumstances, and website Annex-figure 4 gives further such subgroup analyses. The event rate ratios, treatment versus control, are given 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.

Results are given separately for younger women (first half of figure 4) and for older women. 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 (figure 4a) — About half of the available evidence is from trials of CMF-based regimens, and about one 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 cytotoxics other than C, M and F (the remainder involving C, M, F and V). In the anthracycline-based trials the mean duration was 6 months, and the anthracycline used was always adriamycin or epirubicin (66%A, 34%E).

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. 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- versus CMF-based regimens that are presented below).

Presence or absence of tamoxifen (figure 4b) — Some trials were of chemotherapy given with tamoxifen (concurrent chemo-endocrine treatment) versus tamoxifen alone, some were of chemotherapy followed by tamoxifen (sequential chemo-endocrine 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.

Nearly all of the evidence on sequential chemo-endocrine therapy involved older women, among whom it appeared somewhat more effective than concurrent chemo-endocrine treatment, but this comparison is indirect and the difference is not significant. No large, directly randomised comparisons of concurrent versus sequential chemo-endocrine therapy are available in the present data set, although an Intergroup study favouring sequential therapy has recently been published elsewhere.[13]

ER status and tamoxifen (figures 4c and 5) — In ER-poor disease, the trials of tamoxifen versus not (see below) show that tamoxifen has little effect on recurrence or breast cancer mortality. 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). 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 SE 0·05 for older women (both $2p<0·00001$); breast cancer death rate ratios 0·68 SE 0·08 for younger and 0·81 SE 0·05 for older women ($2p=0·0002$ and $2p=0·0004$ 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 (website Annex-figure 4).

In ER+ disease tamoxifen is highly effective,[7] 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+ disease, chemo-endocrine therapy is significantly better than endocrine therapy alone (recurrence rate ratios 0·64 SE 0·08 for younger women and 0·85 SE 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+ disease is given in website 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+ disease are given subsequently.

Even if the proportional risk reductions were the same for ER-poor as for ER+ disease, the 5-year gains would be about twice as great for ER-poor disease as for tamoxifen-treated ER+ 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+ disease (see Discussion). Figure 5 illustrates the absolute 5-year benefits of chemotherapy in ER-poor disease (left) and in tamoxifen-treated ER+ 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+ disease. The 15-year gains are, however, less strongly dependent on ER status: see Discussion.

Nodal status (figures 3 and 4d) — Among younger women, the proportional reductions in recurrence and in breast cancer mortality that are produced by chemotherapy appear to be exactly the same in N- as in N+ disease, and among older women nodal status appears to be of little relevance to the proportional reduction in recurrence (and, the association between nodal status and ER status in figure 5 is too weak to produce any material interaction between nodal status and treatment outcome). Hence, nodal status may well be of little relevance to the proportional reduction in breast cancer mortality in either age group, in which case the best estimate of the breast cancer death rate ratio, treatment versus control, among older women would be about 0·88 (ie, the overall risk ratio for all older women) both for N- and for N+ disease, and the absolute benefit would be appreciably greater for N+ disease, despite appearances to the contrary in figure 3.

Period of follow-up (figures 2 and 4e) — 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). In 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 not only during the first 5 years but also, separately, during years 5-9 and 10+ among younger women (figure 4e: entry age <50 years).

Among older women, the main divergence in recurrence takes place within just the first two 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 SE 0·04 during years 2-4, 0·96 SE 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 time 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+ (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 a chance instability, but even if it were ignored the 15-year gain would still be less than 4% among older women.

Other features, and site of first recurrence (website Annex-figure 4) — 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, 40% 2-5, 3% >5 cms). 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. Both among older and among younger women, chemotherapy produced significant reductions not only in distant recurrence but also in 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 period before any recurrence of the original breast cancer. Taking all chemotherapy regimens together, the average non-breast-cancer death rate is 0·7%/year both in the treatment and in the control group, with no significant excess in any particular cause or time period. There is, however, a non-significant excess of such deaths during the first 2 years among women aged 60-69 or 70+, 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.

There is a marginally significant reduction in the incidence of contralateral breast cancers before any other recurrence (0·5%/year versus 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 in table 2.

Directly randomised chemotherapy comparisons

Longer versus shorter chemotherapy — There is a total of only 6000 women in trials that directly compared some months of polychemotherapy versus about twice that duration of the same treatment (weighted mean treatment duration 10·7 vs 5·0 months), of whom 5000 were in trials of longer versus shorter CMF-based regimens: website Appendix to table 1. Almost all had node-positive disease and half suffered recurrence, of whom most died. Although the recurrence rate during the first two 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 particular 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 SE 0·04, CI 0·90-1·06; deaths without recurrence 77/3054 vs 77/3071): website 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 confidence intervals for this treatment comparison were uninformatively wide (recurrence rate ratio 0·83, CI 0·69-1·01; breast cancer death rate ratio 0·95, CI 0·76-1·19; deaths from heart disease or leukaemia 1/360 vs 2/360): website Appendix to table 1.

Anthracycline versus CMF-based regimens (figure 6) — 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 standard errors for the comparison between the two treatment effects, particularly at younger ages, and favour anthracyclines (figure 6). There is a total of 14 000 women (9000 younger, 5000 older) in trials that compare anthracycline-based versus CMF-based regimens.

The anthracyclines tested were adriamycin or epirubicin (60%A, 40%E), usually given for about 6 months in combination with other cytotoxics (eg, as FAC or FEC, which were the most widely studied combinations). The CMF-based regimens used in the control groups were mostly of 6 (mean 6·5) months duration, and involved no other cytotoxics. 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 SE 0·03, 2p<0·00001). The corresponding 10-year probabilities of recurrence, breast cancer mortality and overall mortality are plotted in website Annex-figure 6; in each case the absolute difference between anthracycline-based and CMF-based 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 confidence limits (as do those just in ER+ disease, in N- disease, or in particular time 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 SE 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-based 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 x 0·84] for younger and 0·76 [0·90 x 0·84] for older women). An inverse-variance-weighted average of these direct and indirect estimates suggests that such anthracycline-based regimens would yield breast cancer death rate ratios of about 0·62 SE 0·05 for younger and 0·80 SE 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 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 yields (as above) R, the breast cancer death rate ratio produced by such anthracycline-based regimens.

Among younger women with ER-poor and ER+ disease R=0·61 SE 0·10 and 0·64 SE 0·09 respectively (difference: 2p=0·7) while among older women with ER-poor and ER+ disease R=0·76 SE 0·06 and 0·81 SE 0·05 respectively (difference: 2p=0·5). After standardising for age (in two groups) R does not depend significantly on ER status (difference: 2p=0·2), but after standardising for ER status (in 3 groups: ER-poor, ER unknown or ER+) 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 was no apparent excess of vascular deaths or haematopoietic neoplasms (website Appendix to table 2). But, in the aggregate of all the trials of anthracycline-based versus no chemotherapy at ages <50 and 50-69 (figure 4) and of anthracycline versus CMF-based 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 were 0·46 vs 0·40%/year from all causes (logrank 2p=0·2), 0·08 vs 0·06%/year from heart disease, etc (2p=0·4) and 0·02 vs 0·01%/year from haematopoietic neoplasms (2p=0·10, with corresponding incidence rates of 0·04 vs 0·02%/year, 2p=0·16): table 2 and its footnotes.

These differences in vascular and neoplastic mortality are not significant, and thus far indicate a hazard of only a few per thousand 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 each separate trial of anthracycline-based chemotherapy versus no chemotherapy, or versus CMF, are given on the website Appendix to table 1, and there is no significant heterogeneity between them. But, two of the most widely studied anthracycline-based regimens were 6 months (or, in one trial, 8 months) of FAC and 6 months (or, in one trial, 9 months) of FEC. In the trials of chemotherapy versus not their results were non-significantly better than the average, and in the directly randomised comparisons these were the only two regimens that were separately significantly better than CMF (Figure 6a).The trials of FAC or FEC versus no adjuvant chemotherapy yielded breast cancer death rate ratios of 0·69 SE 0·16 for younger and 0·79 SE 0·07 for older women, the trials of FAC or FEC versus CMF for 6 to 9 (mean 7) months yielded ratios of 0·74 SE 0·06 for younger and 0·78 SE 0·08 for older women, and the trials of CMF alone for no more than 9 months (mean 7 months) versus no adjuvant chemotherapy yielded ratios of 0·64 SE 0·12 for younger and 0·93 SE 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 SE 0·06 (2p<0·0001) for older women. These effects of about 6 months of FAC or FEC on breast cancer mortality are statistically definite, and are, if anything, slightly more promising than the averaged results for all anthracycline-based regimens.

VVarious other ways of subclassifying the trials of anthracycline versus CMF-based regimensno adjuvant chemotherapy were considered (eg, tamoxifen given, or not given, to both chemotherapy groupsduration; use of adriamycin or of epirubicin) without finding any significant heterogeneity of benefit (data not shown), and the same was true of various ways of subclassifying the trials of anthracycline-based regimens versus no adjuvant chemotherapyCMF. 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.are any worthwhile differences in efficacy between the anthracycline-based regimens that they studied.

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+ 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.

Tamoxifen duration and ER status — Among women with ER+ 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 the trials 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+ disease is highly significant ($2p<0{\cdot}00001$ for recurrence, $2p=0{\cdot}0001$ 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 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 unknown ER status are slightly weaker than for those women with ER+ disease.

In website 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 treatment on the ratio of recurrence rates.

5 years of tamoxifen in ER+ disease

Among women with ER+ 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,[12] 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 SE 0·04). Most subsequent analyses of these trials are restricted to women with ER+ (or ER unknown) disease, irrespective of their measured PR status. Figure 8 shows the

15-year recurrence and breast cancer mortality probabilities. The benefits of being allocated active treatment are substantial, and persistent.

Most of the effect on recurrence is seen during the first five years, while tamoxifen was generally still continuing to be given, but most of the effect on breast cancer mortality comes after this period. 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. As 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 (website Annex-figure 8).

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

Figure 8 may slightly under-estimate the effects of actually giving 5 years of tamoxifen in ER+ disease, as 20% had ER unknown disease, so a few per cent 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. In addition, 18% of the recurrences at least 2 years after allocation to tamoxifen were in women allocated to stop at 2 years[14] or at 3 years who had reached their stopping point, while only 10% were in women allocated to continue after 5 years.

Relevance to tamoxifen of dose and of chemotherapy (figures 9a, 9b and 10) — Figure 9 describes the proportional risk reductions produced by about 5 years of adjuvant tamoxifen in various different circumstances (and, website 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 or 40 mg/day (figure 9a). They also appear to be about the same in trials of chemo-endocrine 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 definitely that for women with ER+ disease chemo-endocrine 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 this were available for review in the year 2000. (Results from an Intergroup trial published since then,[13] 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 chemo-endocrine trials do not diverge much during year 0. 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 (figures 9c, 9d and 10) — 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<0·00001), both for those younger than 40 years of age when randomised and for those 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 N+ than for those with N- disease (figure 10).

The 10-year probabilities are given in website Annex-figure 10. For breast cancer mortality the 10-year gains were substantial and definite not only for women with N+ disease (32·0 vs 44·5%, 10-year gain 12·6% SE 2·0, 2p<0·00001) but also for those with N- disease (12·2% vs 17·5%, 10-year gain 5·3% SE 0·9, 2p<0·00001).

Period of follow-up (figures 8 and 9e) — In figure 9e the event rate ratios in years 0-1, 2-4, 5-9 and 10+ are analysed 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 versus control, of recurrence rates in years 5-9 was still 0·69 with narrow confidence limits.

This persistent reduction of about one 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 "carry-over" 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 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 in overall mortality (website Annex-figure 8).

Other features, and site of first recurrence (website Annex-figure 9) — Further subgroup analyses are given on the website, 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 ipsilateral local recurrence and 0·64 SE 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), as 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 (total 61 000 vs 55 000 woman-years respectively), 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 7 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.[15]

If there is a real excess of about 5 deaths (as indicated by doubling the logrank O-E values) from each of these diseases in about 60 000 woman-years then the two together would represent an absolute risk of about 0·2% per decade, which is small in comparison with the 10-year reductions in breast cancer mortality from 5 years of adjuvant tamoxifen (5·3% and 12·2% respectively for N- and N+ disease). Because there are so few deaths from these two conditions 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, as a non-significant excess of stroke (which was not apparent during the first five years, when tamoxifen was generally being taken) and of 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,[16] but could also be chiefly due to the play of chance.

There is a definite decrease of about one third in the incidence of contralateral breast cancer (4·0 vs 6·0 per 1000 per year [244/61·111 vs 331/55·422]), 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+ 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% confidence interval includes the possibility of a reduction of almost one third.

Directly randomised tamoxifen comparisons

Longer versus shorter durations of tamoxifen (figure 11) —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 suffered an event) after randomisation was issued but before the treatment options would differ.

By the year 2000 some 29 000 women had been randomised. 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: figure 11. Since then at least another 10 000 have been randomised (mostly comparing about 10 versus 5 years of tamoxifen),[17] 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 the treatment options would differ is more extreme for recurrence (ratio 0·85 SE 0·02, 2p<0·00001) than for breast cancer mortality (ratio 0·92 SE 0·03, 2p=0·01), perhaps because re-treatment on recurrence was generally allowed. 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%/y: 11 vs 3 deaths, 2p=0·07), stroke (0·08 vs 0·07%/y: 51 vs 45 deaths, 2p=0·5), other vascular causes (0·20 vs 0·21%/y, 128 vs 118 deaths, 2p=0·6) and non-vascular causes (0·66 vs 0·65%/y). Although these differences are not significant, some (eg, the excess of thromboembolic deaths) may well reflect real hazards.

There was no apparent difference in mortality from uterine cancer (13 vs 15 deaths), but the incidence of uterine cancer was significantly increased (0·21 vs 0·11%/y: 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 was outweighed by a somewhat larger decrease in contralateral breast cancer (0·28 vs 0·45%/y: 177 vs 277 cases, 2p<0·00001), and no other cancer incidence rates were significantly affected. Overall, therefore, the incidence of second cancers was 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 provided 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 SE 0·04, 2p=0·01).

These results can be subdivided by time since randomisation (see website Annex-figure 11), finding only a little effect on recurrence, and none on breast cancer mortality, during years 0-1 after randomisation, perhaps because of some "carry-over" of the effects of the first year or two of tamoxifen before randomisation. Both for recurrence and for mortality the main protective effect of the extra few years of treatment was seen during years 2-4 and 5-9 after randomisation (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 SE 0·06) again represent a carry-over benefit, as the few extra years of tamoxifen treatment after randomisation would have ended well before this period began.

In these trials of about 5 versus 1-2 years of tamoxifen (website Annex-figure 11) there was little overall effect of longer treatment on non-breast-cancer mortality (0·97%/y vs. 0·96%/y, 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%/y, 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 events 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. As a "clinical alert" for the use of tamoxifen in node-negative disease was issued in the United States in 1996[18] (suggesting that for women with node-negative, ER+ disease, continuation of adjuvant tamoxifen beyond 5 years was appropriate only in trials), figure 11 is subdivided by nodal status. The apparently unfavourable results for women with node-negative disease (figure 11, a) are, however, not significantly different from the apparently favourable results for women with node-positive disease (figure 11, b).

In these trials of about 10 versus 5 years of tamoxifen, non-breast-cancer mortality appeared to be somewhat greater among those allocated longer treatment, but the difference was not clearly significant either overall (1·2 vs 0·9%/y, 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%/y, 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+ disease of 5 years of tamoxifen on breast cancer mortality

Among women with ER+ disease the directly randomised comparison of about 5 years of tamoxifen versus no adjuvant tamoxifen in figure 7 suggests 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 Annex-figure 9. This suggests that in ER+ disease 5 years of tamoxifen would produce a breast cancer death rate ratio of 0·74 SE 0·05 (0·82 x 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 aged under 50 with ER+ 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 an LHRH inhibitor (3408 women, 26% ER untested, mean follow-up 5 years): figure 12.

Overall, there was a definite effect of ovarian ablation or suppression both on recurrence (2p=0·00001) and on breast cancer mortality (2p=0·004), but it was not as extreme as it had seemed to be in earlier meta-analyses of these trials, when ovarian ablation was not being tested against a background of effective systemic therapy.[6]

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 by year 10 or year 15. 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) 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 aged under 50 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 (website Annex-figure 13: death rate ratio 0·94 SE 0·18, 2p=0·7).

Addition of ovarian treatment to other treatments — There was no indication that the effects of ovarian ablation differed from those of ovarian suppression, or that the risk reductions for women aged <40 at entry differed from those for women aged 40-49. But, in both age groups the effects of ovarian treatment did 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 confidence intervals for some of the subgroup 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 anthracycline-based combinations such as CAF or CEF, or about 5 years of tamoxifen-based hormonal therapy).

Such regimens have been used widely, and were recommended in 2001 by a US NIH consensus development conference,[12] although other regimens are now gaining favour. At least in terms of breast cancer mortality, which is the chief subject of this Discussion, 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+ 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 versus no chemotherapy, one type of chemotherapy versus another, 5 years of tamoxifen versus no tamoxifen) there is no significant trend between years 0-4, 5-9 and 10-14 in the ratio, treatment versus control, of the annual death rates from breast cancer: see 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+ 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, chemoendocrine therapy) is likely to achieve, as 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.

In 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, 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 involve a non-representative sample of hospitals within those countries and of patients within those hospitals. Moreover, patients in these long-term trials were all diagnosed in previous decades, making them systematically different from 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: see figures 4, 6 and 9 (and the corresponding Annex-figures: in particular, the response to tamoxifen appears to depend on the ER, but not the PR, status, as measured in these trials). Hence, 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 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.[19]

Absolute risks in untreated patients, by ER 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, 10 and 15-year breast cancer mortality among the controls illustrates how the prognosis without either treatment used to depend on ER and nodal status.

With 74 000 woman-years of follow-up among untreated controls of known ER and nodal status in these trials (36 000 ER+ N-, 16 000 ER+ N+, 17 000 ER-poor N-, 5000 ER-poor N+), the breast cancer mortality at 5, 10 and 15 years, respectively, is 7%, 20% and 31% in ER+ N- disease, and 23%, 51% and 63% in ER+ N+ disease. Among women of the same nodal status, the breast cancer death rate is about twice as great in ER-poor as in ER+ disease during just the first 5 or 6 years, but is substantially lower in ER-poor than in ER+ disease over the next 10 years, so the 15-year breast cancer mortality of untreated patients is largely independent of ER status (and of age): website Appendix to table 4.

The controls 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 chemo- or endocrine therapy, current and future patients would have somewhat lower stage-specific 15-year risks (eg, about 25% and 50% for N- and N+ disease). Indeed, for many women with small, screen-detected N- tumours the 15-year risks from untreated disease would probably be much less than 25%. Table 4 therefore gives 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- or ER+ disease, age <70 — 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 0.05 and 20% SE 0·04) at ages <50 and 50-69, but were largely untested at older ages. Particular anthracycline-based regimens may well be somewhat more or less effective than this averageThe 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% SE 6) were statistically definite in both age ranges, and appeared at least as promising as the overall average..

These proportional reductions are approximately independent of ER status. (For example, among women aged 50-69 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 are 0·76 SE 0·06 and 0·81 SE 0·05 respectively for women with ER-poor and ER+ disease.) The upper part of table 4 shows, for these proportional reductions, and shows 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.

Chemotherapy, age 70+ — These trials of chemotherapy involved too few women aged over 70 to be reliably informative (even if ER status is ignored) as to whether it confers any net survival benefit.

Endocrine therapy in ER+ disease, age <70 or 70+ — For women of any age with ER+ disease, 5 years of tamoxifen multiplies the breast cancer death rate by about 0·69 (ie, reduces it by 31% SE 0·03). 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. Especially among those aged 70+, 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 footnote to table 4.

Chemo-endocrine therapy in ER+ disease, age <70 — In the particular case of middle-aged women with ER+ disease the anthracycline-based regimens studied in these trials reduce the annual breast cancer death rate by about 38% for women under 50 and 20% for those aged 50-69, even if hormonal therapy is to be given, and 5 years of tamoxifen can 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[13]) approximately halves the average annual death rate from breast cancer during the first 15 years after diagnosis.

Exact multiplicativity would imply a 57% reduction for women aged under 50 and a 45% reduction for those aged 50-69, but such apparent precision may be excessive. Even approximate multiplicativity of the death rate ratios produced by these treatments (as in 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.

As chemotherapy and tamoxifen are effective in postmenopausal women, they should also be effective after ovarian ablation or suppression. The converse, however, is not clearly demonstrated by these trials. Although, for women aged under 50, 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).

Non-breast-cancer mortality

The aggregate of all trials of polychemotherapy versus not involved no net effect on second cancers or mortality before recurrence, although there were 0·6% vs 0·5% such deaths in years 0-1 (96/14 250 vs 76/14 514, 2p=0·09), some perhaps due to the immediate hazards of chemotherapy in older women: table 2.

The trials of anthracycline-based chemotherapy versus no chemotherapy or versus CMF-based chemotherapy, however, 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. The trials of 5 years of tamoxifen also 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, and therefore modifies the net long-term benefit of systemic adjuvant treatment (especially in old age) only 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 aged <70 appear on average to involve net mortality differences of at most a few per thousand per decade, which are one or two orders of magnitude smaller than 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 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 versus no adjuvant treatment) may never be re-visited.

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 five or ten 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 some months of anthracycline-based chemotherapy and at least 5 years of tamoxifen, as recommended by a US NIH consensus development conference published in 2001,[12] can approximately halve the annual death rate from ER+ 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 lease a sixth of those with N- disease and a third of those with N+ 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:[19] 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.[12] In the US, for example, adjuvant treatment of node-negative breast cancer was uncommon in 1987, but increased suddenly during 1988-91, and was in general use by 1992.[20] The present meta-analyses show that such changes must have contributed substantially to the recent decreases in national breast cancer mortality rates that began in several countries during the 1990s, and are still continuing. Figure 14 illustrates this for the UK, US, Netherlands and France, and website Annex-figure 14 illustrates it for 150 major countries for which the WHO provides long-term mortality trends in breast cancer and other major neoplastic diseases (including lung cancer).

Because most of the improvement in 15-year breast cancer mortality produced by adjuvant chemotherapy and hormonal therapy (and by adjuvant radiotherapy[9]) 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) and/or wider use of appropriate treatments 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[210] (despite rising incidence rates) and to the decreases that are now becoming apparent in several other countries (despite, in some cases, rising incidence rates

and previously rising death rates): figure 14. Likewise, 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, the accumulation of many relatively small 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.

Early Breast Cancer Trialists' Collaborative Group

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22. Appendices to tables 1-4 and Annex-figures 1-14. http://www.ctsu.ox.ac.uk/~ebctcg/

Table 1: Availability of relevant trials that began by 1995

Type of comparison†	Available*		Unavailable** (%)	
	Trials	Deaths / women by year 2000	Trials	Approximate nos. by year 2000
Cytotoxic chemotherapy (CT)				
Single-agent CT vs. Not	14	2114 / 3994	0	0
PolyCT vs. Not	60	10173 / 28764	7	1862 (6%)
'Longer' vs. 'Shorter' PolyCT	11	2567 / 6125	2	426 (7%)
Anthracycline vs. CMF-based CT	17	4044 / 14470	6	1269 (8%)
Tamoxifen (Tam)				
1-2 years Tam vs. Not	44	13914 / 33209	6	~1600 (5%)
~5 years Tam vs. Not	12	4071 / 15017	6	~5000 (25%)
'Longer' vs. 'Shorter' Tam	15	5984 / 32047	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%)**

† "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 on the website (Appendix to table 1) give, for each contributory trial, year started, treatments compared, numbers randomised and analyses (and meta-analyses) of recurrence and mortality.

* 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).

Table 2: Polychemotherapy versus not: mortality, and second cancer incidence, without recurrence of the original breast cancer

	Polychemo-therapy (n = 14250)	Adjusted control (n = 14514)	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 / 92592 (0·7%/year)**	**559 / 85599 (0·7%/year)**	**1·4**	**229·3**	**-**
Ditto, anthracycline-based only*	***207 / 27675 (0·7%/year)***	***168 / 25805 (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	-
*Ditto, anthracycline-based only**	*47*	*31*	*6·7*	*11·6*	*0·05*
- Neoplastic	166	161	-5·2	65·8	-
Haematopoietic	17	16	-1·1	7·5	-
*Ditto, anthracycline-based 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.·	-
- Non-breast-cancer mortality in years 0-1 only / years at risk	**96 / 24838**	**76 / 24440**	**10·1**	**34·9**	**0·09**
Entry age <50	5 / 6061	6 / 5570	-0·8	2·3	-
50-59	22 / 8909	18 / 8906	2·1	8·9	-
60-69	52 / 8872	44 / 8821	6·3	19·1	-
70+	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	89	116	-20·8	49·1	0·003
50+	223	217	-4·7	94·1	-
Other site† (without prior such event)	**528**	**466**	**9·0**	**203·2**	**-**
Uterus	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	-
Haematopoietic	34	32	-1·2	13·7	-
*Ditto, anthracycline-based only**	*13*	*7*	*1·3*	*3·5*	-
Other second primary	235	213	7·1	92·8	-

*† Footnotes to table 2 on next page.

Footnotes to table 2 (from previous page)

*Results just for the trials of anthracycline-based vs no chemotherapy. Corresponding results for trials of anthracycline-based vs CMF-based chemotherapy: all-cause mortality 1914/7228 vs 2133/7243 deaths/women ($p<0{\cdot}00001$), non-breast-cancer mortality 105/40750 vs 96/39114 deaths/woman-years without recurrence (0·26 vs 0·25%/year), including heart etc 9 vs 7 deaths and haematopoietic neoplasms 7 vs 3 deaths (out of 17 vs 9 incident cases). In trials of longer vs shorter anthracycline duration there were only 1/360 vs 2/360 cardiac or haematopoietic deaths. (See website, 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 on the website (in the Appendix to table 2).

Table 3: About 5 years of tamoxifen versus not: mortality, and second cancer incidence, without recurrence of the original breast cancer. All women, irrespective of ER status

	~ 5 years of tamoxifen (n = 7512)	Adjusted control (n = 7505)	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 / 61111 (0·8%/year)**	**416 / 55422 (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*	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	-
Haematopoietic	14	8	1·8	5·2	-
Other neoplastic	51	46	0·2	23·5	-
*cervix, corpus or unspecified					
- 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**	**331**	**-53·1**	**139·6**	**<0·00001**
ER-poor original breast cancer	69	75	-0·8	35·3	-
ER+ or ER unknown " "	175	256	-52·3	10·3	<0·00001
Uterus (cervix, corpus or unspecified uterine site)	**118**	**32**	**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	-
Haematopoietic	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 on the website (in the Appendix to table 3).

Table 4: Estimated effects of anthracycline-based chemotherapy and/or 5 years of tamoxifen 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%)

Systemic adjuvant treatment and age at diagnosis (years)	Annual breast cancer mortality rate, treatment versus control		15-year breast cancer mortality, % (and absolute gain) with treatment versus M, the corresponding 15-year % mortality without treatment		
	Ratio of rates, R	Proportional reduction	M=10-15, eg low-risk N-	M=25, eg N-	M=50, eg N+
Chemotherapy only in ER- or ER+ disease:*					
None: any age	1·0	-	12·5 (-)	25 (-)	50 (-)
Anthracycline: age <50	0·62	38%	7·9 (4·6)	16·3 (8·7)	34·9 (15·1)
50-69	0·80	20%	10·1 (2·4)	20·6 (4·4)	42·6 (7·4)
70+	?	?	?	?	?
Endocrine, or chemo-endocrine, therapy in ER+ disease:*					
None: any age	1·0	-	12·5 (-)	25 (-)	50 (-)
Tamoxifen: any age	0·69	31%	8·8 (3·7)	18·0 (7·0)	38·0 (12·0)
Anthracycline + tamoxifen: age <50	0·62 x 0·69	57%	5·6 (6·9)	11·6 (13·4)	25·7 (24·3)
50-69	0·80 x 0·69	45%	7·1 (5·4)	14·7 (10·3)	31·8 (18·2)
70+	? x 0·69	?	?	?	?

Anthracycline: several months of anthracycline-based adjuvant chemotherapy, 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 website 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- than for ER+ 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 versus no chemotherapy do not depend significantly on ER status). Combination of the direct and indirect randomised evidence yields breast cancer death rate ratios, treatment versus control, of 0·62 SE 0·05 at age <50 and 0·80 SE 0·04 at ages 50-69 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.)

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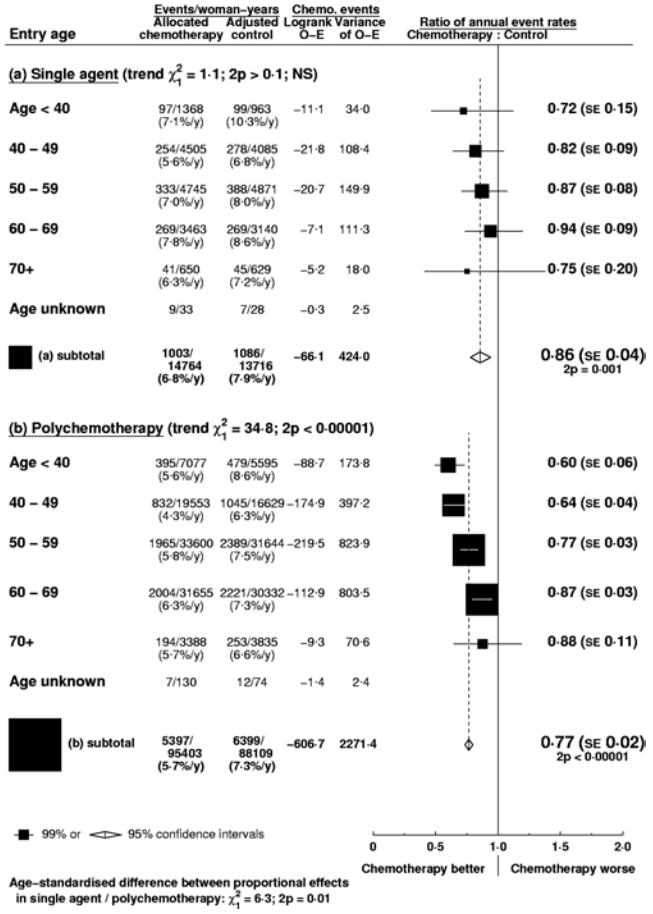
Figure 1: Single agent chemotherapy versus not and polychemotherapy versus not, by 10-year age groups: annual event rate ratios, treatment versus control, for recurrence and for breast cancer mortality

Recurrence / Woman-years



Breast cancer mortality / Women

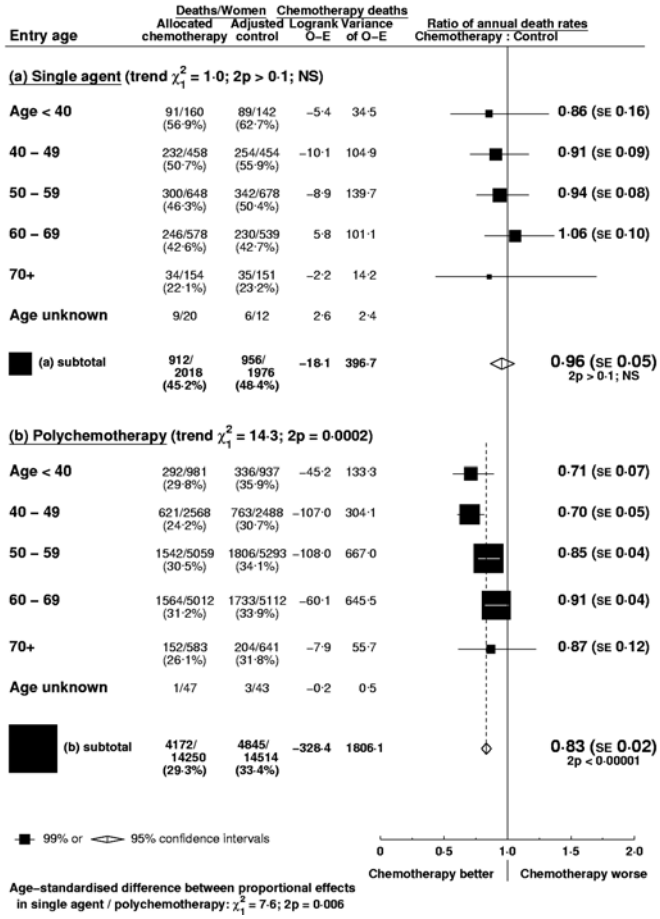


Figure 2: Polychemotherapy versus not, for entry age <50 or 50-69 years: 15-year probabilities of recurrence and of breast cancer mortality

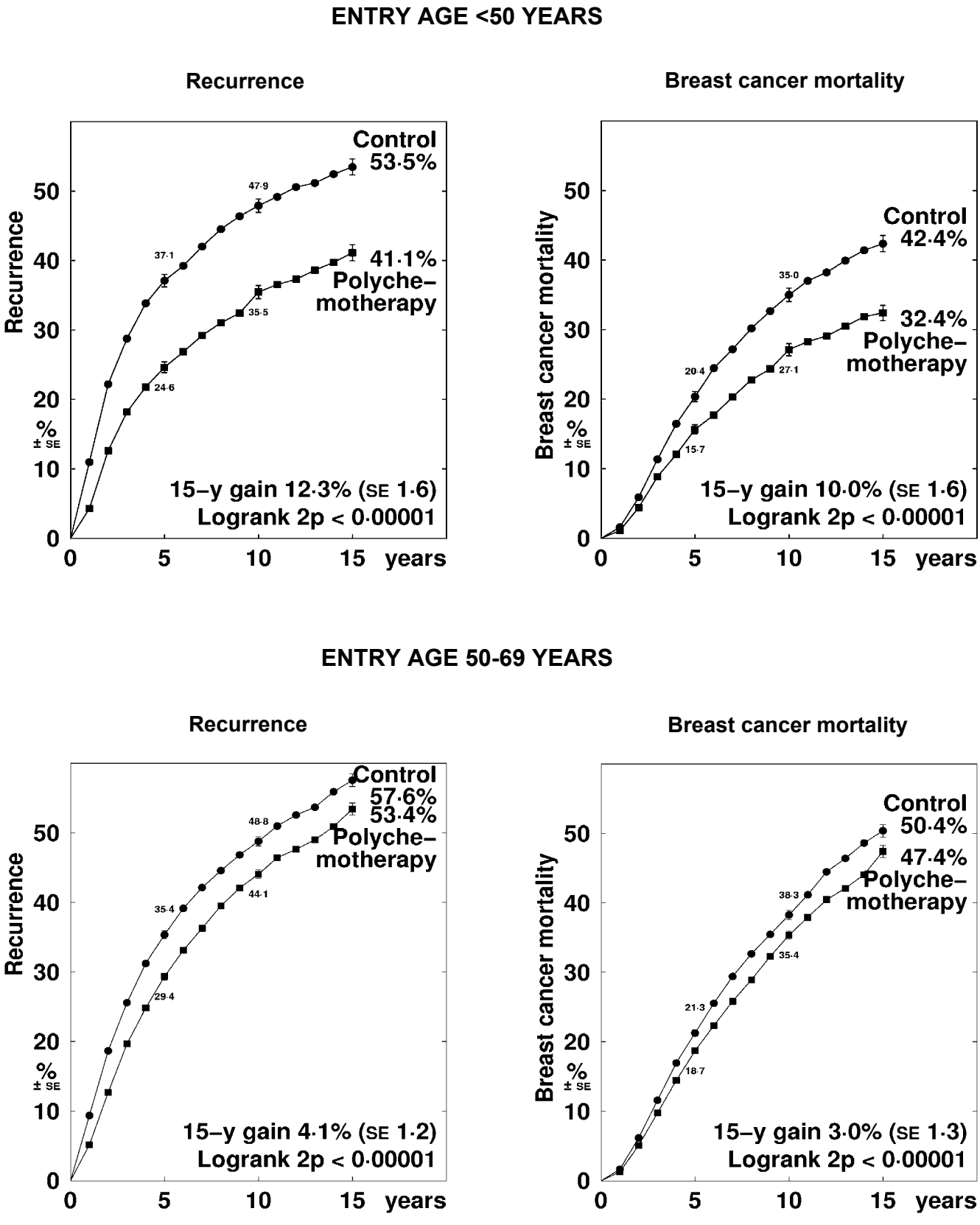


Figure 3: Polychemotherapy versus not, by nodal status and entry age: 5-year probabilities of recurrence

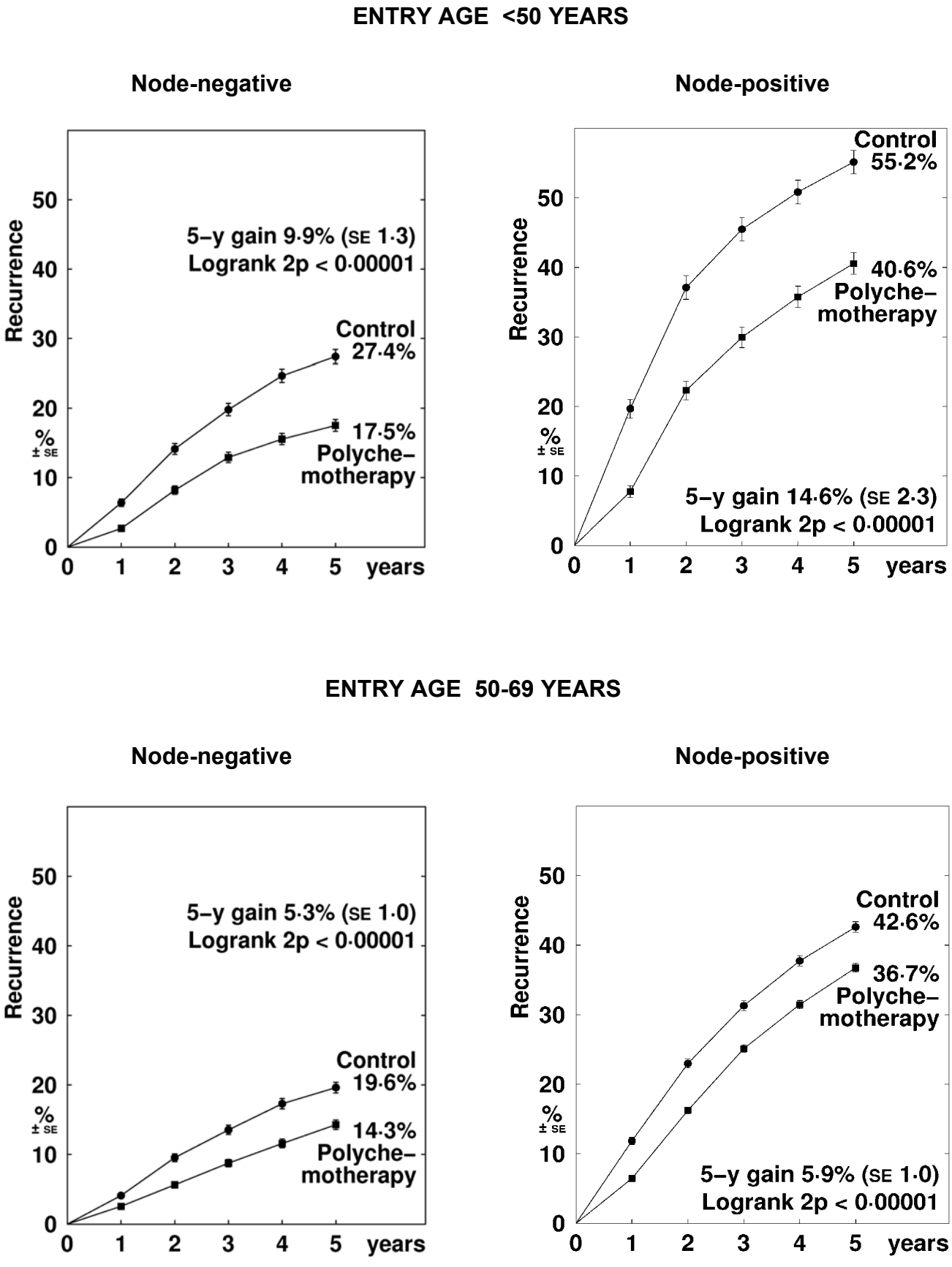
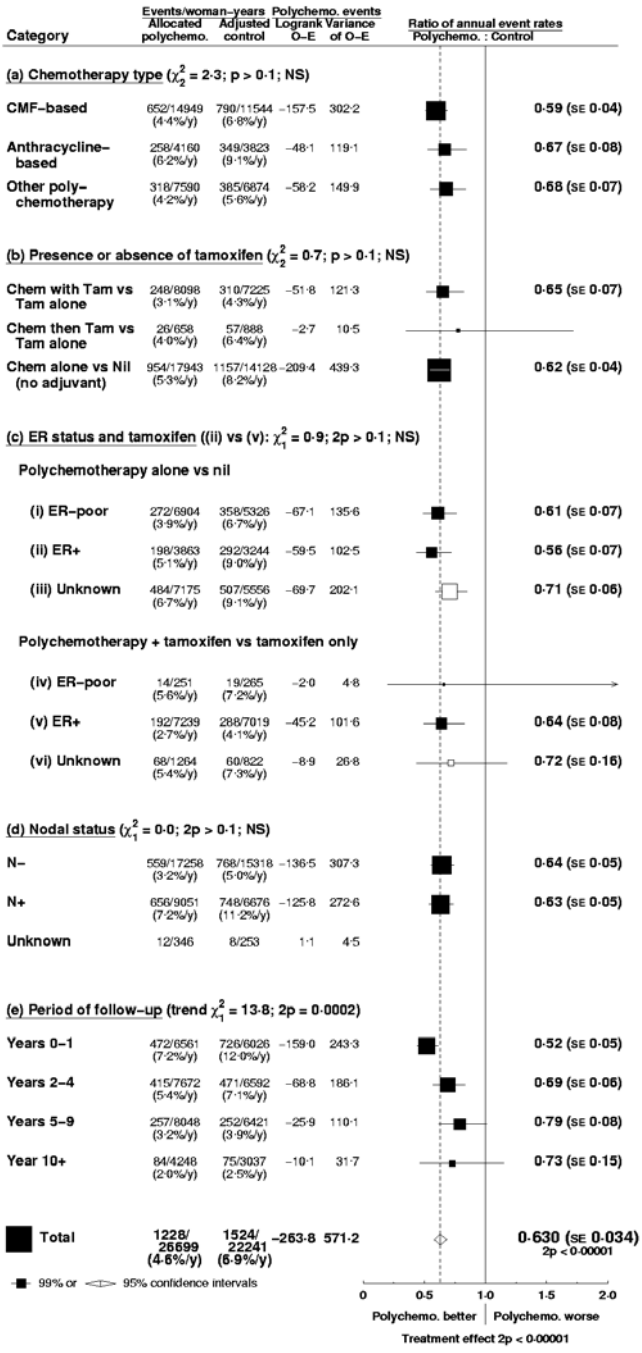


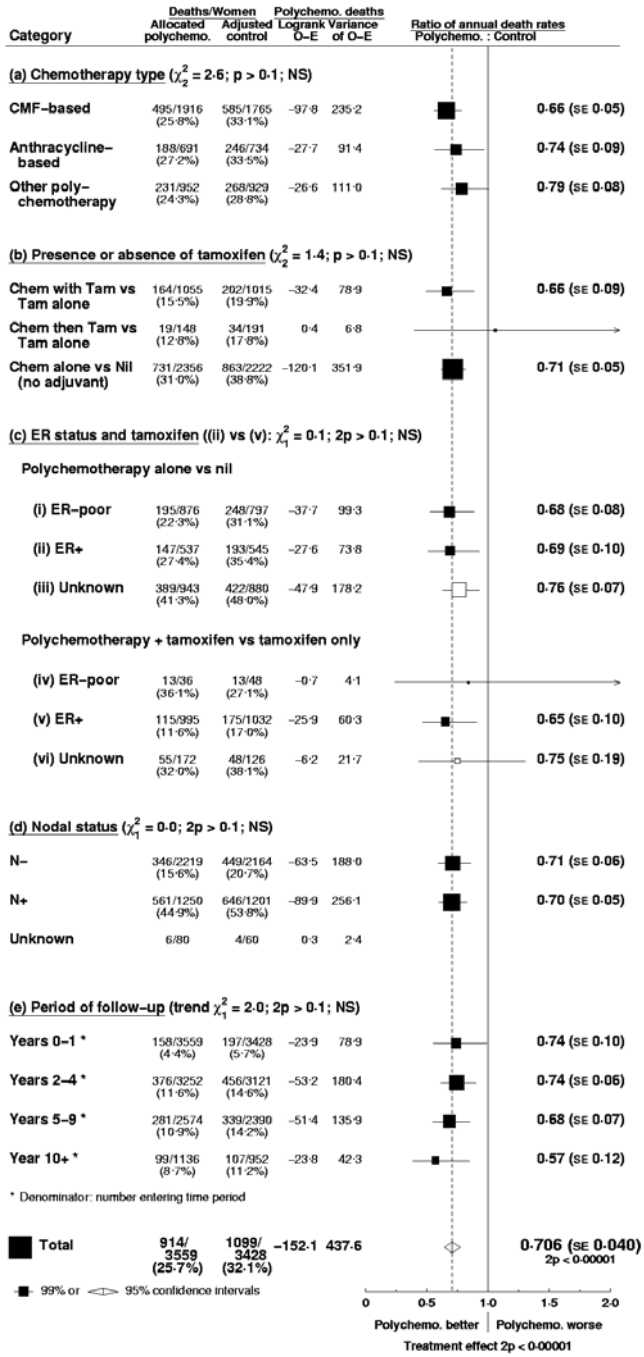
Figure 4: Polychemotherapy versus not, by type of chemotherapy, use of tamoxifen, ER status, nodal status or period of follow-up, for entry age <50 or 50-69 years: event rate ratios

ENTRY AGE <50 YEARS

Recurrence / Woman-years



Breast cancer mortality / Women

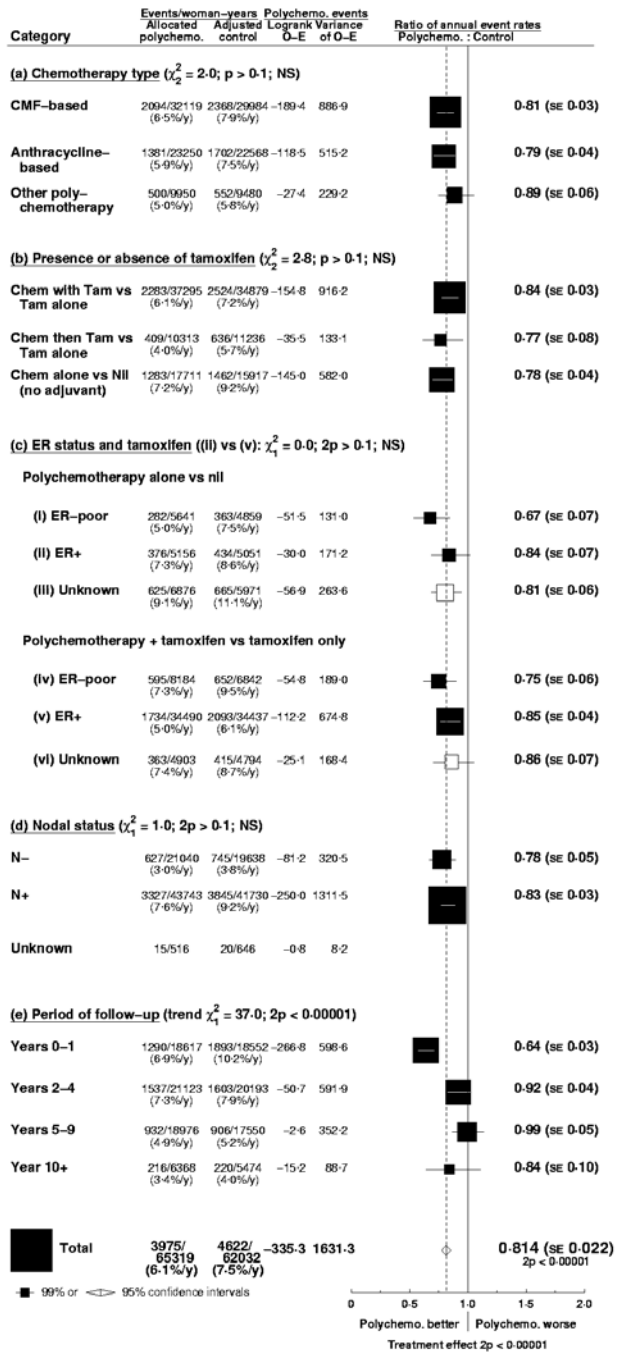


(Figure 4 continues on next page for entry age 50-69)

Figure 4 (continued from previous page)

ENTRY AGE 50-69 YEARS

Recurrence / Woman-years



Breast cancer mortality / Women

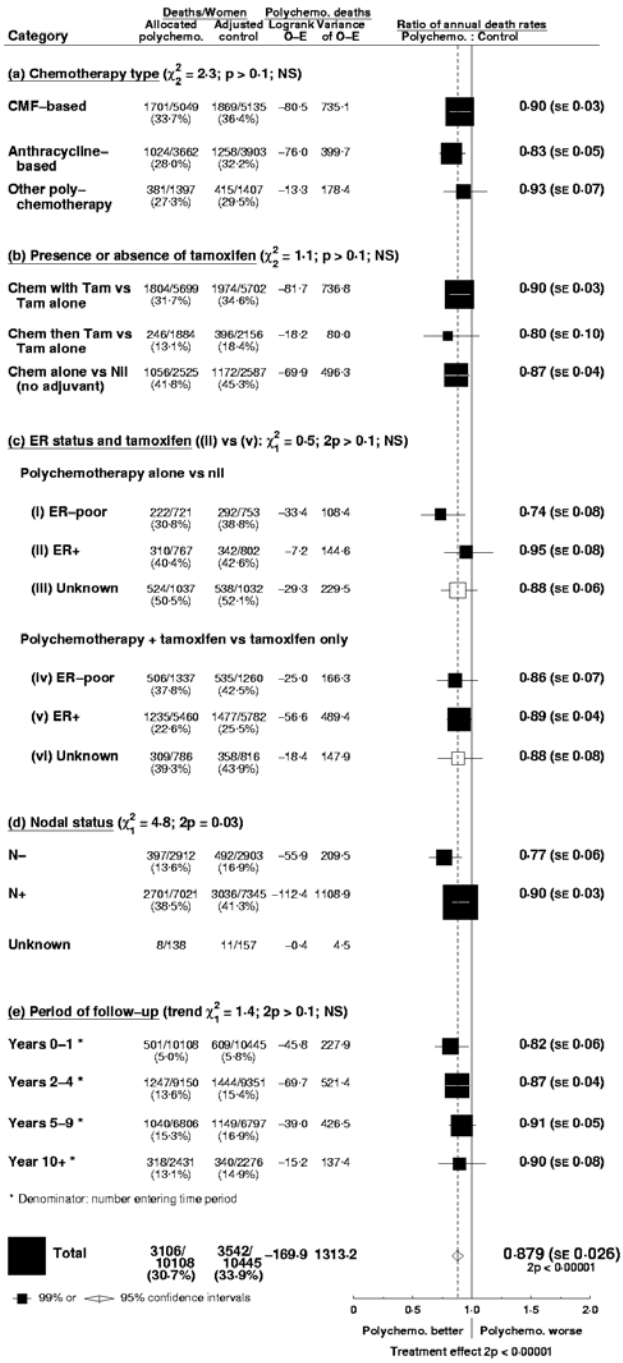
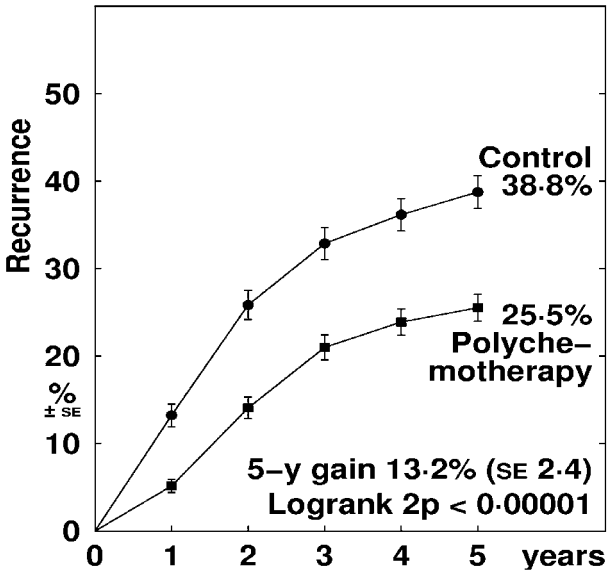


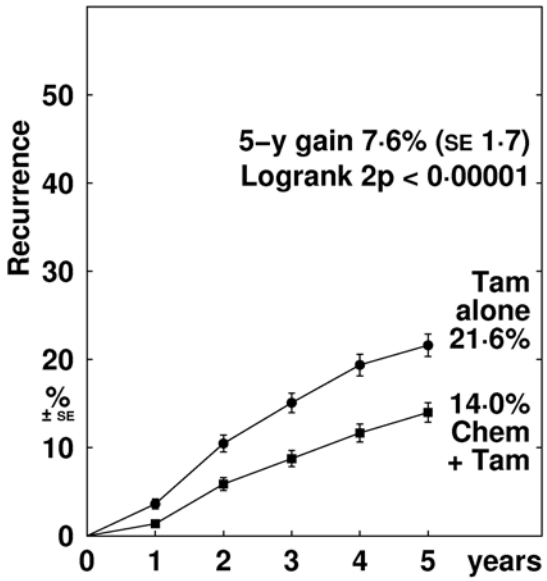
Figure 5: Polychemotherapy versus not in ER-poor disease or in tamoxifen-treated ER+ disease, for entry age <50 or 50-69 years: 5-year probabilities of recurrence (ER+ includes 12% ER unknown)

ENTRY AGE <50 YEARS

ER-poor: Polychemo vs. Not (1757 women: 20% N+)

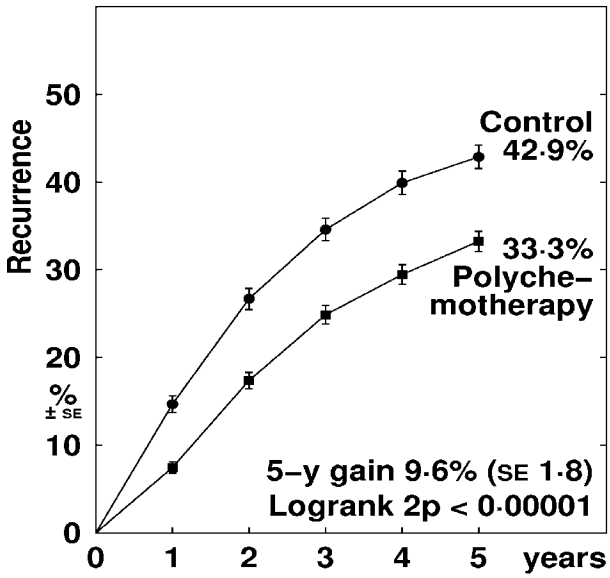


ER+: Polychemo+Tam vs. Tam (2254 women: 34% N+)



ENTRY AGE 50-69 YEARS

ER-poor: Polychemo vs. Not (4071 women: 66% N+)



ER+: Polychemo+Tam vs. Tam (11 333 women: 73% N+)

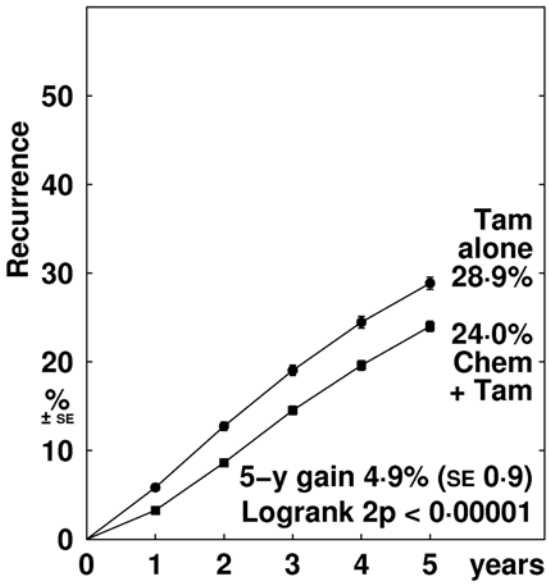
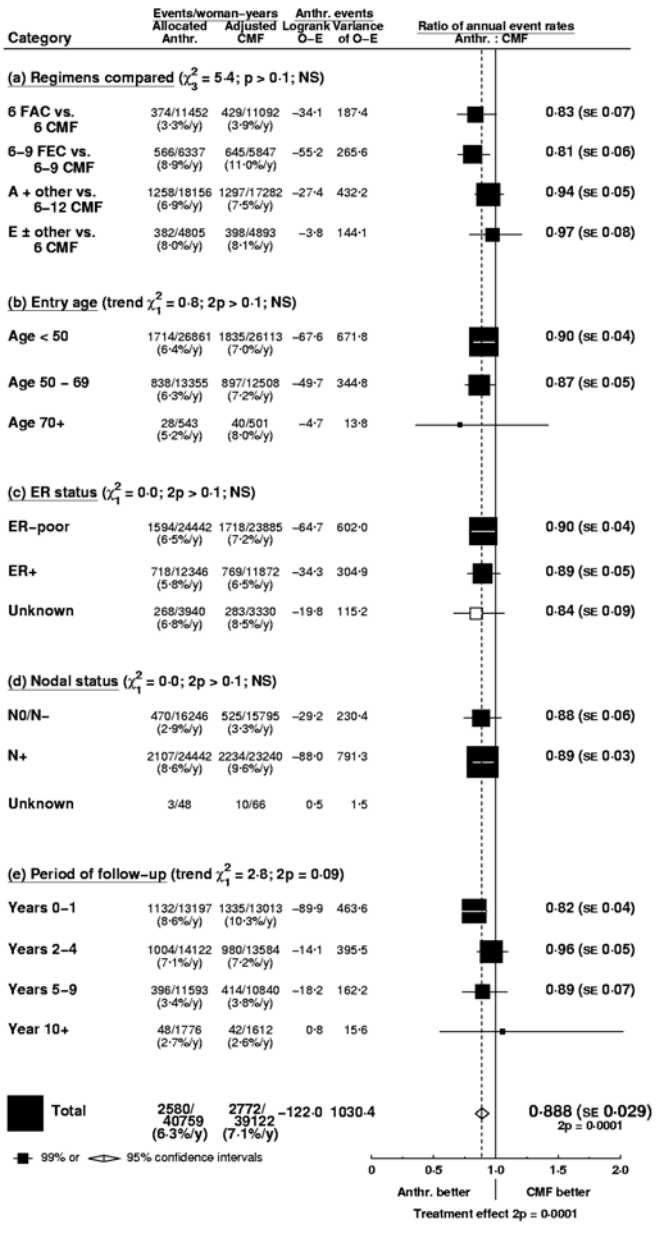


Figure 6: Anthracycline-based polychemotherapy vs CMF by type of chemotherapy, entry age, nodal status or period of follow-up: event rate ratios

Trials of either adriamycin or epirubicin (A or E), usually with other cytotoxics (eg, as FAC or FEC), vs 6-12 (mean 6·5) cycles of CMF

Recurrence / Woman-years



Breast cancer mortality / Women

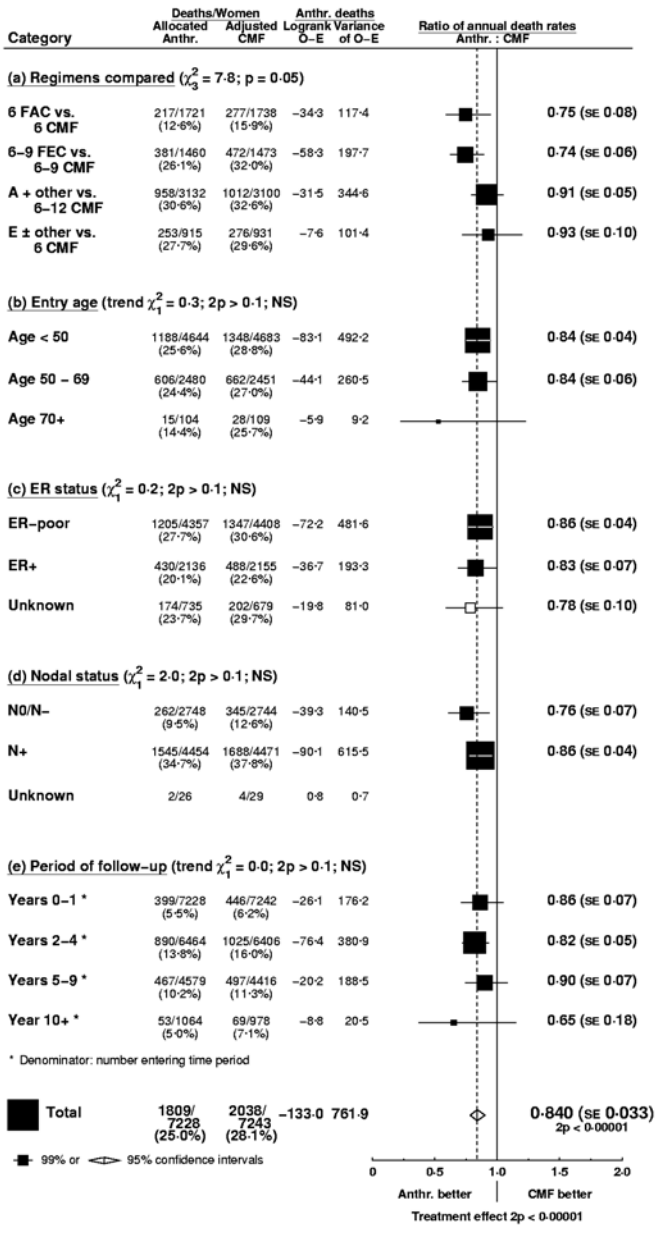
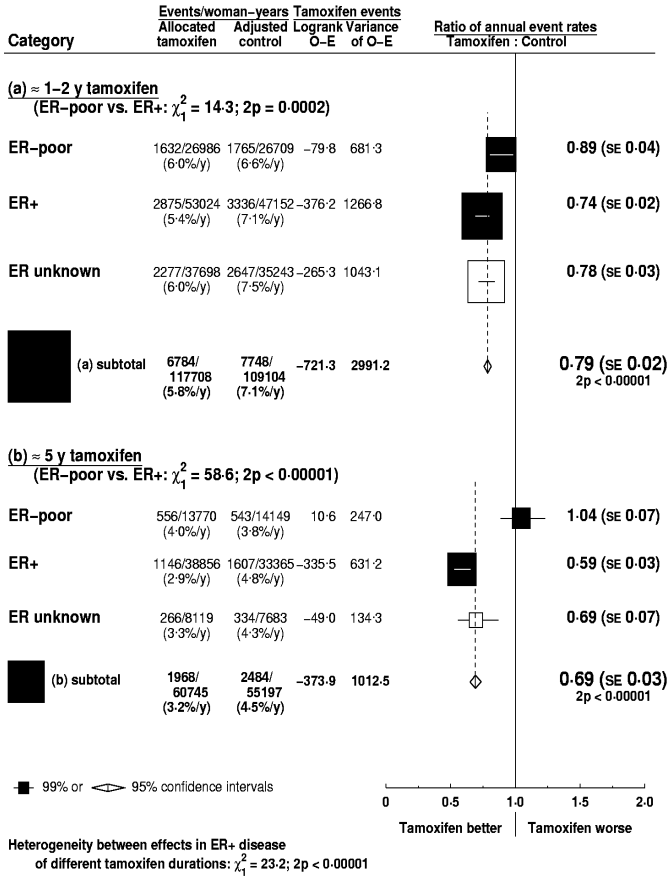


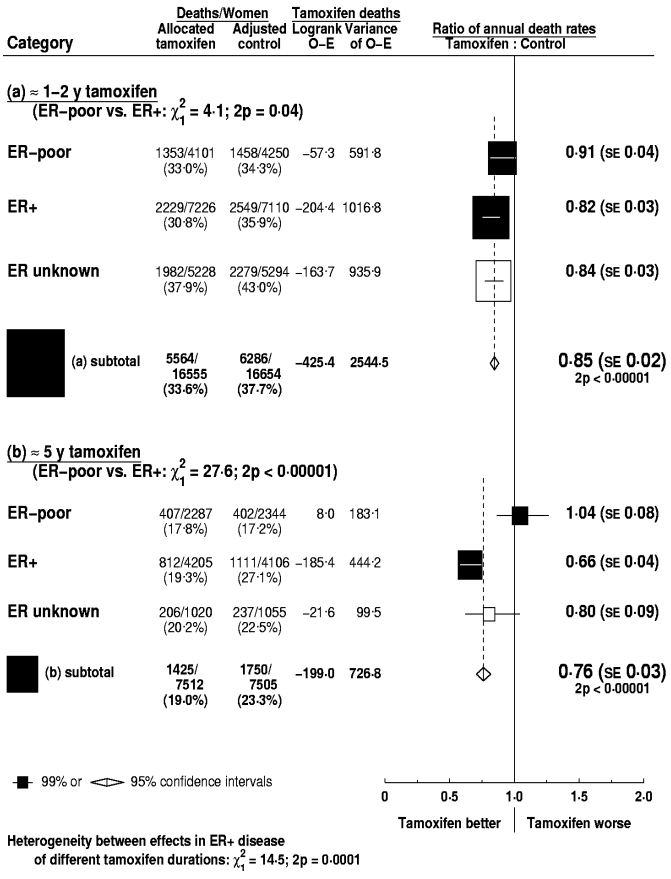
Figure 7: Tamoxifen versus not, by ER status and treatment duration (about 1-2 years or about 5 years of tamoxifen): event rate ratios

Recurrence / Woman-years



Heterogeneity between effects in ER+ disease of different tamoxifen durations: χ^2_1 = 23·2; 2p < 0·00001

Breast cancer mortality / Women



Heterogeneity between effects in ER+ disease of different tamoxifen durations: χ^2_1 = 14·5; 2p = 0·0001

Figure 8: About 5 years of tamoxifen versus not in ER+ (or ER unknown) disease: 15-year probabilities of recurrence and of breast cancer mortality (10,386 women: 20% ER unknown, 30% N+)

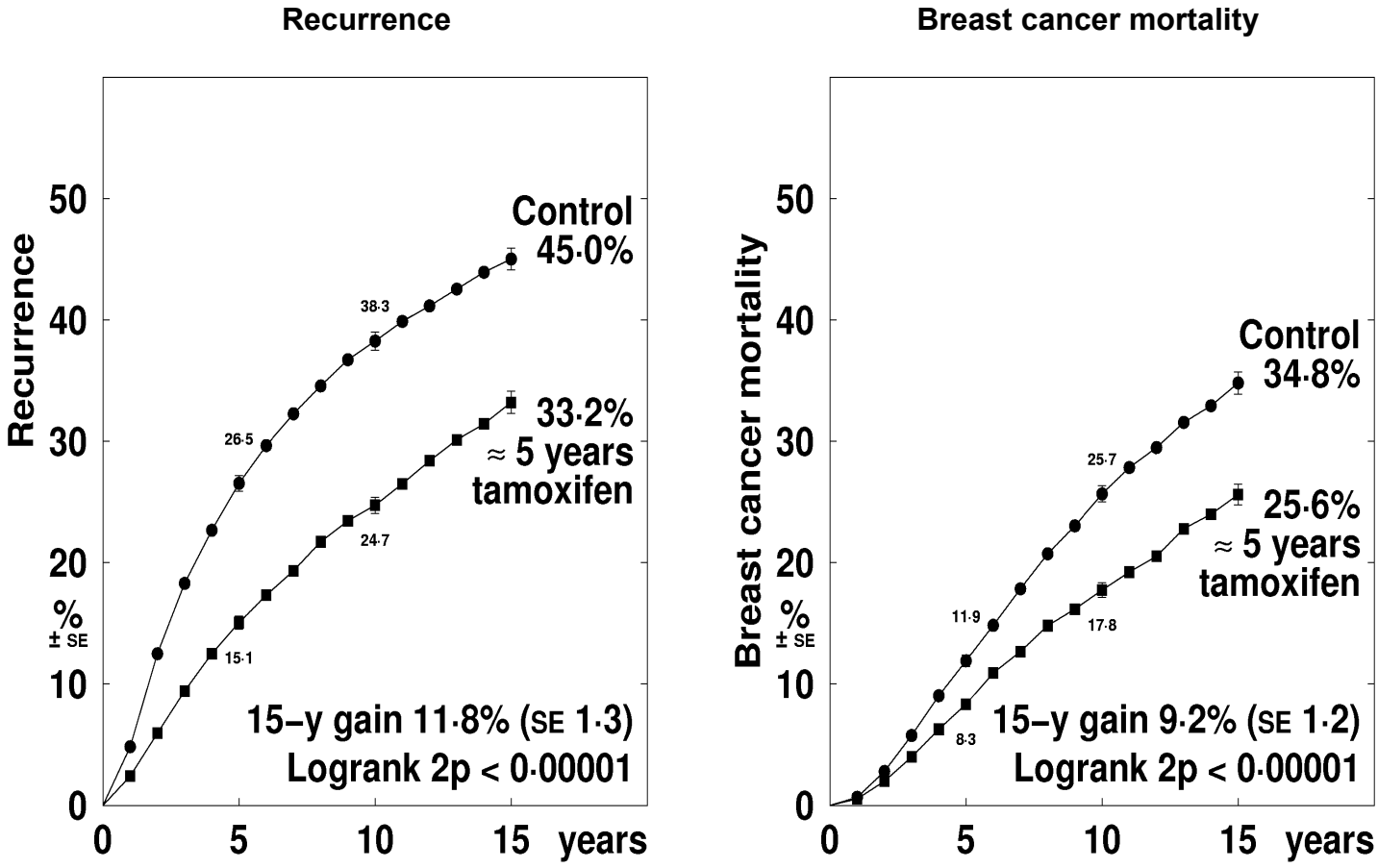
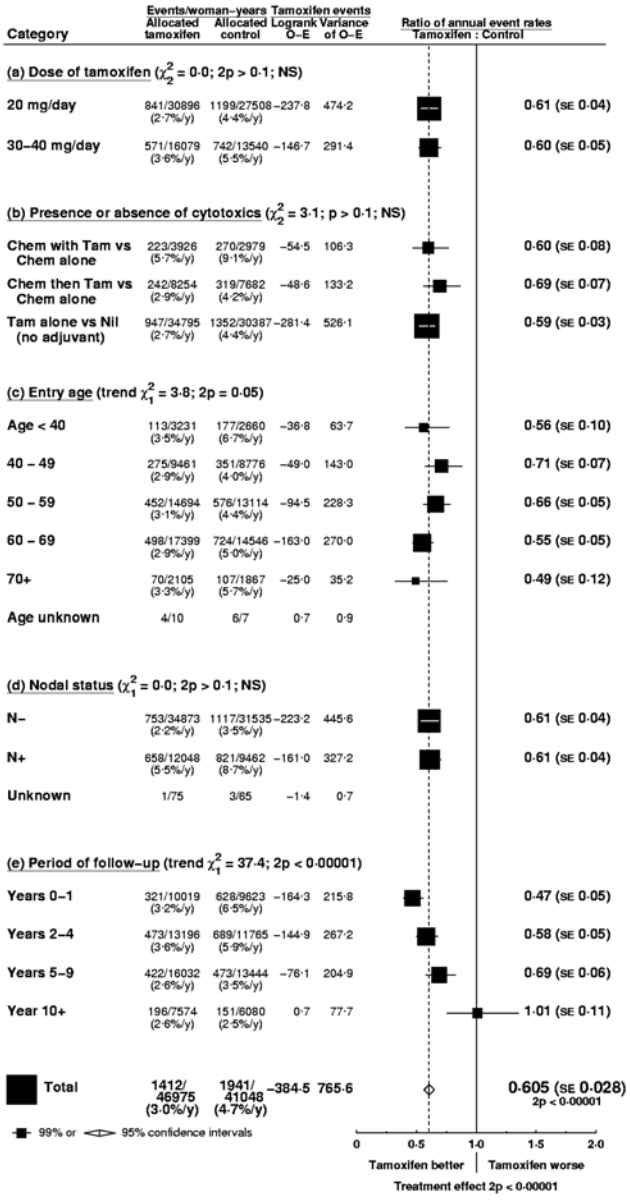


Figure 9: About 5 years of tamoxifen versus not in ER+ (or ER unknown) disease, by tamoxifen dose, use of chemotherapy, age, nodal status or period of follow-up: event rate ratios

Recurrence / Woman-years



Breast cancer mortality / Women

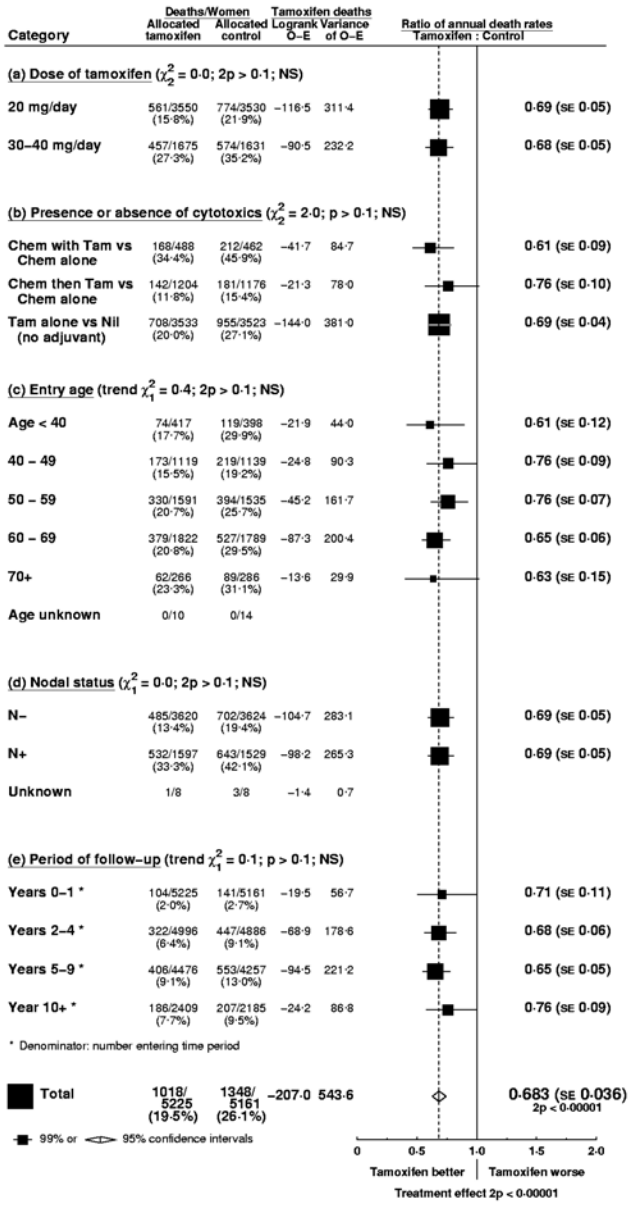


Figure 10: About 5 years tamoxifen versus not in ER+ (or ER unknown) disease, by use of chemotherapy, entry age or nodal status: 5-year probabilities of recurrence

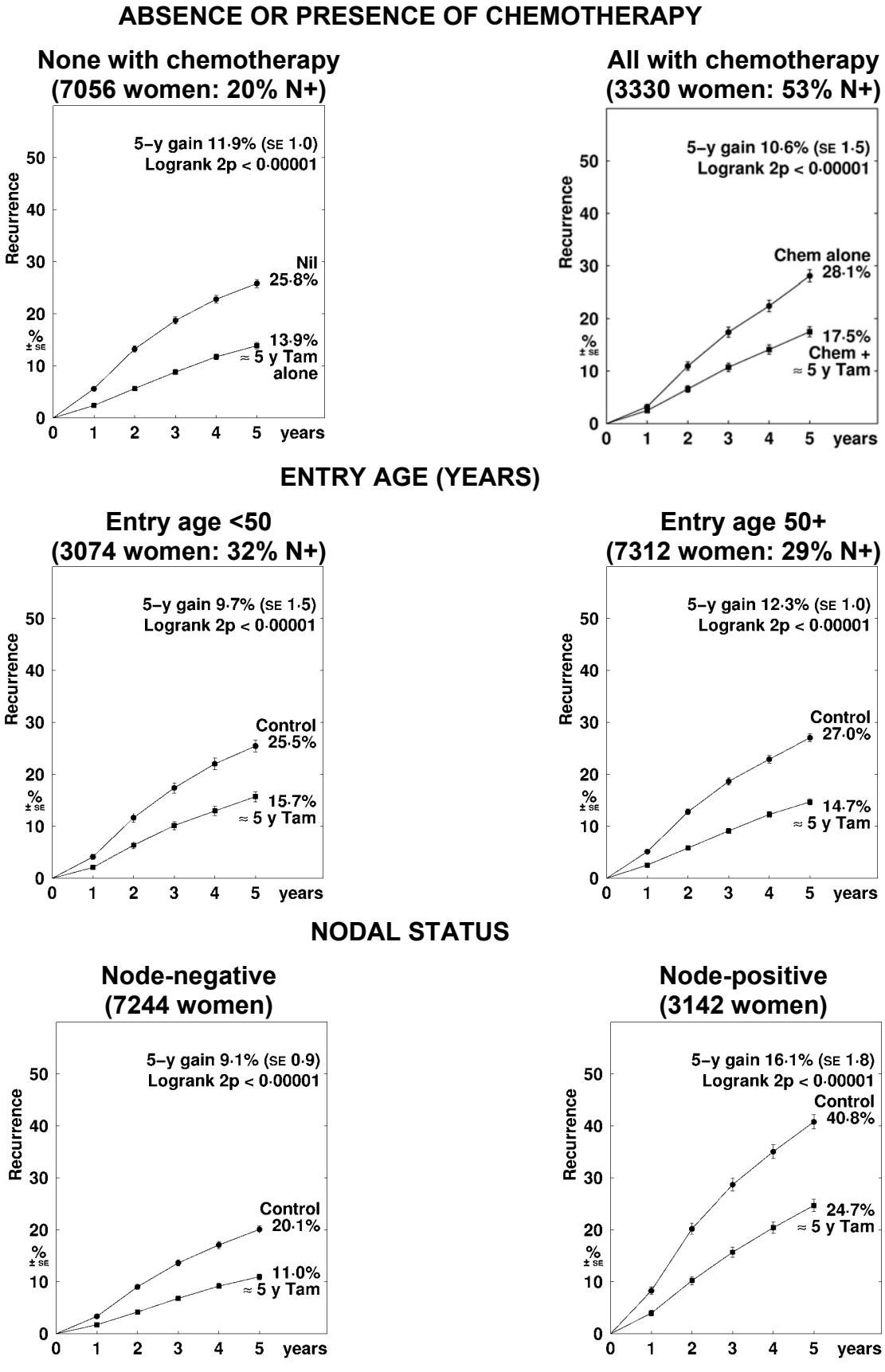
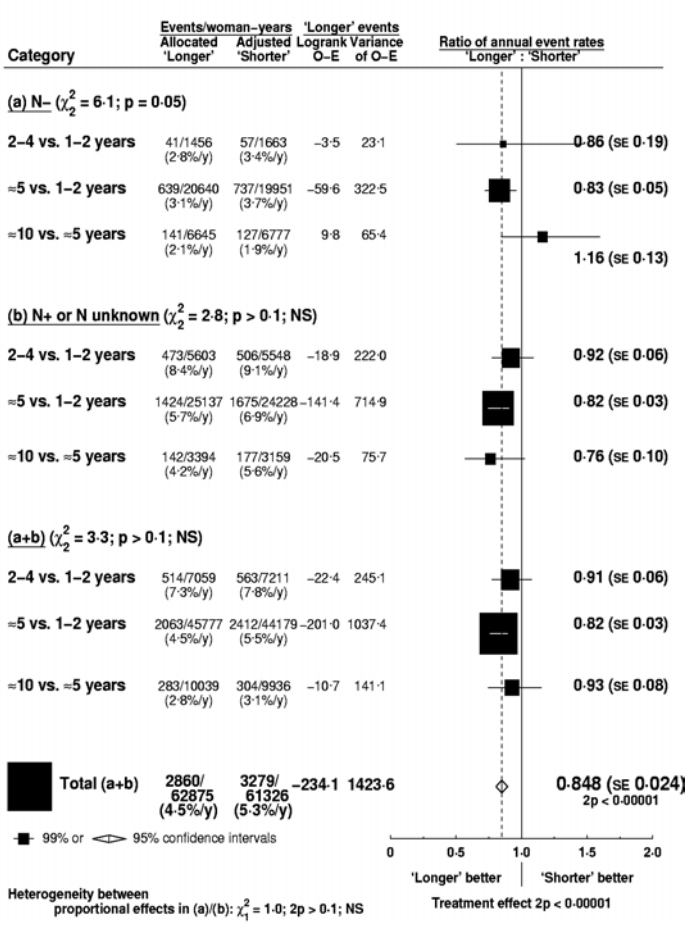


Figure 11: 'Longer' versus 'shorter' tamoxifen duration in ER+ (or ER unknown) disease, by treatment type and nodal status: event rate ratios

Recurrence / Woman-years



Breast cancer mortality / Women

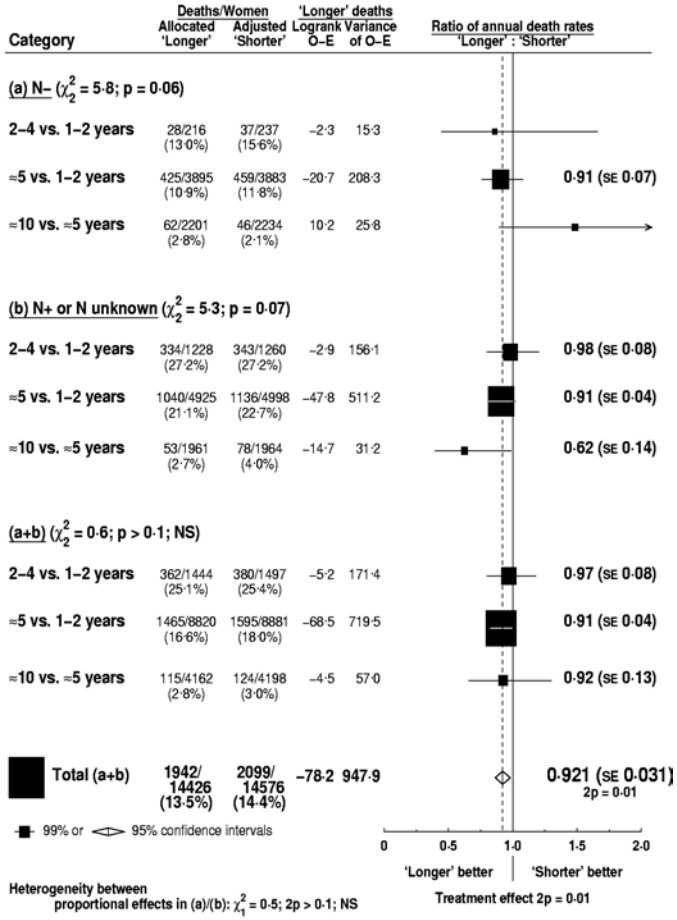
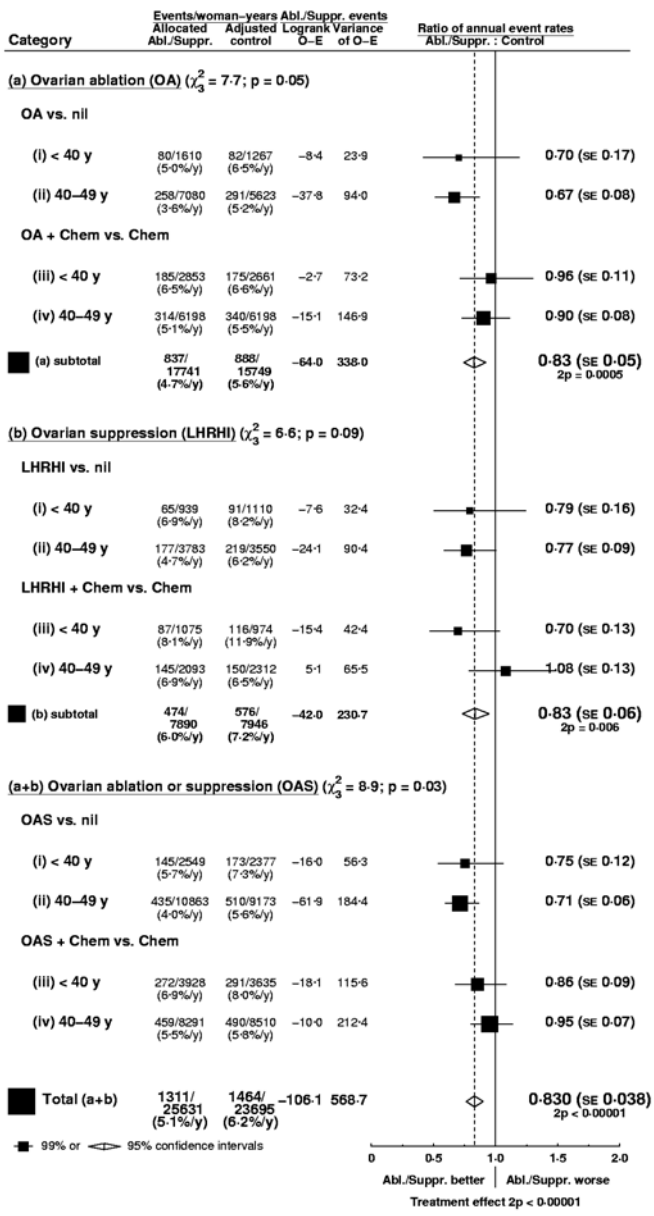


Figure 12: Ovarian ablation or suppression versus not in ER+ (or ER unknown) disease, by treatment type and 10-year entry age groups (<40 or 40-49 only): event rate ratios

Recurrence / Woman-years



Breast cancer mortality / Women

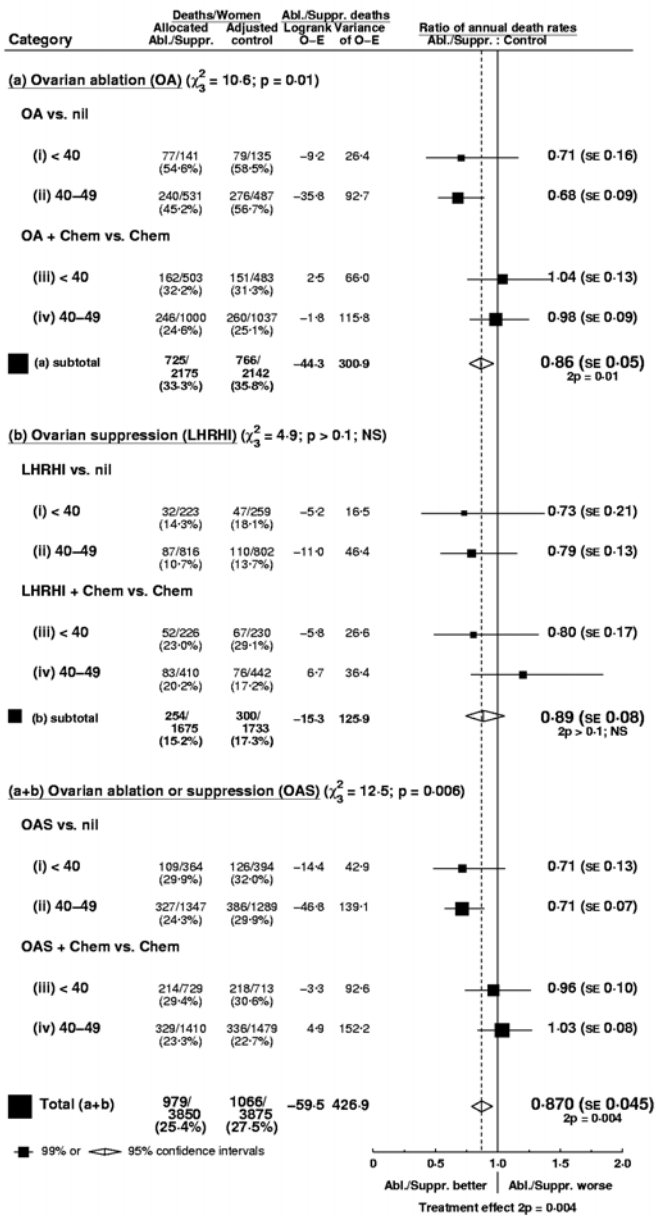


Figure 13: Ovarian ablation or suppression versus not in ER+ (or ER unknown) disease: 15-year probabilities of recurrence and of breast cancer mortality (7601 women, with entry age <50: 47% ER unknown, 61% N+)

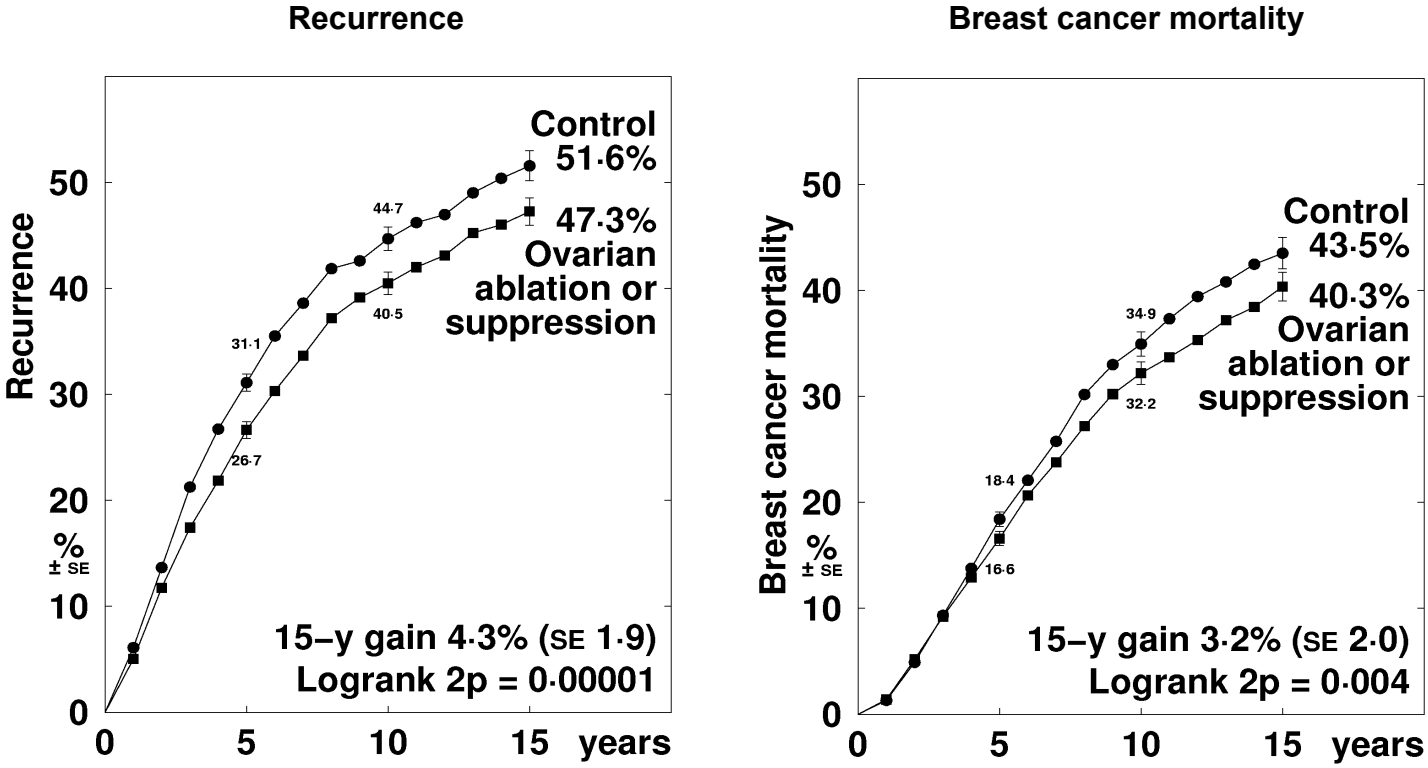
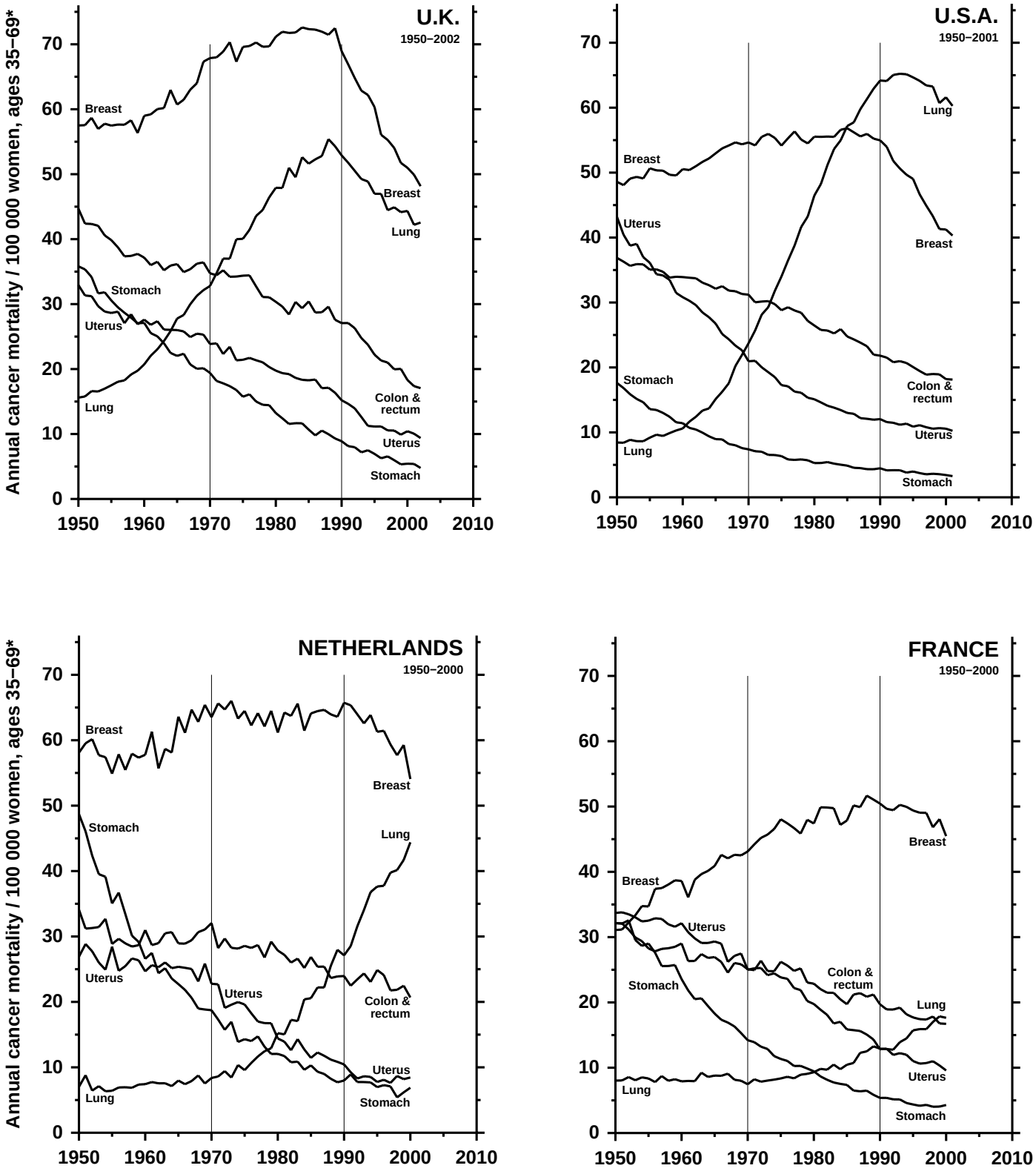


Figure 14: Trends since 1950 in age-standardised (35-69) death rates, comparing breast and selected other types of cancer: UK, USA, Netherlands and France



*Mean of annual rates in the component 5–year age groups

Source: WHO mortality & UN population estimates