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Adjuvant polychemotherapy in oestrogen-receptor-poor breast cancer: meta-analysis of individual patient data from the randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)*

Running Head: Adjuvant chemotherapy in ER-poor breast cancer

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Summary

Background The long-term effects of adjuvant polychemotherapy regimens in oestrogen receptor poor (ER-poor) breast cancer, and the extent to which these effects are modified by age or tamoxifen use, can be assessed by an updated meta-analysis of individual patient data from the randomised trials.

Methods Collaborative meta-analyses of individual patient data for about 6000 women with ER-poor breast cancer in 46 trials of polychemotherapy versus not (non-taxane-based polychemotherapy, typically about 6 cycles; trial start dates 1975-96, median 1984) and about 14 000 women with ER-poor breast cancer in 50 trials of tamoxifen versus not (some trials in the presence and some in the absence of polychemotherapy; trial start dates 1972-93, median 1982).

Results In women with ER-poor breast cancer, polychemotherapy significantly reduced recurrence, breast cancer mortality and death from any cause, among those aged less than 50 years and among those aged 50-69 years at entry into the trials of polychemotherapy vs not. Among those aged less than 50 years (1907 women, 15% node-positive), the 10-year risks were: recurrence 33% vs 45% (ratio of 10-year risks 0.73, $2p<0.00001$), breast cancer mortality 24% vs 32% (ratio 0.73, $2p=0.0002$) and death from any cause 25% vs 33% (ratio 0.75, $2p=0.0003$). Among those aged 50-69 years (3965 women, 58% node-positive), the 10-year risks were: recurrence 42% vs 52% (ratio 0.82, $2p<0.00001$), breast cancer mortality 36% vs 42% (ratio 0.86, $2p=0.0004$) and death from any cause 39% vs 45% (ratio 0.87, $2p=0.0009$). Few were aged 70 or more years. Tamoxifen had little effect on recurrence or death in women who were classified in these trials as having ER-poor disease, and did not significantly modify the effects of polychemotherapy.

Interpretation In women with ER-poor breast cancer aged under 50 and 50-69 years, these older adjuvant polychemotherapy regimens were safe (ie, had little effect on mortality from causes other than breast cancer) and produced substantial and definite reductions in the 10-year risks of recurrence and death. Current and future chemotherapy regimens could well yield considerably larger proportional reductions in breast cancer mortality.

Introduction

The natural history of early breast cancer depends on both the nodal status and the biological characteristics of the primary tumour, such as the oestrogen receptor (ER) status. If the excised primary tumour is ER-poor then the 5-year recurrence rate is relatively high and hormonal therapy has little effect on it (1,2), so the effects of adjuvant chemotherapy are of particular interest. In advanced breast cancer, the effects of chemotherapy on macroscopic primary or secondary lesions can be observed directly and may be substantial (3-9). In early disease, however, the effect of chemotherapy is not directly observable in individual patients and trials are needed. Because any one trial of adjuvant chemotherapy may include too few patients with ER-poor disease for statistical stability, the short-term and, particularly, the long-term effects on recurrence and mortality in such women are best studied by periodically updated meta-analyses of all relevant randomised trials.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) was set up in 1984-85 to coordinate 5-yearly meta-analyses of centrally collected data from every woman in all randomised trials of the treatment of early breast cancer. The reports from the 1990 (second) and 1995 (third) cycles of the collaboration indicated that, taking all types of primary tumour together, the effects of adjuvant chemotherapy on long-term outcome were, on average, greater at younger ages (<50 years) than at older ages (mainly 50-69 years, as few women older than this had been studied) (10,11). The report from the 2000 (fourth) cycle (1) showed that, at ages 50-69 years, the effects of chemotherapy on mortality were, on average, somewhat greater than had been indicated by the previous EBCTCG

reports. It was, however, still difficult to determine reliably the effects in particular types of patient.

Unless indicated otherwise, in the present report the term chemotherapy denotes prolonged adjuvant treatment with various standard combinations of older drugs: eg, about 6 courses of CMF (45% of randomised women) or about 6 courses of FAC or FEC (31% of randomised women) (C=cyclophosphamide, M=methotrexate, F=5-fluorouracil, A=doxorubicin [synonym: adriamycin], E=epirubicin). None of the regimens studied were taxane-based or deliberately myeloablative.

Various hypotheses have been raised about the efficacy of chemotherapy in ER-negative breast cancer. *In vitro* studies suggested that the presence of tamoxifen might reduce the uptake and cytotoxic activity of 5-fluorouracil and melphalan in ER-negative breast cancer cell lines (12). An observational study on women with advanced disease concluded that an objective response to chemotherapy was more likely in ER-negative than in ER-positive disease (3). But, later such studies did not replicate this finding and concluded either that the response to chemotherapy does not correlate with ER-status (4,5), or even that it is increased by ER-positivity (6-9).

A meta-analysis of the trials of single-cycle peri-operative polychemotherapy (PeCT) versus no adjuvant therapy (13), including a total of some 4000 patients (1000 with ER-poor disease), indicated an effect on long-term survival that was less definite than in the trials of more prolonged polychemotherapy. These PeCT trials included both pre- and post-menopausal women, irrespective of ER status,

and did not give adjuvant tamoxifen. In one of the PeCT trials, however, a significant reduction in recurrence was seen just in the subgroup of 160 postmenopausal women with ER-poor disease (14,15). In view of this, it was suggested that chemotherapy might be particularly effective in older women with ER-poor disease and no tamoxifen, and that the EBCTCG analyses of prolonged chemotherapy should address this explicitly (16). It was therefore agreed that the first report from the 2005/6 (fifth) cycle should address directly the totality of the evidence regarding the effect of adjuvant polychemotherapy versus no chemotherapy in ER-poor disease, including not only the trials in which no tamoxifen was given but also those in which tamoxifen was given to women in both arms of the trial.

Materials and methods

The methods of seeking collaboration and of data collection, collation, checking, and presentation are as in the previous EBCTCG report (1), as are the roles of the funding sources. The EBCTCG has received ethical approval from the Oxford Research Ethics Committee. In the present cycle, trials were eligible if they began by 2000 (range of actual start dates 1972-96) and, for most of them, the latest available follow-up information was re-sent to Oxford in 2005-06. Analyses are by allocated treatment and, as previously, recurrence means the first detection after randomisation of any breast cancer (local, contralateral or distant). For the present (2005/6) cycle, information was available on about 20 000 women with ER-poor disease in trials of chemotherapy and/or tamoxifen (Table 1). Of these, about 6000 were in 46 trials of polychemotherapy versus not (chemotherapy alone versus no adjuvant therapy: about 3000 women; chemotherapy and tamoxifen

versus tamoxifen alone: about 3000 women) and about 14 000 were in 50 trials of tamoxifen versus not (mostly chemotherapy and tamoxifen versus the same chemotherapy alone).

Forest plots in the website appendix to this report give separately, for each of these 96 trials and for the 4 trials of PeCT, a brief summary of the treatment regimen tested and of whether the active treatment group was allocated both chemotherapy and tamoxifen, the numbers of women with ER-poor disease (treatment versus control) and the main results among these women (webfigures 9-11). Further details of the trials and treatment regimens are given in the website appendix to the previous EBCTCG report (1).

In this report, ER-poor tumours are defined by receptor measurements done many years ago, and different techniques were used in different trials (or, sometimes, even in the same trial). They therefore include not only tumours with no ER expression at all (ER-absent) but also tumours with a little ER expression (<10 femtomoles per mg cytosol protein, where quantitative measurements were available) and, perhaps, some more strongly ER-positive tumours with false negative receptor measurements.

Statistical methods

Detailed descriptions of the main statistical methods have previously been published (1, 17) and are also available online (17). Logrank statistics are used to assess the effects (active versus control) on outcome, and to estimate (by the one-step method) event rate ratios and their confidence limits (1). Results for fine subdivisions are plotted as black squares with horizontal lines that denote 99% confidence intervals (99% CIs). The use of 99% rather than 95% CIs is to help make some allowance for multiple testing. Results for totals and subtotals are plotted as white diamonds that denote 95% CIs. To test for a trend between strata (eg, of age) in the effects of treatment, suppose that stratum number s (s = 1,2…) has logrank statistics (o-e) and v (with grand total over all strata O-E and V). 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), as before (1). The variance of T, var(T), is then the sum, one term per stratum, of $(s-m)^2/v$. The trend test statistic (ie, the change from one stratum to the next in the log of the event rate ratio) is then T/var(T), which has variance 1/var(T). Tests of whether two trends are the same involve subtraction of the corresponding trend test statistics from each other. A chi-squared statistic on one degree of freedom (χ_1^2) for testing whether some quantity Q differs significantly from zero is given by $Q^2/var(Q)$.

The following two questions are formally equivalent: (i) whether tamoxifen reduces the proportional efficacy of chemotherapy, and (ii) whether chemotherapy reduces the proportional efficacy of tamoxifen. This can be illustrated by considering a hypothetical 2x2 factorial trial of chemotherapy, tamoxifen, both, or neither.

Suppose that in one particular stratum (of follow-up duration and of patient characteristics) the event rates in the 4 treatment arms are, respectively, chem, tam, both, & nil. Two different chemotherapy comparisons can be made, and then compared. For the efficacy of chemotherapy on its own the rate ratio is A=chem/nil, and for the efficacy of chemotherapy in the presence of tamoxifen (ie, with tamoxifen in both groups) the rate ratio is B=both/tam. Comparing A and B to answer question (i), the value of B/A will tend to be less than 1 if tamoxifen reduces the efficacy of chemotherapy. Likewise, two different tamoxifen comparisons can be made, and then compared. For the efficacy of tamoxifen on its own the rate ratio is C=tam/nil, and for the efficacy of tamoxifen in the presence of chemotherapy (ie, with chemotherapy in both groups) the rate ratio is D=both/chem. Comparing C and D to answer question (ii), the value of D/C will tend to be less than 1 if chemotherapy reduces the efficacy of tamoxifen. B/A is, however, identically equal to D/C, illustrating the equivalence in principle of questions (i) and (ii).

Role of the funding sources

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Results

Figures 1-4 describe various analyses of time to first recurrence. Website figures 1-4 [ref to URL to be inserted] show the same recurrence analyses, and also give the corresponding analyses for breast cancer mortality and death from any cause.

Proportional risk reductions

Recurrence — For the trials of polychemotherapy versus not, the recurrence rate ratios are subdivided in figures 1 and 2 both by age when randomised (entry age <50, 50-59 or 60-69 years; few were older than this) and by the use of tamoxifen (ie, by the absence or presence of adjuvant tamoxifen in both of the treatment regimens being compared). In figure 1 the analyses are subdivided first by the use of tamoxifen and then by age, while in figure 2 the same analyses are subdivided first by age and then by the use of tamoxifen.

Relevance of age to effects of chemotherapy (figure 1) — Figure 1(a) describes the trials of polychemotherapy alone (ie, in the absence of tamoxifen), and suggests a substantial proportional risk reduction that is approximately independent of age (although, if each age range is considered separately, then the confidence intervals for the effects at ages 50-59 and 60-69 years are both wide). In contrast, in the aggregate of all trials of polychemotherapy versus not (section a+b in the lower part of figure 1), the proportional risk reduction appears to be about twice as great at entry age <50 as at entry age 60-69, and there is a conventionally significant trend towards greater efficacy of chemotherapy at younger ages (treatment versus control recurrence rate ratios,0.61 [SE 0.07] at entry age <50 years and 0.81 [SE 0.07] at entry age 60-69 years; test for trend of

greater effect at younger ages 2p=0.03). This is because, in the presence of tamoxifen, there is a trend towards a greater effect of chemotherapy at younger ages: figure 1(b). The apparent difference between the trends with age in figures 1(a) and 1(b) is, however, not conventionally significant (2p=0.09; footnote to figure 1). That is, the apparently null trend with age in figure 1(a) and the apparently strong trend with age in figure 1(b) are both compatible with the moderate trend with age in the overall results in figure 1(a+b).

Irrelevance of tamoxifen to effects of chemotherapy (figures 2&3) — Within each of the age ranges <50, 50-59 and 60-69 years in figure 2, tamoxifen does not significantly modify the effects of chemotherapy. In the first two age ranges (<50 and 50-59: figures 2(a) and 2(b)), chemotherapy appears somewhat more effective in the presence of tamoxifen, whereas in the third (60-69: figure 2(c)) it appears somewhat less effective in the presence of tamoxifen. In no age range, however, are these apparent differences in efficacy statistically significant; nor is an overall age-stratified test of whether tamoxifen influences the efficacy of chemotherapy (chi-squared=0.1 on 1 degree of freedom, 2p=0.83: footnote to figure 2).

Although figure 2(c) could be taken as evidence that tamoxifen reduces the efficacy of chemotherapy in women aged 60-69, figure 3(c) provides evidence against this. For, in figure 3(c) the effect of tamoxifen plus chemotherapy actually appears somewhat better than that of chemotherapy alone. This is the opposite of what would be expected if tamoxifen reduced the efficacy of chemotherapy. Taken together, the opposite interactions in figures 2(c) and 3(c) (neither of which

is statistically significant), suggest that tamoxifen is of little relevance to the efficacy of chemotherapy in ER-poor disease. (see Statistical methods for illustration of the equivalence of these two questions)

Mortality — The results for breast cancer mortality and death from any cause (website figures 1-3) are similar to those for recurrence (figures 1-3), except that the trends with age do not reach statistical significance. Also, if the 60-69 age range is considered on its own then the mortality reductions in the trials of chemotherapy are not conventionally significant in the absence of tamoxifen, in the presence of tamoxifen or in both combined (age 60-69 only: overall relative risks 0.90 [SE 0.08] for breast cancer mortality and 0.91 [SE 0.07] for death from any cause: both 2p=0.2).

Absolute reductions in 10-year risks

Recurrence and mortality — Figure 4 shows the 10-year recurrence risks for polychemotherapy versus not, subdivided as in figures 1 and 2 by age and by the use of tamoxifen, while figure 5 shows the corresponding 10-year results for death from any cause. The 10-year differences just in breast cancer mortality are similar to those in death from any cause (website figure 4).

In figures 4 and 5 (as in figure 1) the upper parts (a) give the age-specific results in the absence of tamoxifen, the middle parts (b) give the age-specific results in the presence of tamoxifen, and the lower parts (a+b) give the overall age-specific results. In no age range is the difference significant between (a) the absolute

effects of chemotherapy in the absence of tamoxifen and (b) the absolute effects of chemotherapy in the presence of tamoxifen.

The overall results (ie, the lower parts (a+b) of figures 1, 4 and 5) are, of course, based on larger numbers than (a) or (b) alone. Even here information is available on only about 2000 women in each of the 3 age ranges (<50, 50-59 and 60-69 years). This is still not enough for results in individual age ranges to be numerically stable, particularly for mortality in the older age ranges. Thus, although the mortality reduction at ages 60-69 is not conventionally significant on its own, it should be interpreted in the context of the highly significant mortality reduction at ages 50-59. In assessing the effects of chemotherapy in older women, it may be appropriate to consider the data in these two 10-year age ranges together, given the limited numbers randomised.

The overall results (a+b) in this 20-year age range (50-69) and in younger women are given in figure 6 (and in website figures 5 and 6), which compares the findings for recurrence, breast cancer mortality and death from any cause. In both age ranges (<50 and 50-69 years), the effect of chemotherapy on the 10-year probability of death from any cause is highly significant (age <50 years 24.9% vs 33.0% dead, absolute difference 8.1% [SE 2.3], 2p=0.0003; age 50-69 years 39.0% vs 45.0% dead, absolute difference 6.0% [SE 1.7], 2p=0.0009). The effects on death from any cause are about the same as the effects on breast cancer mortality (figure 6), suggesting little effect of these regimens on 10-year non-breast-cancer mortality, even at 50-69 years of age.

Proportional risk reductions by nodal status

Among the younger women (<50 years) in these trials, 85% had node-negative disease and only 15% had node-positive disease, whereas 58% of those aged 50-69 years had node-positive disease. Recurrence rates were much higher in node-positive than in node-negative women but, despite this, neither the age-stratified nor the age-specific proportional risk reductions were significantly affected by nodal status (age-stratified: χ_1^2 = 0.4 [2p=0.53]; age-specific: χ_1^2 =0.3, 0.0, and 0.4 [2p=0.6, 0.92, and 0.53] for age-groups <50, 50-59, and 60-69 respectively). The corresponding results for breast cancer mortality and death from any cause are given in website figure 7.

Proportional risk reductions in other subgroups

The three parts of website figure 8 give further subgroup analyses with respect to type of chemotherapy, menopausal status (stratified by age), nodal status (stratified by age), use of tamoxifen (in both treatment groups), tumour size (in all women, and just in women with node-negative disease), tumour differentiation (ditto), and progesterone receptor status. None of these factors significantly modifies the proportional risk reductions produced by chemotherapy. Although the anthracycline-based FAC or FEC regimens appear somewhat more promising than older regimens such as CMF, more reliable evidence for this conclusion comes from the much larger numbers in the directly randomised comparisons of such regimens versus CMF (1). Website figure 8 also shows that 25% of the recurrences were specified to be local or contralateral (and some of the unspecified ones may also have been local or contralateral); that the proportional

reductions in local and in distant recurrence were similar; and that the main effect on recurrence was in just the first few years after randomisation, as already seen in figure 4.

Website figure 9 gives the results separately for each of the 46 trials of chemotherapy versus not, and website figure 10 gives the results separately for each of the 50 trials of tamoxifen versus not. For completeness, website figure 11 gives the results separately for each of the 4 trials of a single course of peri-operative polychemotherapy (PeCT) versus no adjuvant chemotherapy.

Discussion

A large amount of data from previous trials is now available, and the present results show that long-term follow-up of such trials can continue to yield useful results. The effects of adjuvant polychemotherapy on recurrence and mortality are substantial, and statistically definite, both for women with ER-poor disease aged less than 50 and for those aged 50-69 years (figure 6). How should these findings inform the current and future care of such women? The chemotherapy was probably not given as intensively as it would be now, particularly in older women, and none of the patients in the present analysis received newer drugs such as taxanes. Hence, current and future adjuvant regimens could well produce substantially greater proportional risk reductions in recurrence and breast cancer mortality than the regimens tested in these trials.

Assessing the effects of chemotherapy

Although tamoxifen would not nowadays be used in ER-negative disease, it was given to many of the women in these trials. To estimate the absolute effects of chemotherapy on recurrence and mortality that would have been seen in these trials if no tamoxifen had been used, two approaches are possible. One is chiefly to emphasise just the upper parts (a) of figures 1, 4, and 5 on the grounds that these were the only chemotherapy comparisons in which tamoxifen was not given. The other is chiefly to emphasise the overall results in the lower parts (a+b) of these figures on the grounds that, as tamoxifen is of little relevance to the effects of chemotherapy in ER-poor disease, this is the totality of the randomised evidence comparing chemotherapy versus no chemotherapy. The former approach has the advantage of simplicity, but it also has the disadvantage of smaller numbers of women and hence larger random errors, particularly if the age ranges 50-59 (943 women) and 60-69 (only 539 women) are considered in isolation from each other.

In the age ranges <50 and 50-59 years, the relative risks and the 10-year gains are similar in the upper parts (a) and lower parts (a+b) of figures 1, 4 and 5, so both approaches would yield similar estimates of benefit, although the findings at ages <50 and 50-59 are more highly significant with the larger numbers in the lower parts (a+b). In the age range 60-69 years there is independent evidence that tamoxifen does not directly or indirectly (eg, by modifying compliance) reduce the efficacy of chemotherapy in this age range (figure 3(c)). Therefore, it may be more appropriate to emphasise all of the randomised evidence (part (a+b); 1770 women) rather than just a fraction of it (part (a); 539 women).

Age-specific overall results

In the overall results (a+b), the mortality reduction is highly significant when the age ranges 50-59 and 60-69 are combined, as in figure 6. This, together with the significant recurrence reductions in both age ranges (see figure 4), indicates that there is an appreciable mortality reduction not only at ages 50-59 but also at ages 60-69, even though the latter reduction may be somewhat smaller. At present there is very little direct information on the benefits or hazards of chemotherapy in women over the age of 70, as few older women were randomised in these trials.

At least a quarter of the recurrences were isolated local or contralateral recurrences, and the 10-year reduction in mortality is only about two-thirds as great as the 10-year reduction in recurrence (figure 6). In both of the age ranges in figure 6 (<50 and 50-69 years) the absolute reduction in the 10-year risk of death from any cause is about as great as the reduction in breast cancer mortality, in line with other evidence that these chemotherapy regimens had, on average, little adverse effect on mortality from other causes during the first 10 years after treatment (1).

Proportional and absolute mortality reductions

In considering the general implications of these trial results, it is appropriate to consider mortality from breast cancer and mortality from other causes separately. For breast cancer, the proportional risk reductions may well be more stable than

the absolute risk reductions, as was the case with nodal status (web figure 7). They are, therefore, more likely to be widely generalisable. Approximate proportional risk reductions can be obtained from the ratio, treatment versus control, of the 10-year breast cancer mortality risks in figure 6. Mortality from causes other than breast cancer will depend mainly on age, on various other epidemiological risk factors, and on whether some life-threatening disease other than breast cancer is already present.

For women less than 50 years of age at diagnosis the ratio of these 10-year breast cancer mortality risks is 0.73 (23.6% vs 32.2%), while for women 50-69 years of age it is 0.86 (36.0% vs 42.1%: figure 6). These ratios suggest that, in the absence of other causes of death, a 10-year breast cancer mortality of 25% might be reduced to about 18% (age <50) or 21% (age 50-69), and that a 10-year risk of 50% might be reduced to about 37% (age <50) or 43% (age 50-69). These risk reductions are approximately as indicated (for regimens such as FAC or FEC) by the previous EBCTCG report (1). If, however, the best of the drug combinations tested in these trials were to be given optimally then appreciably better results might be achieved.

Overall, tamoxifen appears to be slightly protective in women who were classified as having ER-poor disease (event rate ratio for each endpoint 0.94 [SE 0.03] in website figure 10). However, this could well be because some of the women who were classified as having ER-poor disease in the earlier trials did, in fact, have some ER expression and, hence, some ER-mediated treatment effects. This apparent protective effect was somewhat stronger in the trials of up to 2 years of

tamoxifen (which typically began around 1980), whilst in the trials of 3 or more (mean: 5) years of tamoxifen versus not (which typically began more recently and involved a total of some 6000 women who were classified as having ER-poor disease) there was no apparent protective effect (web figure 10), suggesting that even 5 years of tamoxifen has little or no effect on disease that really is ER-absent.

Generalisability

Current and future chemotherapy regimens could be substantially more effective than the regimens in these trials and could, therefore, yield substantially better proportional risk reductions and future EBCTCG reports will address this directly. If in some categories of patients with ER-absent disease (as, for example, those with small, well-differentiated node-negative tumours) the absolute risk is low even without adjuvant chemotherapy then the absolute benefit from a given proportional risk reduction will also be low. If, however, the risk of recurrence in any category of untreated ER-absent disease is substantial then even these older regimens could produce an appreciable absolute reduction in it, as indicated by figure 6.

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Conflict of interest
The writing committee and secretariat declare that they have no conflict of interest.

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Table 1: Numbers of women with ER-poor disease, by age, in trials of polychemotherapy (Poly) &/or tamoxifen (Tam) that began before 2000

	Age (years) at entry				
	<50	**50-59**	**60-69**	**70+**	**Any**
Polychemotherapy versus Not (ie, vs no adjuvant chemotherapy)					
(a) Poly alone vs Nil	1722	943	539	35	3239 (24%[†])
(b) Poly + Tam* vs same Tam (ie, vs Tam alone)	185	1252	1231	116	2784 (24%[†])
(a+b) Total: Poly vs Not (46 trials)	1907	2195	1770	151	6029[‡]
Tamoxifen versus Not (ie, vs no adjuvant tamoxifen)					
(a) Tam alone vs Nil	766	1041	1097	297	3201
(b) Poly + Tam[§] vs same Poly (ie, vs Poly alone)	5546	3009	1653	299	10507
(a+b) Total: Tam vs Not (50 trials)	6312	4050	2750	596	13717[‖]

Control patients in 3-way trials (or trial strata) count only once.
Numbers of woman-years are given in web figures 1-3.

*Tamoxifen and polychemotherapy were given concurrently for 83% of women in these trials and sequentially in the remainder.

[†]Percentage of women in trials of regimens containing anthracyclines

[‡] Includes 6 with age not known

[§]Tamoxifen and polychemotherapy were given concurrently for 85% of women in these trials and sequentially in the remainder.

[‖] Includes 9 with age not known

***Figure 1: Polychemotherapy* versus not in ER-poor disease, subdivided first by type of comparison (absence or presence of tamoxifen in both treatment groups) and then by age at randomisation: event rate ratios for recurrence**

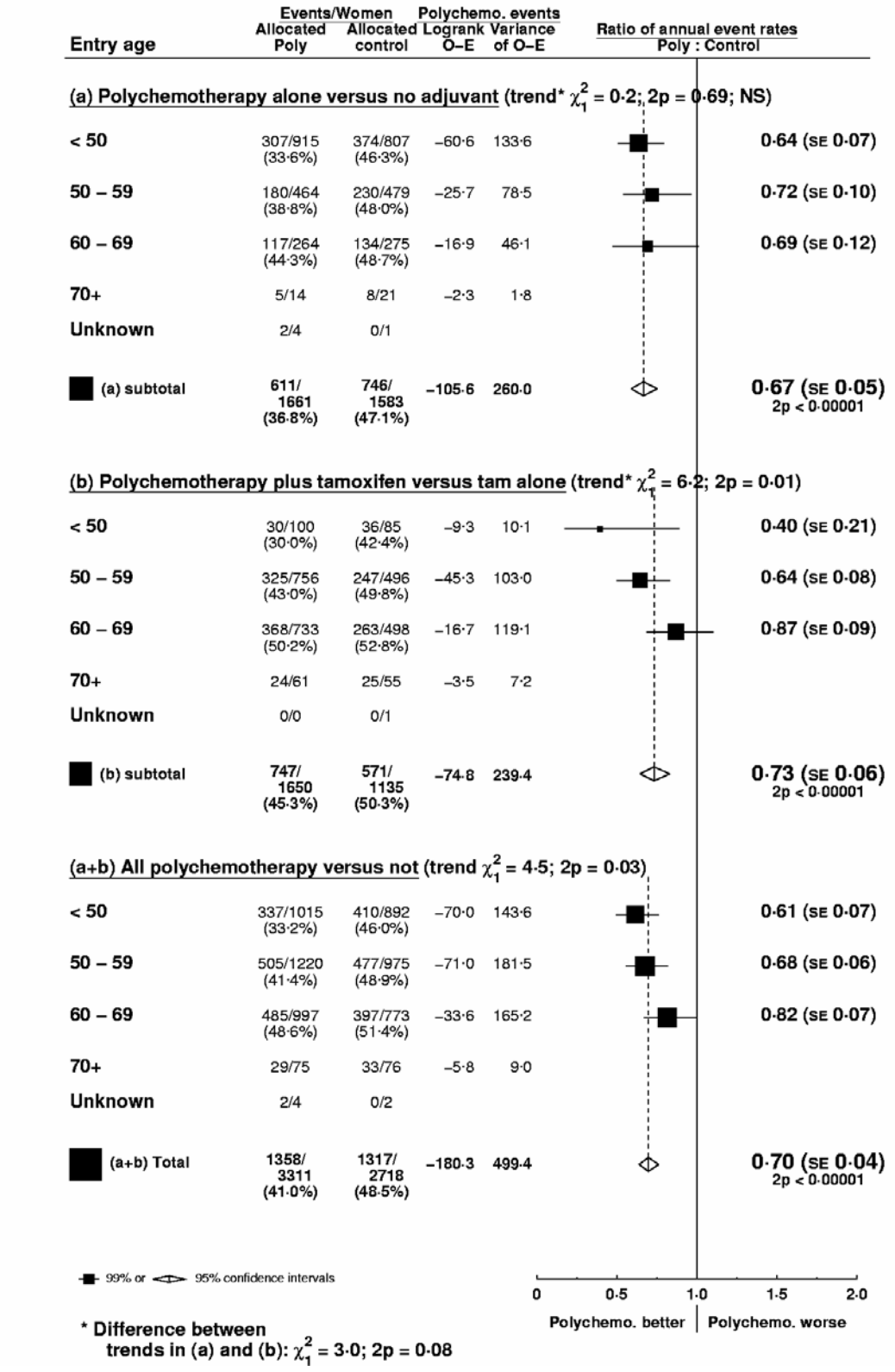


Figure 2: **Polychemotherapy versus not in ER-poor disease, subdivided first by age at randomisation and then by type of comparison (absence or presence of tamoxifen in both treatment groups): event rate ratios for recurrence**

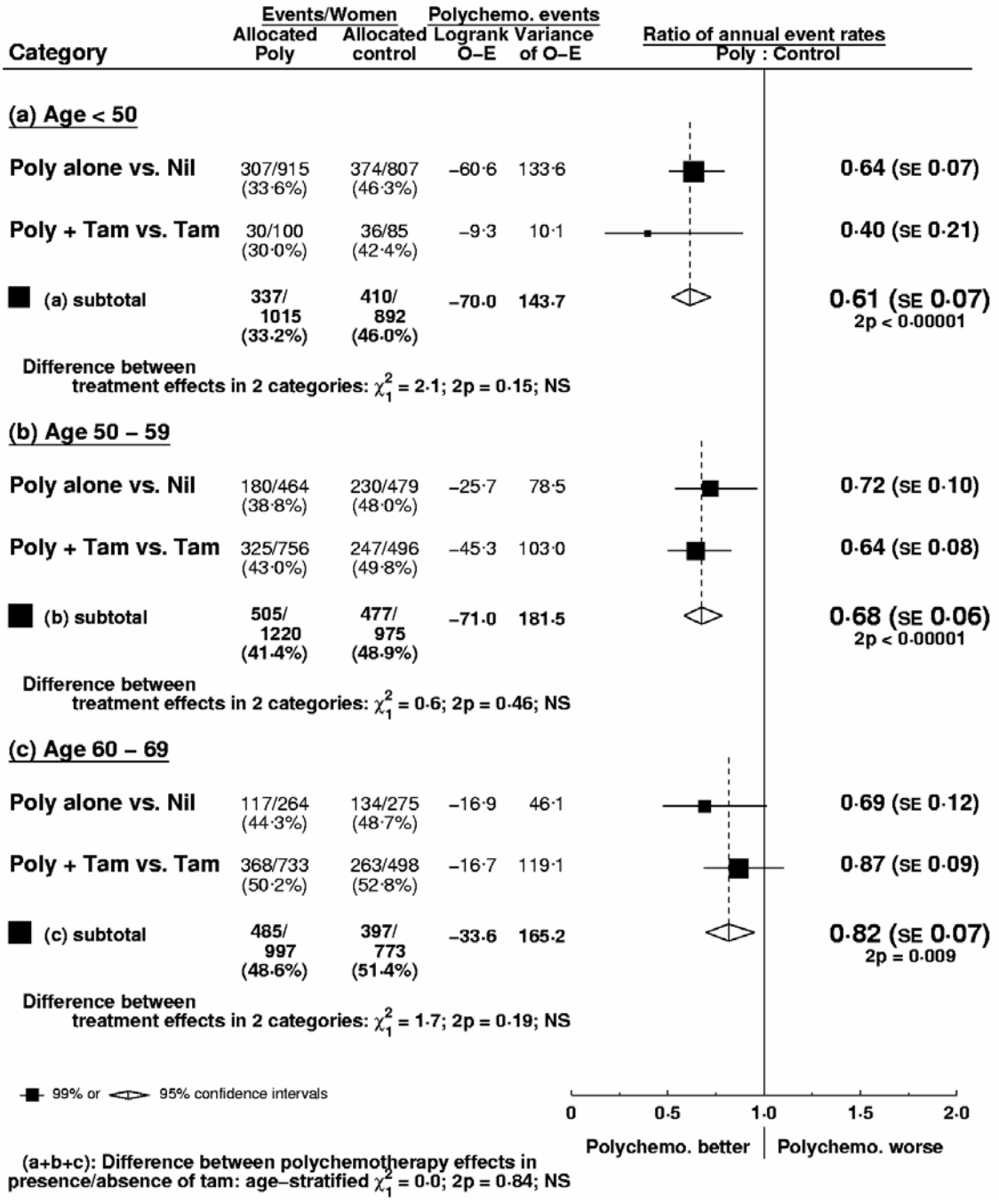
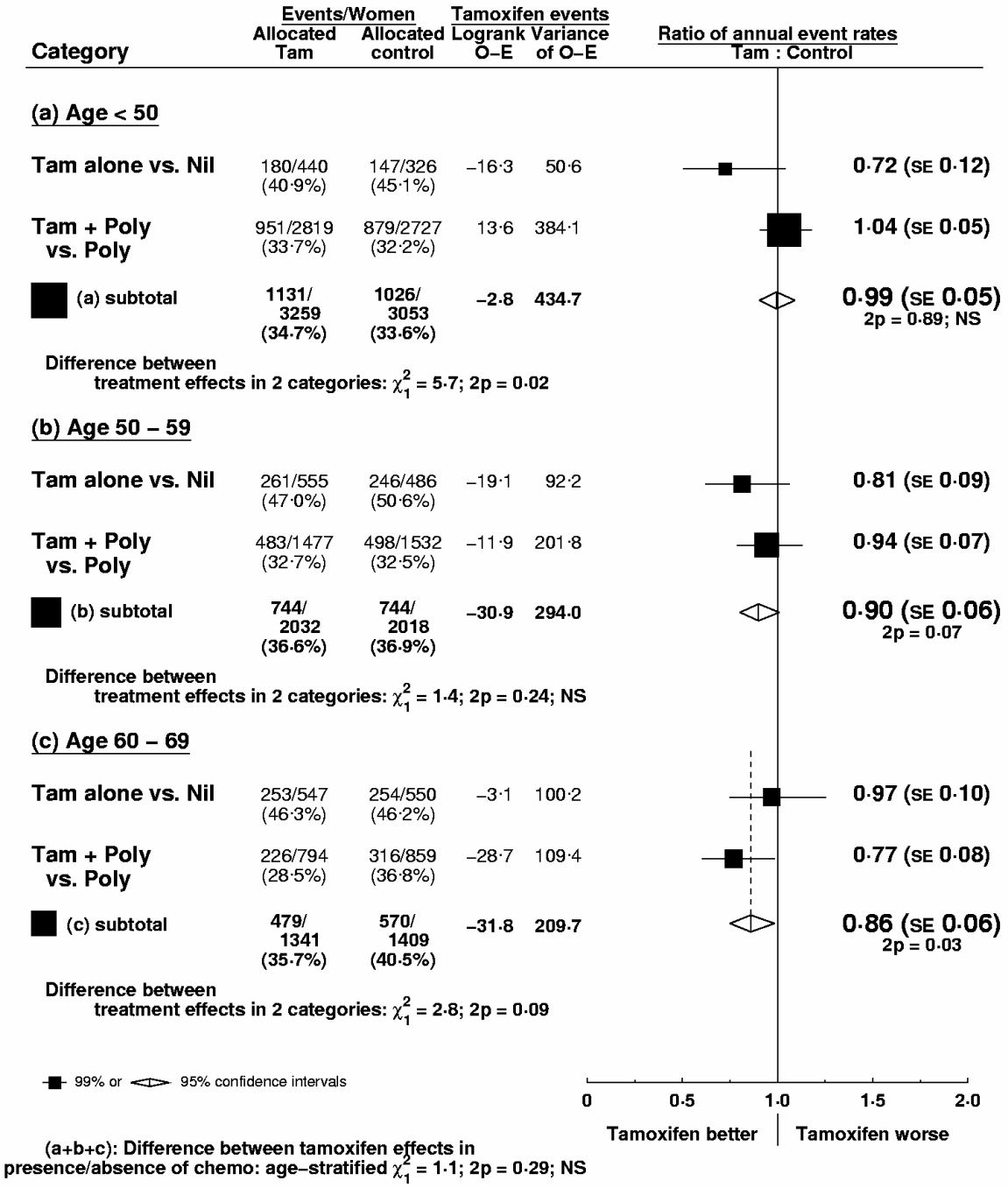


Figure 3: **Tamoxifen versus not in ER-poor disease, subdivided first by age at randomisation and then by type of comparison (absence or presence of chemotherapy* in both treatment groups): event rate ratios for recurrence**



* Polychemotherapy in 29 trials, single-agent chemotherapy in 3.

Figure 4: **Polychemotherapy versus not in ER-poor disease, by type of comparison (absence or presence of tamoxifen in both treatment groups) and age at randomisation: 10-year probabilities of recurrence**

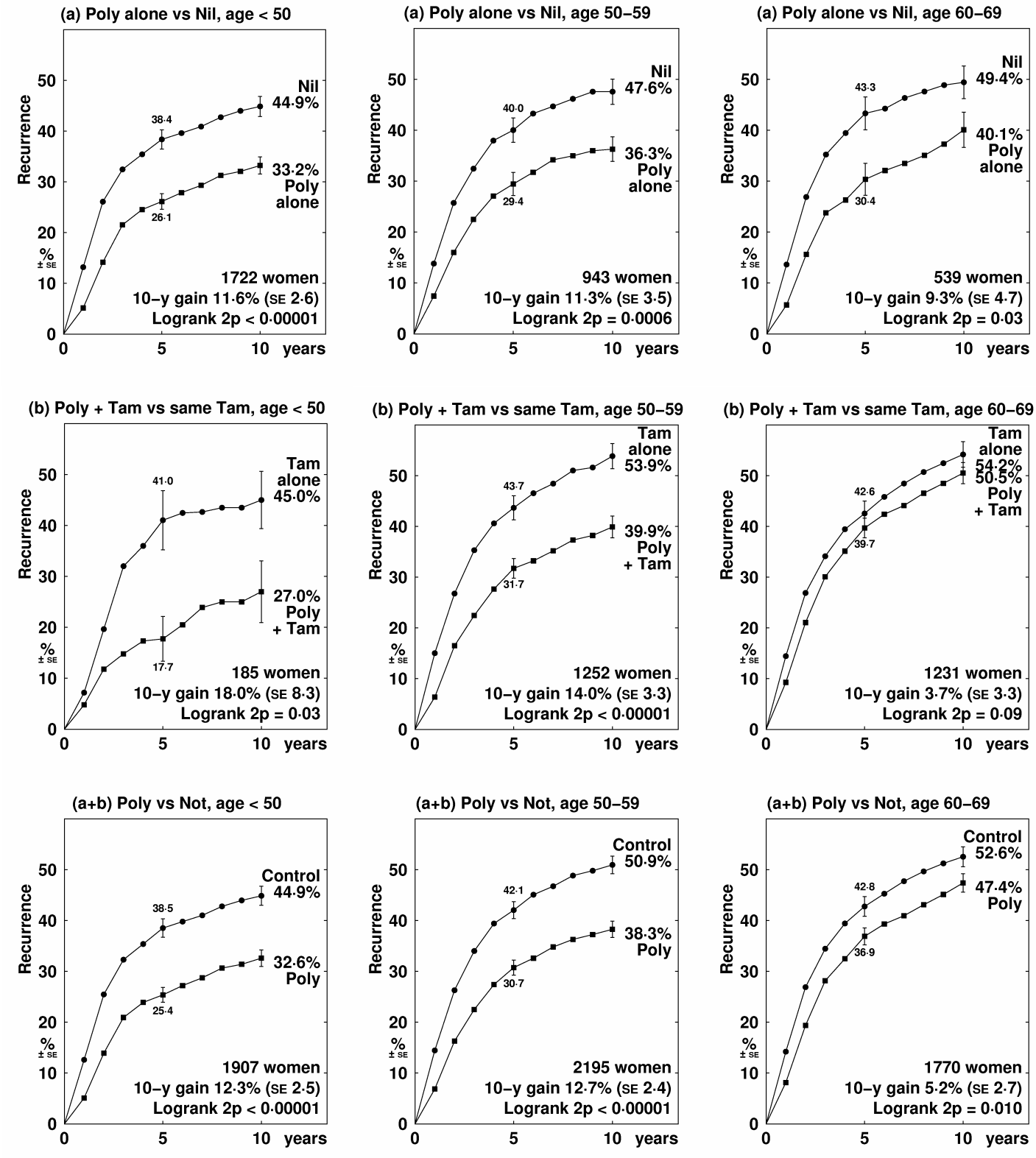


Figure 5: **Polychemotherapy versus not in ER-poor disease, by type of comparison (absence or presence of tamoxifen in both treatment groups) and age at randomisation: 10-year probabilities of death from any cause**

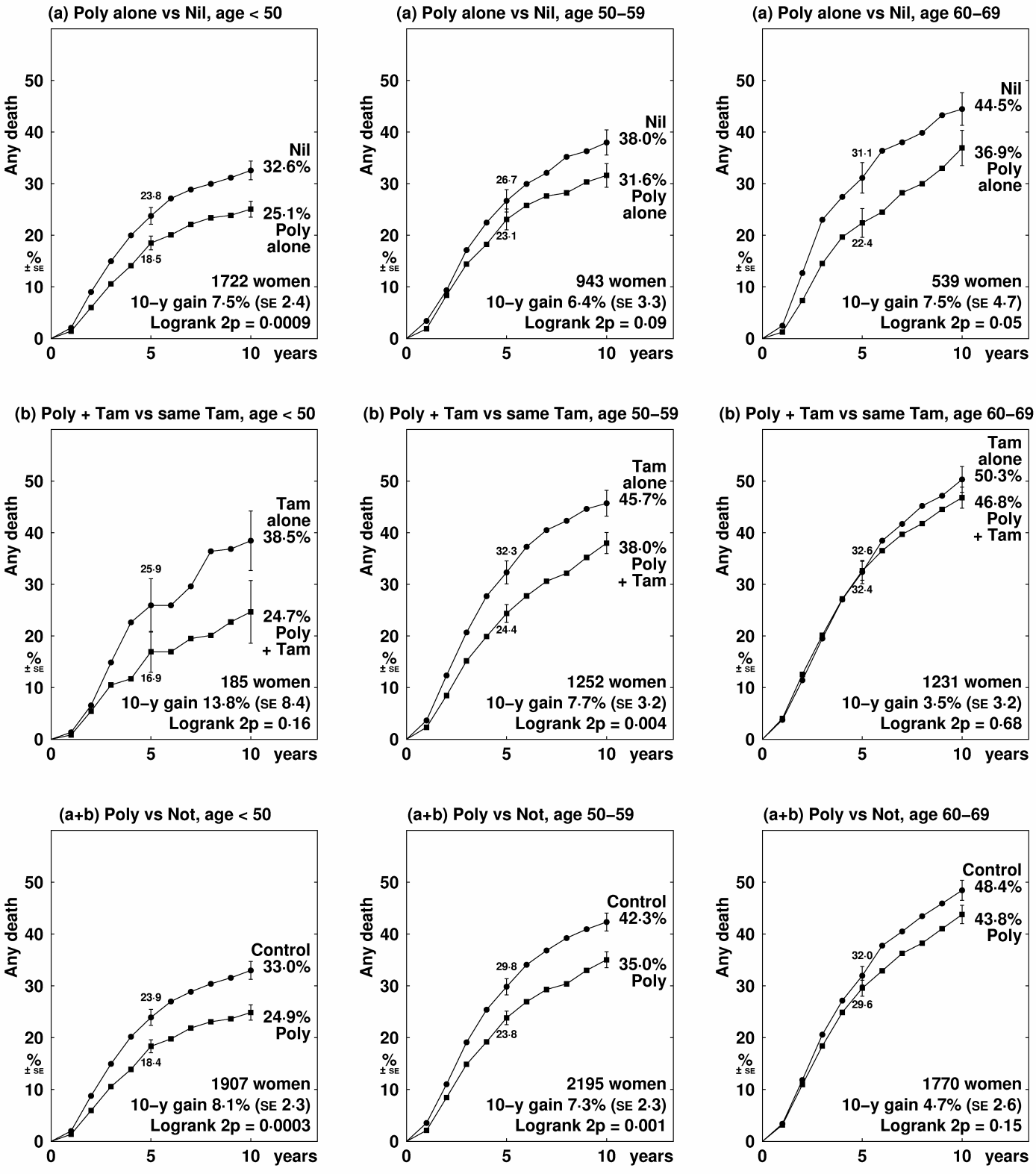
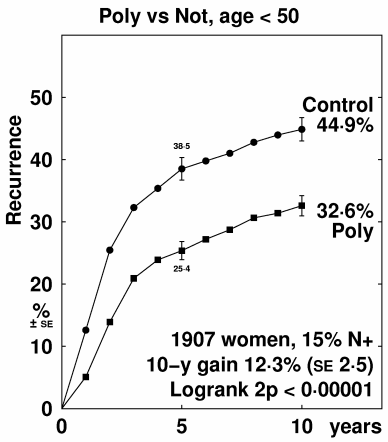
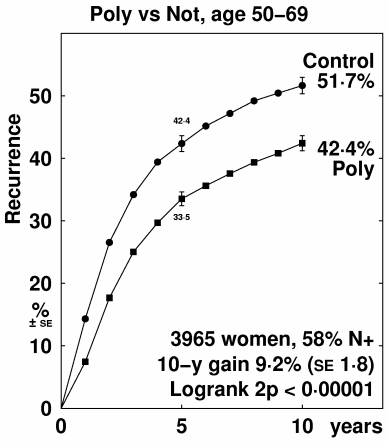


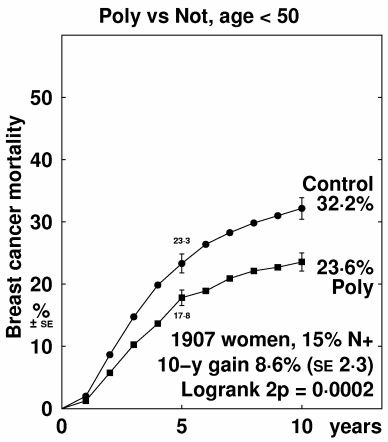
Figure 6: **All trials* of polychemotherapy versus not in ER-poor disease for patients with ages <50 and 50-69 at randomisation: 10-year probabilities of (i) recurrence, (ii) breast cancer mortality and (iii) death from any cause**

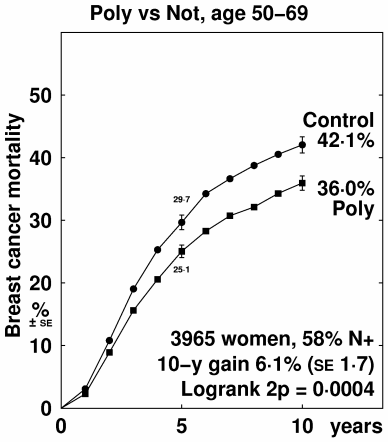
(i) Recurrence



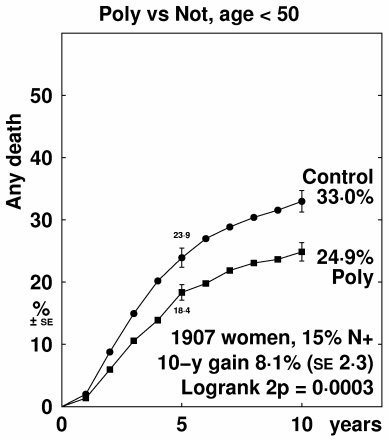


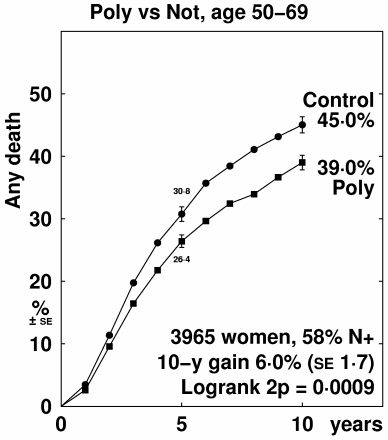
(ii) Breast cancer mortality





(iii) Death from any cause





* *i.e.* comparison (a+b) in Figs. 4 & 5: pooled data from all unconfounded randomised trials of prolonged adjuvant polychemotherapy, irrespective of whether or not tamoxifen was included in both of the treatment regimens being compared.