Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials

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Abstract 300 words, text 3494 words

Summary

Background As trials of 5 years of tamoxifen in early breast cancer mature, the relevance of hormone receptor measurements (and other patient characteristics) to long-term outcome can be assessed increasingly reliably.

Methods Collaborative meta-analysis of individual patient data from 20 trials (n=21,457) of about 5 years of tamoxifen *vs* no tamoxifen, with about 80% compliance. Receptor (ER/PR) positivity generally meant ≥10 fmol/mg cytosol protein. Recurrence and death rate ratios (RR±1SE) were from logrank analyses by allocated treatment.

Findings In ER+ disease (n=10,645; 13-year median follow-up of survivors), allocation to ~5 years tamoxifen substantially reduced recurrence rates both during and after treatment (RR=0.53±0.03 and 0.68±0.06 during years 0-4 and 5-9 [both 2p<0.00001], but RR=0.97±0.10 during years 10-14). This included similar proportional reductions in contralateral, local and distant recurrence (each 2p<0.00001). The effects were similar, and highly significant, in ER+PR+ and ER+PR– disease. The recurrence reduction was substantial even in marginally ER+ disease and somewhat greater in strongly ER+ disease (RR=0.67±0.08 and RR=0.52±0.07 for ER measurement 10-19 and ≥200 fmol/mg, both 2p<0.00001). Proportional reductions were approximately independent of age, nodal status or other treatment, so absolute recurrence reductions from tamoxifen depend on absolute 10-year recurrence risks (after any chemotherapy) without tamoxifen. Breast cancer mortality was reduced by about one-third throughout the first 15 years (RR=0.71±0.05, 0.66±0.05 and 0.68±0.08, respectively, during years 0-4, 5-9 and 10-14; 2p<0.0001 for extra gain in each period). Overall non-breast-cancer mortality was little affected, despite small absolute increases in thromboembolic and uterine cancer mortality, so all-cause mortality was substantially reduced. In ER– disease, however, tamoxifen had little or no effect on recurrence (again approximately independently of PR status).

Interpretation Five years of adjuvant tamoxifen safely reduces 15-year risks of recurrence and death. ER was the only recorded factor importantly predictive of the proportional reduction.

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Introduction

In the trials of about 5 years of adjuvant tamoxifen vs no tamoxifen for early breast cancer, follow-up now extends well into the second decade since randomisation. This allows better assessment of long-term effects on breast cancer mortality and other mortality, and of the effects of endocrine therapy in disease that is only weakly hormone-receptor-positive. We report updated meta-analyses of data on each individual woman in these trials, relating the effects of tamoxifen to quantitative measurements of hormone receptor levels, use of chemotherapy and other factors.

Methods

Trial identification and data handling procedures have been described previously.[1-3] We sought updated data from each randomised trial in early breast cancer of adjuvant tamoxifen *vs* not where only tamoxifen differed (ie, unconfounded trials). DCIS trials are excluded. Results on only 1-2 years of adjuvant tamoxifen (n=33,000 women randomised) are essentially unchanged since previously reported,[1] and are given only in the webappendix. We report here the trials of longer tamoxifen durations (described as about 5 years of tamoxifen: n=21,457). Most[4-15] (n=12,551) were of exactly 5 years of tamoxifen, four[16-20] (n=2750) were of only 3 years, one[21] (n=2196) re-randomised some at year 2 to stop or continue to year 5, and two[22-25] (n=4215) re-randomised some at year 5 to stop or continue to year 10 (webappendix, pp18-35).

As in previous EBCTCG meta-analyses, information was sought for each individual patient on date of randomisation, allocated treatment, age, menopausal status, tumour diameter, grade, spread to locoregional lymph nodes, and any oestrogen or progesterone receptor (ER/PR) measurements, mostly in femtomoles of receptor protein per mg cytosol protein (fmol/mg). Values ≥10 fmol/mg were, as before[1], described as receptor-positive, with lower values described interchangeably as receptor-negative or receptor-poor. Other receptor-positive or receptor-poor measurements (including the few by immunohistochemistry) were those given only qualitatively. Information was generally unavailable on assay methods and on whether assays were performed centrally or at local hospitals. Within-trial receptor measurement distribution (0, 1-3, 4-9, 10-19, 20-29, 30-49, 50-99, 100-199 and 200+ fmol/mg) was inspected to help assess assay quality, revealing no obvious anomalies.

Follow-up was updated on dates of first recurrence of any breast cancer (locoregional, contralateral [either could include new onset] or distant), other second primary cancer and death. Summary information on a whole-trial (not individual) basis was sought on approximate levels of compliance 2-3 years later with the treatment allocation.

Methods of analysis are as before,[1-3] except that analyses are stratified by trial, age at entry (<45, 45-54, 55-69 and 70+ years), nodal status (node-negative by local criteria, 1-3 nodes positive after axillary clearance, 4+ nodes positive, other or unknown) and ER status (ER-poor, ER+, ER unknown), defining 4x4x3 strata. Logrank statistics and their variances were calculated separately in each stratum and summed, yielding the stratified result. To avoid over-stratification, subgroup analyses of tumour grade or diameter were stratified by only 2 categories of age (50+ years, other/unknown) and nodal status (negative, other/unknown), defining 2x2x3 strata.

Survival curves illustrate time to recurrence, breast cancer mortality (BCM) and any mortality. Annual BCM rates assess the excess mortality when the mortality rate among women without recurrence is subtracted from the overall mortality rate among all women. Correspondingly, BCM rate ratios are estimated from logrank analyses of mortality with recurrence, obtained by subtracting the logrank analyses of mortality without recurrence (ie, censored at recurrence) from those of all mortality.

If a logrank statistic (O−E) has variance V, then, defining $z=(O-E)/\sqrt{V}$ and $b=(O-E)/V$, $RR=\exp(b)$, the event rate ratio, is taken to have $SE=(RR-1)/z$ and 95% CI $\exp(b\pm1.96/\sqrt{V})$. Results cite RR±1SE. P-values (2-sided) are obtained by comparing z with a standard normal distribution, so z=1.96 yields p=0.05 (described in the Figures as 2p, for consistency with previous reports).

Role of funding sources Funding agencies had no role in data collection, analysis, interpretation or reporting. The secretariat had full access to all data and analyses and accept responsibility for this report. Final analyses and a draft report were presented and discussed at a meeting of many trialists, after which a revised report was circulated to all trialists for written comment and revised again. Report preparation and submission was only by the writing committee.

Results

Information is available for 99% (21,457/21,712) of all women known to have been randomised into trials of about 5 years of adjuvant tamoxifen (webappendix, pp18-35). Although 21 trials began, one[27] with 255 women was abandoned early (for organisational reasons, so its unavailability causes no bias). All were randomised evenly between tamoxifen and control. Six major trials described compliance with the tamoxifen allocation (in NSABP, 75% completed ≥3 years; in GROCTA, IBCSG, ICCG, NCIC and SWOG, respectively, 89%, 78%, 82%, 69% and 86% [weighted mean 82%] completed ≥2 years). Compliance with allocation to control was unavailable, but should have been good in early trials (though perhaps less so for women with ER+ disease in later trials, when treatment guidelines were recommending tamoxifen).

In ER+ disease, allocation to tamoxifen halved the recurrence rate during years 0-4 and reduced it by a third during years 5-9 (with little further effect after year 10), so over all time periods the recurrence rate reduction averaged 39% (RR[±SE]=0.61±0.03 [2p<0.00001] for any recurrence and RR=0.62±0.07 [2p<0.00001] for contralateral disease incidence). In ER-poor disease, however, there was no apparent effect on recurrence (RR=0.97±0.05 for any recurrence; RR=0.94±0.12 [95%CI 0.73-1.20] for contralateral disease) (webappendix, p9). Although the overall prognosis for ER-poor disease appeared (somewhat misleadingly) about as good as that for tamoxifen-treated ER+ disease, this comparison was confounded by nodal status (most ER-poor disease was node-negative) and by widespread use of chemotherapy in ER-poor disease.

ER and PR status were strongly associated; PR (where measured) was positive in 76% (7378/9688) of ER+ and only 21% (1236/5984) of ER– (strictly, ER-poor) disease. Given ER status, however, PR status was not significantly predictive of response. For ER+PR+ and ER+PR– disease, respectively, RR=0.63±0.03 and 0.60±0.05, both 2p<0.00001. For ER–PR+ and ER–PR– disease, respectively, RR=0.90±0.10 and 1.03±0.06 (figure 1).

Analyses of quantitative ER and PR measurements did not materially change these findings (figure 2). If the ER measurement was <10 fmol/mg cytosol protein (ie, ER-poor disease, mostly treated with chemotherapy) there was no apparent benefit from adding tamoxifen. Above 10 fmol/mg, however, tamoxifen reduced recurrence substantially, even for weakly positive ER (RR=0.67±0.08 for ER 10-19 fmol/mg), and the proportional effect at much higher ER was slightly larger (RR=0.52±0.07 for ER≥200 fmol/mg, trend in RR

with ER [if ER≥10] p=0.002). In ER+ disease, the PR measurements were not predictive of who would respond to tamoxifen, so subsequent analyses ignore PR and are limited to the 10,645 women with ER+ disease, with median follow-up in survivors 13 (IQR9-18) years.

The 10-year recurrence risks for women with node-negative and node-positive ER+ disease are illustrated in figure 3, subdivided by use of chemotherapy. Even if chemotherapy was given (lower panels), tamoxifen was of substantial further benefit (ie, chemotherapy plus tamoxifen was better than chemotherapy alone), producing a further reduction of about one-quarter in 10-year recurrence risk (from 25% down to 18% in N- disease and 48% down to 36% in N+ disease).

Figure 4 subdivides the results for ER+ disease according to daily tamoxifen dose tested, use of background chemotherapy (present or absent, and if present, concurrent or sequential), entry age, nodal status, tumour grade (poorly differentiated or moderately/well differentiated), diameter (1-20, 21-50 or >50mm), site of first recurrence (isolated locoregional, contralateral or distant) and time since randomisation (0-1, 2-4, 5-9 or 10+ years), finding substantial and highly significant recurrence reductions in every subgroup (except the period 10+ years after entry). Corresponding subgroup analyses for breast cancer mortality (ie, mortality rate in all women less that in women without recurrence) yield generally similar findings (webappendix, p4), except that a substantial mortality reduction continued well beyond year 10 (RR during years 10+ after entry=0.73±0.07, p<0.00001). Thus, the recurrence reduction during years 0-9 caused a highly significant reduction in breast cancer mortality both during and after years 0-9.

The recurrence reduction appeared somewhat greater in trials of higher daily doses (p=0.02 for trend between RRs for 20, 30 and 40 mg/day), but there was no such dose effect for breast cancer mortality (webappendix, p4) or endometrial cancer incidence (data not shown). There were highly significant effects both in the 6 trials with no chemotherapy (RR=0.56±0.04) and in the 14 trials of chemotherapy plus tamoxifen *vs* the same chemotherapy alone (RR=0.67±0.04), with – in both trial categories – a slightly greater effect of tamoxifen in those with greater degrees of ER positivity (data not shown). For patients receiving chemotherapy, tamoxifen was of further benefit whether it started concurrently with the chemotherapy (RR=0.62±0.06) or after it (RR=0.71±0.05). The slight superiority of starting concurrently is, however, not significant, and these tamoxifen trials did not randomise timing. In all regimens, tamoxifen had a substantial effect: figure 4(a-c).

The proportional risk reductions were slightly, but not significantly, greater at older ages, but benefits were substantial and consistent for women in each age range (including the many with entry age <45 years [and the few with entry age 70+ years: 41/146 *vs* 68/156 recurrences/patients, 2p=0.001]). Nodal status, tumour grade and diameter did not materially affect proportional risk reductions. They were, however, importantly predictive of the absolute risk without tamoxifen, and hence of the absolute benefit of giving tamoxifen. Local recurrence, contralateral breast cancer (generally new primary) and distant recurrence were all substantially reduced by tamoxifen (each p<0.00001).

The proportional effects on recurrence rates were very different during different time periods: figure 4(i). Recurrence was reduced by more than half during the first 2 years (when almost all those allocated treatment would have been partially or fully treated) and by almost half during the next 3 years. During years 5-9 after randomisation there was (in all but two trials[23,25]) no difference in adjuvant tamoxifen usage between the treatment and control groups, yet the recurrence rate was still almost one-third lower in those originally allocated tamoxifen (RR=0.68±0.06, p<0.0001). After year 10, recurrence rates were similar (RR=0.97±0.10), indicating no loss after year 10 of the gains during years 0-9.

Figure 5 shows 15-year results for recurrence (left) and breast cancer mortality (right) in all women with ER+ disease. Remarkably, the annual breast cancer mortality rate was reduced by about one-third (RR=0.70±0.05, p<0.00001) throughout the first 15 years after randomisation, with highly significant extra benefit during each of years 0-4, 5-9 and 10-14 (RR=0.71±0.05, 0.67±0.06 and 0.66±0.08, respectively, each p<0.00001: foot of figure 5, webappendix p4). The absolute mortality difference was only 3% (9% *vs* 12%) at year 5, by which time trial treatment had ended (in all except the few re-randomised to continue after year 5), but it was three times as great (24% *vs* 33%) by year 15.

In ER+ disease, the reductions in recurrence and mortality during years 0-4 were almost as great in trials of only 1-2 years as in trials of about 5 years of tamoxifen (webappendix p2, pp18-23). The reductions in recurrence during years 5-9 were, however, greater in the trials of about 5 years of tamoxifen than in trials of only 1-2 years of tamoxifen. Although 1-2 years of tamoxifen had little further effect on recurrence it had some further effect on mortality after year 5, although smaller than that of about 5 years of tamoxifen.

Table 1 shows, for women with ER+ disease, effects on cause-specific mortality and on second cancer incidence before any recurrence of the original breast cancer. (Effects on diseases other than breast cancer were not materially affected by ER status: webappendix, pp11-17.) As tamoxifen delayed or prevented recurrence, the tamoxifen groups spent longer than controls at risk of death without recurrence (56,747 *vs* 48,876 woman-years). Hence, absolute numbers of deaths before recurrence in treatment and control groups are not directly comparable, but logrank analyses account for this.

The main life-threatening side-effects of tamoxifen are uterine cancer and thromboembolic disease.[1,26] In ER+ disease (mean 10 years follow-up) there were 9 *vs* 1 deaths from uterine cancer (excluding cervix) and 6 *vs* 0 deaths from pulmonary embolus during the first 5 years (but no apparent excess afterwards), suggesting about 0.2% 10-year mortality from these two side-effects. Otherwise, there were no definite differences in mortality without recurrence. A non-significant excess of stroke deaths – 3 extra per 1000 women during the first 15 years, none of it during the treatment period – was balanced by a non-significant shortfall in cardiac deaths – 3 fewer per 1000 women during the first 15 years – so there was little net effect on overall vascular mortality (webappendix p14).

Tamoxifen increased uterine cancer incidence (excluding cervix cancer, RR=2.40±0.32, p=0.00002), reduced contralateral breast cancer incidence by, in each age range, a larger absolute amount and had no significant effect on other types of cancer (Table 1 and webappendix pp16-17). These adverse and protective effects persisted for some years after treatment ended (webappendix, pp 9-13). The uterine cancer risk was strongly correlated with age, with little effect for entry age <45 or 45-54 years, but 15-year incidence 3.8% *vs* 1.1% for entry age 55-69 years (absolute increase 2.6%, SE 0.6). In contrast, the absolute (and proportional) decrease in contralateral breast cancer was independent of age, with 15-year incidence 6.5% *vs* 9.8% in ER+ disease (absolute reduction 3.2%, SE 0.8). In ER-poor disease the 15-year incidence of contralateral disease was 7.1% in both treatment groups (absolute reduction 0.1%, SE 1.1).

In the hypothetical absence of breast cancer mortality, 15-year probabilities of death from other causes in these trials for entry ages <45, 45-54 and 55-69 years were, respectively, 3%, 6% and 20% (similar to population mortality rates). As this 20% risk for age 55-69 years applied similarly to the tamoxifen and to the control group, in both groups 15-year overall survival is one-fifth smaller than 15-year breast cancer survival, so the 15-year gain

is one-fifth smaller for overall mortality than for breast cancer mortality (Figure 6), but this does not suggest any adverse effect on mortality from causes other than breast cancer. For entry age <45 years, where intercurrent mortality was low, 15-year gains in overall mortality and in breast cancer mortality were similar.

Discussion

Longer follow-up of the trials of about 5 years of tamoxifen has greatly strengthened the evidence that substantially reduced breast cancer mortality rates continue well beyond year 10, as a delayed effect of the greatly reduced recurrence rates during years 0-9. It has also produced strong evidence of a substantial effect even in disease that was only weakly ER-positive (10-19 fmol/mg), though not in disease that was wholly ER-negative.

If all trials had been of exactly 5 years of tamoxifen *vs* no adjuvant tamoxifen, with full compliance in both groups, the benefit would have been somewhat greater. For, one-sixth of the treated patients in these trials of about 5 years of tamoxifen were allocated only 2-3 years of tamoxifen, of patients allocated at least 5 years of tamoxifen about 18% discontinued adjuvant treatment within 2 years, and both direct comparisons[1] and indirect comparisons (webappendix, p2) show greater mortality reduction with about 5 years than with about 2 years of tamoxifen. Moreover, particularly in the later trials, some controls with ER+ disease might eventually have started adjuvant hormonal therapy anyway.[28,29] Although the combined effects of drop-out and drop-in cannot be quantified exactly, the breast cancer death rate ratio of 0.70±0.06 in the present meta-analyses of outcome by allocated treatment means that full compliance with 5 years of tamoxifen would reduce 15-year breast cancer mortality rates by at least a third, or perhaps slightly more.

Measured ER status of the original primary was the only patient or tumour characteristic recorded that strongly predicted tamoxifen efficacy (ie, the proportional risk reduction). Among women with ER-poor primary breast cancers tamoxifen did not significantly reduce the overall recurrence rate, and did not even appear to reduce the incidence of contralateral breast cancer. The results are, however, compatible with the hypothesis that the proportional reduction produced by tamoxifen in the incidence of ER+ contralateral disease is unaffected by the ER status of the original primary. (In the US SEER cancer registries[30] only about half of the contralateral tumours arising more than a year after ER-negative primary cancers are ER-positive, as against 80% after ER-positive primaries.)

There appeared to be a fairly sharp cut-off in tamoxifen efficacy with respect to the quantitative ER measurement between little effect at 4-9 fmol/mg and substantial benefit at 10-19 fmol/mg. (Reassuringly, ≥10 fmol/mg has been the criterion for ER positivity used in most trials, and by the EBCTCG.[1]) However, given the limitations of the ligand-binding ER assay method used in these trials,[31,32] a sharp efficacy cut-off at a particular measurement value is not plausible. Although the evidence of substantial benefit from tamoxifen at ER levels of only 10-19 fmol/mg is robust, the evidence of zero benefit at 4-9 fmol/mg is not, as the CI for tamoxifen efficacy just in this subgroup is wide, despite over 10,000 woman-years of follow-up.

If there is a continuous relationship between the measured ER level and the efficacy of tamoxifen but the play of chance suggested a sharp cut-off, then detailed re-examination of these trial results is unlikely to clarify matters. The most appropriate use of the trial findings may be to conclude from them the remarkable importance of preventing any stimulation of breast cancer cells by any functional ER in those cells, and the need to use sensitive and reliable ER assay methods in future patients.

Contemporary assessment of ER status is generally by immunohistochemistry (IHC, percentage of tumour cells stained by anti-ER antibody). As, however, there is good concordance between ligand-binding and IHC assays of ER positivity,[31-35] the present finding of a substantial effect of tamoxifen even at relatively low levels of ER positivity remains relevant to current practice. Recent guidelines on IHC assays[36] recommend defining ER positivity as ≥1% cells staining, but with some uncertainty about whether to include the range 1-10%. Few patients if tested properly have 1-10% cells staining, however,[31,32] and a low cut-off minimises life-threatening false negative ER results due to technical error. Interpretation of marginally positive ER assays may in future be helped by ER gene expression assays. (Preliminary studies of new assay methods may, however, engender false negative claims about endocrine effects in some ER+ subgroup.[37])

Given ER status, the PR measurement did not appear to be importantly predictive of efficacy. In disease recorded as ER+ there was substantial and highly significant benefit even if the sample was recorded as PR-poor. The absolute recurrence reduction at 15 years appeared if anything somewhat greater in ER+PR-poor than in ER+PR+ disease, perhaps because of the somewhat higher background risk of recurrence without treatment. Conversely, in disease reported to be ER-poor, positive PR measurements did not identify

a subgroup with significant benefit. There did appear to be some slight early benefit from tamoxifen in disease that was measured to be ER-poor, PR+ but this was not significant, and might reflect inclusion in this category of a few patients with false-negative ER assays. As assays improve, fewer breast cancers are reported as ER-PR+ (4% in the early 1990s but only 1% in recent years in the SEER cancer registry data[30]). For the few still reported as ER-PR+, repeat testing on another tissue sample has been recommended[34,36] to rule out a false-negative ER assay in a patient who could benefit from endocrine treatment.

Although age is not a strong independent correlate of distant recurrence or of tamoxifen efficacy, being relatively young is a major determinant of the gain in life expectancy from avoiding distant recurrence. Moreover, for pre- or peri-menopausal women of age <45 or 45-54 years tamoxifen remains a major hormonal medical treatment option (as ovarian activity cannot be controlled by aromatase inhibitors), and there is little uterine cancer risk from giving tamoxifen at such ages.

The key quantitative finding likely to be generalisable to future patients[37] is the *proportional* risk reduction produced by about 5 years of tamoxifen in ER+ disease, which is approximately independent of age, nodal status, tumour grade, diameter, chemotherapy use and timing of chemotherapy (concurrent or sequential). This suggests that if chemotherapy was being given then the additional therapeutic effects of giving tamoxifen were approximately independent of any therapeutic effects of that chemotherapy (a conclusion strongly reinforced by meta-analyses[1,39] of the trials of chemotherapy, which found that the proportional risk reduction produced by chemotherapy was unaffected by whether or not tamoxifen was being given).

Insofar as any of these factors substantially affect absolute risk in women without tamoxifen, they substantially affect the absolute reduction in risk produced by tamoxifen. Many treatment guidelines recommend endocrine treatment for disease with any degree of ER-positivity.[38] Consistently with this, the present meta-analyses show a definite and substantial protective effect even at ER levels of only 10-19 fmol/mg, and demonstrate that on average among all women with ER+ disease full compliance with 5 years of adjuvant tamoxifen would reduce the breast cancer mortality rate during the first 15 years after the start of treatment by at least a third, in comparison with no adjuvant endocrine therapy.

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