**Meta-analyses of adjuvant therapies for women with early breast cancer: the Early Breast Cancer Trialists’ Collaborative Group overview**

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**introduction**

Systematic reviews of the effects of health care attempt to bring together all relevant evidence on a particular intervention or treatment, so that people choosing between different interventions are more informed and can make better decisions. These reviews can vary in scale and scope from the very broad; for example, a systematic review of all analgesics for the relief of all types of mild pain to the narrow; for example, a comparison of two specific drugs for the treatment of headache. Without up-to-date systematic reviews, we are faced with either having to identify, appraise and synthesize all the relevant evidence ourselves or with having to rely simply on individual pieces of the evidence, without knowing what the totality might show. And, in such circumstances, we may be faced with an undue emphasis on the results of individual trials that have generated most publicity because of their striking results. Instead, what is needed is a systematic collection of all the relevant evidence and, in order for this to be as free from bias and as reliable as possible when considering the effects of treatments, it needs to come from randomized trials.

For more than two decades, the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) has been striving to do this for all treatments of early (i.e. operable) breast cancer, involving the global community of researchers who have done relevant randomized trials over the last half-century and more. This paper discusses the reviews done by the EBCTCG, highlights some of the key findings and describes how these systematic reviews have produced reliable findings that influence the treatment for hundreds of thousands women with breast cancer, worldwide.

The most recent set of publications from the EBCTCG were based on analyses done in the first half of the first decade of the 21st century. The major findings of that cycle of reviews are:

Women with a hormone-receptive breast cancer tumor who take at least a few years of tamoxifen have substantially improved long-term survival, which is largely irrespective of other characteristics (such as age and nodal status) and whether they also have other treatments such as chemotherapy. To date, the largest benefit has been shown for about five years of tamoxifen, with an average reduction in breast cancer deaths by year 15 of about 9%. However, the question of whether tamoxifen for longer than this is beneficial remains unanswered [1].

The proportion of women who survive for at least 15 years after having breast cancer diagnosed and treated when they are less than 50 years of age is typically about 10% higher if they have a few cycles or more of multi-agent chemotherapy following surgery. Among women aged 50–69, the improvement in survival is about 3%. The benefits are greater for anthracycline-based regimens, compared to those based on CMF (cyclophosphamide, methotrexate and 5-fluorouracil) [1].

Premenopausal women who have ovarian ablation are, at least in the absence of chemotherapy, significantly more likely to survive long-term [1].

A combination of anthracycline chemotherapy and tamoxifen might reduce the risk of dying from breast cancer by more than one half in women under 50 years of age and by slightly less than one half in women aged 50–69 [1].

Radiotherapy which is effective enough to reduce the risk of local recurrence in the breast after breast-conserving surgery or elsewhere (such as the chest wall or regional nodes) following mastectomy reduces 15-year breast cancer mortality by about 5% [2].

**history of the EBCTCG**

In the early 1980s, there was recognition among several breast cancer trialists that their separate trials were probably too small to assess reliably whether the effects of some treatments on recurrence and death were moderate or non-existent. Even though there had been some relatively large trials, most trials had randomized less than a few hundred women and were therefore unable to detect differences in 5- and 10-year survival of 5–15%. In 1984, many of the people responsible for randomized trials of tamoxifen or chemotherapy met together at Heathrow Airport in London, UK to share their findings and to allow a simple meta-analysis to be performed of the aggregate results from their trials. This group became the founders of the Early Breast Cancer Trialists’ Collaborative Group, which has since expanded to include hundreds of researchers from around the world who have conducted randomized trials of any aspect of the treatment of early breast cancer where death was a main outcome.
The 1994 meeting included the presentation of preliminary results based on aggregate data which revealed the need for a more in-depth analysis [3]. It was decided to collect data at the level of the individual woman, so as to increase the power of the analyses, to be able to conduct standardized analyses of each trial and to explore the effects of treatments in different subgroups of women [4]. These data were collected from randomized trials of hormonal and cytotoxic therapy over the following year and led to a presentation of preliminary analyses before the National Institutes of Health (NIH) Consensus Conference in Washington in September 1985. Following further work, the results were published in 1988 [5], with a fuller monograph including design details and analyses for each trial being published 2 years later [6]. These early results showed the beneficial effects of tamoxifen and of multi-agent chemotherapy on reducing recurrence and improving survival, at least in the short term.

The collaboration was extended in 1989 to all aspects of the treatment of early breast cancer, including local treatments such as the extent of surgery and the use of radiotherapy. That second cycle produced definitive findings on the benefits of ovarian ablation, tamoxifen and prolonged multi-agent chemotherapy on 10-year outcomes. It also showed that any effect of the types of immunotherapy that had been studied up until the 1980s was likely to be very small or non-existent [7]. The overview also showed that the types of radiotherapy studied until that time had little effect on overall survival in the first decade after treatment, and that 10-year survival was similar following different types of surgery, such as breast-conserving surgery or mastectomy [8].

The third cycle of the overview began in 1994, and led to publications for different treatments in 1996 (ovarian ablation) [9], 1998 (tamoxifen and chemotherapy) [10, 11], and 2000 (radiotherapy) [12]. These reports have also been reproduced as Cochrane reviews [13–16]. These reviews consolidated the evidence on the 10-year benefits of hormonal and chemotherapy, and were able to begin to explore the direct randomized evidence for different types of chemotherapy and different durations of tamoxifen. Because of improvements in the collection of data on specific causes of deaths, it was also possible to show that the overall balance of benefit and harm, at least in terms of 20-year survival, for the types of radiotherapy studied in trials before the 1990s was favorable only for younger women at high risk of local recurrence.

The results of the fourth cycle of the EBCTCG overview, which began in 1999 were published in two large papers in the Lancet in 2005. This cycle sought data from all randomized trials of any aspect of the treatment of women with early breast cancer, where survival was a primary outcome, which had started by 1995. The second of the two papers dealt with local therapy, including radiotherapy and the extent of surgery [2]. The findings for adjuvant tamoxifen and chemotherapy are summarized here [1].

tamoxifen

Preliminary analyses from the fourth cycle of the EBCTCG overview were discussed with the collaborating trialists at a meeting in Oxford, England in September 2000 and presented to the NIH Consensus Development Conference in the United States a couple of months later. The NIH Consensus Statement reflected the EBCTCG findings on the effect of tamoxifen, concluding ‘Although tamoxifen has been associated with a slight but definite risk of endometrial cancer and venous thrombo-embolism, the benefits of tamoxifen far outweigh its risks’. In regard to different durations of tamoxifen, the NIH Consensus Statement said ‘the meta-analysis has shown that 5 years of tamoxifen are superior to 1–2 years of such treatment. Trials should be conducted to better define the risks and benefits of continuing tamoxifen beyond 5 years’ (http://odp.od.nih.gov/consensus/cons/114/114_statement.htm). It is to be expected that this statement will have a major impact on the treatment of breast cancer, not only in the USA, but worldwide.

Following refinements to the underlying data and to the analyses, the final results of the fourth cycle were published in May 2005 and the general conclusions noted in the preceding paragraph still apply. In considering these conclusions, it is important to note that the EBCTCG overview involves only a limited amount of data on each woman from the time of her randomization and a limited amount of detail for a small number of outcome measures. These restrictions are necessary to keep the overview manageable and to maximize the likelihood that these key data will be supplied. But, as a consequence, some analyses are not possible. The baseline data for each woman include her age, menopausal status, nodal status, hormone receptor measurements, allocated treatment and date of randomization. Information, which is as up-to-date as possible is also sought on the dates and sites of any second cancers and the dates for first recurrence and first distant recurrence. If a woman is known to have died, the date of death and the cause of death are requested. For other women, the date that she was most recently known to be alive is sought.

The first EBCTCG review of tamoxifen, in the mid-1980s included data from a total of 16 500 women in 28 randomized trials, of whom nearly 3800 were known to have died [5]. This grew to 40 trials, 30 000 women and 8200 deaths in the second cycle [7]; and further still to 55 trials, involving more than 12 000 deaths among 37 000 women in the 1998 publication [10]. By the 2000–2005 cycle, the growth in the number of trials included had levelled off at 56, but further accrual to some of these trials and five more years of follow-up for many of them meant that the number of women in the analysis had increased to 48 000; with a total of 18 000 deaths [1]. This represented 88% of the total number of women randomized into eligible trials of adjuvant tamoxifen versus no immediate tamoxifen worldwide. Most of the missing data was for women who were entered into trials too recently to contribute useful additional information on long-term outcomes.

The main division in the analyses was, as previously, into women who were classified as having estrogen receptor ‘negative’ disease (ER-poor), and women who were either judged to be ER positive or had not had their estrogen receptor status measured. The effects on recurrence and breast cancer mortality of one or two years of tamoxifen compared to no immediate tamoxifen for the 8000 ER-poor women was of borderline statistical significance (ratio of annual rates: 0.89 standard error (SE) 0.04 and 0.91 SE 0.04, respectively). However, given that this apparent benefit was not confirmed
in the more recent trials of 5 years of tamoxifen, in which 5000 women were randomized (ratio of annual recurrence rates: 1.04 SE 0.07 and ratio of annual breast cancer death rates: 1.04 SE 0.08), the apparent benefit might have been due largely, or wholly, to false-negative ER measurements, perhaps inflated by the play of chance.

In contrast, the effect in women whose tumors were found to be ER-positive is clear and definite. For the trials of 1 or 2 years of tamoxifen, both recurrence (ratio of annual recurrence rates: 0.74 SE 0.02) and deaths due to breast cancer (ratio of annual death rates: 0.82 SE 0.03) were significantly reduced among the 14 000 ER-positive women randomized. The effects were even larger among the 8000 ER-positive women in the trials of five years of the drug. Comparing women allocated to take five years of tamoxifen with those allocated not to receive tamoxifen after their surgery, the annual rate of recurrence was reduced by about 40% (ratio of annual recurrence rates: 0.59 SE 0.03). Deaths due to breast cancer were 34% lower (ratio of annual death rates: 0.66 SE 0.04). By 15 years after initial treatment for breast cancer, these benefits translate into average absolute reductions in recurrence of 11.8% (SE 1.3, logrank 2p<0.00001) and in breast cancer mortality of 9.2% (SE 1.2, logrank 2p<0.00001). Thus, for every 11 women allocated to 5 years of tamoxifen there was one fewer death from breast cancer by year 15, because of tamoxifen.

The large scale randomized evidence available in the EBCTCG overview allows reliable assessment of whether the effects of tamoxifen are similar or different for different types of women. This reveals that the proportional risk reductions for women who were not known to have estrogen receptor negative tumors are similar, largely regardless of their age or menopausal status, nodal status and the daily dose of tamoxifen, with 20 mg and 30–40 mg appearing to be similarly effective. Tamoxifen was also shown to confer an additional benefit in women who also received chemotherapy. This proportional benefit was similar in size to that found in trials where no chemotherapy and tamoxifen had been compared with no adjuvant therapy.

Whether tamoxifen should be continued beyond this first 5 years remains uncertain. The fourth cycle of the EBCTCG overview was able to include data from 18 000 women randomized to 5 years versus 1–2 years of tamoxifen. This confirmed that the longer duration was associated with fewer recurrences and deaths from breast cancer. However, although there were 8000 women in trials comparing about 10 versus 5 years of the drug their median follow-up was only a couple of years, and this is insufficient to detect, or refute, important differences between these durations. In the 5 years since those data were first collected, at least another 10 000 women have been randomized into trials assessing longer than 5 years of tamoxifen and the fifth, and sixth, cycles of the EBCTCG overview will help resolve the uncertainty about the relative benefits and harms of 5 and 10 years of treatment.

The scale of the tamoxifen review also provides a strength for assessing reliably serious side effects of this drug, such as second cancers and non-breast-cancer deaths. In considering these effects all 15 000 women in trials of 5 years versus no immediate tamoxifen can be analyzed, including those who were ER-poor. These analyses show a small excess in deaths from thrombo-embolic disease and endometrial cancer, which, combined, is equivalent to an absolute risk of about 0.2% per decade among women allocated to 5 years of tamoxifen. This should be contrasted with the benefits in the absolute reductions in breast cancer deaths of 5.3% and 12.2% for node-negative and node-positive women, respectively.

**chemotherapy**

Like tamoxifen, the number of randomized trials of chemotherapy also increased substantially over the first two decades of the EBCTCG overview, with a shift from trials comparing chemotherapy with no chemotherapy, to trials of different types of chemotherapy. In the first cycle of the overview, 31 randomized trials of no chemotherapy versus chemotherapy using one or more drugs were included. This involved a total of 9000 women, of whom 2900 had died [5]. Subsequent cycles refined this to focus on trials of prolonged multi-agent chemotherapy. By the third cycle, this analysis was based on 18 000 women in 47 trials, and it had risen further to 60 trials, 29 000 women and 10 000 deaths by the fourth cycle [1].

Among women under 50 years of age when diagnosed with breast cancer, the use of prolonged polychemotherapy was shown to change the average proportion of women who had a recurrence by 15 years in these trials from 53.5% in the control group to 41.1% in the chemotherapy group. The effect on breast cancer mortality was such that the absolute risk by 15 years was reduced by 10.0% (SE 1.6, logrank 2p<0.00001). The effect in women aged 50–69 years was smaller but still statistically significant. By year 15, the reduction in recurrence was 4.1% (SE 1.2, logrank 2p<0.00001) and the reduction in breast cancer mortality was 3.0% (SE 1.3, logrank 2p<0.00001). Subgroup analyses showed that chemotherapy was beneficial in both ER-poor and ER-positive women, and that among the latter, chemotherapy was also beneficial if the woman took tamoxifen. Too few women (a total of less than 1300) over 70 had been randomized for a robust analysis of the long-term effects of chemotherapy among this population.

The directly randomized comparisons of CMF-based regimens versus anthracycline-containing regimens drew on data from 17 trials of 15 000 women (4000 deaths). These analyses showed that anthracycline-containing polychemotherapy produced greater beneficial effects on recurrence and breast cancer mortality than CMF. The ratio of annual recurrence rates for anthracyclines compared to CMF was 0.89 SE 0.03 (2p=0.001) and the breast cancer death rate ratio was 0.84 SE 0.04 (2p<0.00001). Combining the results of the tamoxifen and the chemotherapy analyses reveals that a combination of anthracycline containing chemotherapy and 5 years of tamoxifen might reduce the risk of dying from breast cancer by more than one half in women under 50 years of age and by slightly less than one half in women aged 50–69 [1]. For example, if the risk of a woman aged under 50 who is newly diagnosed with breast cancer dying over the next 15 years is 25% without adjuvant therapy, this could be reduced to 11.6% with this combination of adjuvant therapies. If her risk was higher to begin with, at say 30%, this could be reduced to 25.7%.
Similarly, although the effect of chemotherapy is smaller for women aged 50–69, a 25% risk of dying of breast cancer in the next 15 years would be reduced to 14.7% and a 50% risk would go down to 31.8%.

Discussion
Attributing the fall in the number of deaths due to breast cancer in countries such as the UK and USA over the last two decades to the uptake of the treatments shown to be beneficial by the EBCTCG overview is difficult because other factors, such as earlier diagnosis, will have also played a part [1, 17]. However, the EBCTCG overview has clearly shown the benefits of adjuvant treatments, such as tamoxifen and prolonged polychemotherapy, and these results are well known and increasingly form the basis of clinical practice policies and guidelines.

In the period since the first EBCTCG review, tamoxifen has been taken by many hundreds of thousands of women diagnosed with breast cancer and this had probably prevented tens of thousands of breast cancer deaths each year worldwide by the time of the 1998 report of the EBCTCG overview [10]. Shortly before then, tamoxifen was not being considered as a possible treatment for a substantial number of women with breast cancer of the types who were shown to be likely to benefit from this drug [18]. The findings of the 1998 EBCTCG report may, therefore, have led to changes in practice that could have prevented several additional tens of thousands of breast cancer deaths in the subsequent decade. Assuming that one million women are currently taking tamoxifen, the 2005 EBCTCG results imply that, among these million women, there will be approximately 90,000 fewer deaths within the first 15 years after diagnosis, if the tamoxifen is taken for about 5 years.

Decisions on the treatment for every woman with breast cancer should be based on the best evidence. This requires a combination of information about the patient, her setting, values and preferences, along with evidence on the effectiveness of the treatments being considered. This evidence needs to be as reliable as possible and; if the differences between possible treatments are moderate, small or non-existent; the evidence has to come from studies in which systematic biases have been kept to a minimum. Large scale randomized evidence, from systematic reviews of randomized trials can provide this. By drawing together the worldwide randomized evidence and analyzing it appropriately and periodically, the EBCTCG is now seen as a definitive provider of reliable information on the effects of treatments for early breast cancer on recurrence and mortality.

Future cycles of the EBCTCG overview will include further analyses of the comparisons described in this paper. Newer treatments will also be assessed. These include ovarian suppression with drugs such as luteinising hormone releasing hormone agonists (e.g. goserelin), aromatase inhibitors; selective estrogen receptor modulators (SERMs), modern single agent chemotherapy using anthracyclines (e.g. epirubicin), taxanes, high-dose chemotherapy and autologous progenitor-cell transplantation, and trastuzumab.

The results of the EBCTCG overview have already had a major influence on clinical practice worldwide. They are widely disseminated and the papers published to date have been cited by thousands of other articles [19]. Adoption of the treatments shown to work by the overview will prolong the lives of many tens of thousands of women.

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References