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

CRD summary
This meta-analysis assessed the long-term effects of systemic adjuvant therapies on breast cancer recurrence and survival. The authors concluded that the breast cancer mortality rate could be halved with anthracycline-based chemotherapy followed by 5 years of adjuvant tamoxifen in middle-aged women with oestrogen receptor-positive disease. The thoroughness of this individual patient data analysis suggests that the conclusions are likely to be reliable.

Authors' objectives
The authors aim was to provide an assessment of the 10- and 15-year effects of systemic adjuvant therapies on breast cancer recurrence and survival.

Searching
The authors stated that the process of trial identification was reported elsewhere (see Other Publications of Related Interest nos.1-2). Under the supervision of the collaborating group (Early Breast Cancer Trialists’ Collaborative Group, EBCTCG), this process included communication with trial investigators and drug manufacturers, consultation with trials registers and conference proceedings, along with a computer-aided literature search.

Study selection
Study designs of evaluations included in the review
The review included individual patient data (IPD) from randomised controlled trials (RCTs) that had started by 1995.

Specific interventions included in the review
Studies of systemic adjuvant therapy were eligible for inclusion. The interventions included CMF (cyclophosphamide, methotrexate, fluorouracil), anthracycline-based combinations such as FAC (fluorouracil, doxorubicin, cyclophosphamide) or FEC (fluorouracil, epirubicin, cyclophosphamide), tamoxifen and ovarian suppression. There were no trials involving taxanes, trastuzumab, raloxifene or modern aromatase inhibitors.

Participants included in the review
Studies of women diagnosed with early breast cancer were eligible for inclusion. Women aged 70 years and older were underrepresented amongst the included participants.

Outcomes assessed in the review
The outcomes of interest were breast cancer first recurrence (including second primary breast cancers and local or distant recurrences of the original cancer), breast cancer mortality, overall mortality, cause-specific mortality before recurrence, and the incidence of other types of cancer before breast cancer recurrence. Deaths from unknown causes were included with deaths from breast cancer, unless it was stated that the death was not due to breast cancer.

How were decisions on the relevance of primary studies made?
The relevance of trials for inclusion in the review was agreed by communication with the trial investigators.

Assessment of study quality
The authors stated that the data handling procedures were also reported elsewhere (see Other Publications of Related Interest nos.1-2), affirming that the data were extensively checked for internal consistency and completeness. Amendments and updates were agreed with the trial investigators. The authors did not state how judgements of validity were made, in terms of who made the decisions. The trials were selected on the basis that they provided an
unconfounded comparison of therapies exceeding 1 month’ duration.

Data extraction
The trial investigators were asked to provide data for every woman in each eligible trial. A list of data categories was presented in the paper. Data were extracted on recurrence and mortality. The outcomes were measured by time-to-event analysis and follow-up was extended (where possible) to the year 2000.

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis of IPD using intention-to-treat log rank analysis. Separate event rates for each trial (stratified by nodal status, age, and year of follow-up) were used to generate a log rank statistic and its variance. These statistics were pooled to give a weighted average of the time-to-event treatment effects in the different trials. Ninety-five per cent confidence intervals (95% CIs; 99% CIs for subgroups) and exact P-values were presented. Proportional (percentage change) and absolute benefits (percentage) were reported. Recurrence and percentage mortality were displayed graphically for the analysed years. Standard error (SE) calculations were also carried out. Six meta-analyses were conducted based on the following comparisons: anthracycline-based versus no chemotherapy (8,000 women); CMF-based versus no chemotherapy (14,000); anthracycline-based versus CMF-based chemotherapy (14,000); approximately 5 years of tamoxifen versus none (15,000); approximately 1 to 2 years of tamoxifen versus none (33,000); approximately 5 years versus 1 to 2 years tamoxifen (18,000); ovarian ablation or suppression versus nothing (8,000 women).

How were differences between studies investigated?
The authors described the tests of heterogeneity or trend (including chi-squared) that were used in the analysis. A subgroup analysis was conducted in terms of age, type of treatment regimen, presence or absence of tamoxifen, oestrogen receptor (ER) status and tamoxifen use, nodal status and follow-up period.

Results of the review
IPD from 194 trials (approximately 145,000 women) were included. Thirty-four trials were not included because of the unavailability of data (approximately 13,000 women).

Anthracycline-based polychemotherapy (using FAC or FEC) was significantly more effective (2P=0.0001 for recurrence, 2P<0.00001 for breast cancer mortality). Six months of anthracycline-based polychemotherapy reduced the annual breast cancer death rate by approximately 38% (SE=5) for women under the age of 50 when diagnosed and by approximately 20% (SE=4) for women aged between 50 and 69 years when diagnosed. These results were independent of tamoxifen use, ER status, nodal status or other tumour characteristics. For those women with ER-positive disease only, approximately 5 years of adjuvant tamoxifen reduced the annual breast cancer mortality rate by 31% (SE=3). This was independent of the use of chemotherapy, age, progesterone receptor status or other tumour characteristics. A longer duration of tamoxifen (5 years) was significantly more effective than 1 to 2 years of the drug (2P<0.00001 for recurrence, 2P=0.01 for breast cancer mortality). For ER-positive tumours, the cumulative reduction in mortality was more than double at 15 years as at that reported at 5 years after diagnosis. Reductions in breast cancer mortality were also seen in those women allocated to ovarian ablation or suppression (8,000 women), but only where other systemic treatments were not present.

Further detailed results were presented in the paper. Supplementary information to all results is available on the EBCTCG website (accessed 05/01/2006). See Web Address at end of abstract.

Authors' conclusions
Long established adjuvant drug treatments that were previously found to reduce 5-year breast cancer recurrence rates can also reduce 15-year mortality rates. For middle-aged women with ER-positive disease, the breast cancer mortality rate would be halved with the administration of 6 months of anthracycline-based chemotherapy followed by 5 years of adjuvant tamoxifen. The combined mortality reductions from chemotherapy plus tamoxifen would mean that final
mortality reductions would be 57% and 45%, respectively, for women under 50 and between 50 and 69 years.

**CRD commentary**
The review objective was clear in terms of the interventions, outcomes and study design, but less so for the participants. The adopted strategy to identify eligible trials was thorough (with the exception of any reference to unpublished material) and this was supported by the use of a collaborative group to check for completeness and accuracy of the data. The authors made clear the number of participants for whom data could not be retrieved. It was proposed that this lack of data would have little effect on the findings, given that it represented minimal contribution to follow-up. The data were analysed using methods appropriate for the meta-analysis of IPD and the authors justified their choice of subgroup analysis. Given the thoroughness of this review, the conclusions are likely to be reliable. This was the fourth quinquennial cycle of the worldwide collaboration on reviews of early breast cancer (references for previous reviews were given).

**Implications of the review for practice and research**

**Practice:** The authors stated that further improvements in long-term survival might continue to arise from newer drugs, or better use of older drugs, in terms of different combinations, doses or sequencing.

**Research:** The authors stated that investigators of current and older trials should consider arrangements for at least 20-year follow-up of recurrence and cause-specific mortality.

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**Other publications of related interest**

This additional published commentary may also be of interest. Smith TJ, Khatcheressian J. Review: chemotherapy and hormonal therapy reduce recurrence and mortality at 15 years in early breast cancer. ACP J Club 2005;143:58.

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Record Status
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the reliability of the review and the conclusions drawn.