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The Early Breast Cancer Trialists' Collaborative Group: a brief history of results to date

Sarah Darby, Christina Davies, and Paul McGale

9.1 Introduction

Breast cancer is the commonest type of cancer among women in most developed countries. There are about a million new cases diagnosed each year worldwide, and around 35,000 new cases annually in the United Kingdom alone (Quinn *et al.* 2001). For such a common disease, widely practicable treatments that produce only moderate effects on long-term survival, such as increasing the number of women surviving for more than ten years after diagnosis from 50% to 55%, could result in the avoidance of many thousands of deaths each year. Therefore, it is important to be able to distinguish such treatments from those that have no effect, or even a deleterious effect, on overall survival.

In developed countries, most women who are diagnosed with breast cancer are diagnosed when the disease is at an early stage and is detected only in the breast itself—'node-negative' women—or in the breast and the lymph nodes near the affected breast—'node-positive' women. The primary treatment for most such women is surgery. However, the extent of the surgery considered necessary has varied substantially at different times and in different countries. There is also a wide variety of 'adjuvant' treatments that can be given in addition to surgery, and many hundreds of trials comparing the different treatments and combinations of treatments have been undertaken. The design of most of these trials is that women who satisfy a pre-specified set of entry criteria, for example in terms of age or extent of disease at diagnosis, are allocated at random to one of two possible treatment 'arms' that differ only with respect to the treatment being evaluated. For example the extent of surgery might be identical in both trial arms, but the women allocated to one of the trial arms might also be offered radiotherapy.

Where there are several trials that address similar, although not necessarily identical, questions, it is possible to obtain estimates of the differences between treatments by combining the data from them. This approach is much more precise than the estimates given by any individual trial. Inevitably, trials with extreme results tend to receive more attention than those with more moderate results. This produces a natural tendency for unduly selective emphasis on those trials or subcategories of patients where, by chance alone, the results are

misleadingly positive or misleadingly negative. Most such biases can be avoided by appropriate combination of the results of all trials that address similar questions. This combination cannot be done satisfactorily from published data alone (Stewart and Parmar 1993), and the inclusion of unpublished as well as published data is necessary to avoid bias. Furthermore, the information available from the published trials is not sufficient to allow a uniform analysis of all the available data with appropriate stratification for factors that will affect survival such as age, time since diagnosis, or nodal status. Thus, analysis based on individual patient data is necessary.

With these issues in mind, collaboration was sought in 1983–1984 between the co-ordinators of all randomized trials of the treatment of early breast cancer that satisfied certain criteria, and in 1985 the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) was initiated. It has continued since then in five-yearly cycles. At the time of writing, the analyses resulting from the fourth cycle of the EBCTCG have been finalized, and initial preparations are being made for the fifth cycle, which will include data up to 2005. The fourth-cycle analyses now available via the University of Oxford Clinical Trial Service Unit website, `www.ctsu.ox.ac.uk`, and in the published literature. See the note added in proof on page 196. The present chapter summarizes the main results of the earlier cycles of the EBCTCG, both in Table 9.1 and in the text, and it also comments on recent trends in breast cancer mortality. The results presented here are mainly those for overall survival. However, the original publications also consider other endpoints, including mortality from breast cancer and mortality from other specific causes of death, as well as breast cancer recurrence, that is, the return of the original cancer after a period of remission. In almost all cases, where a treatment has a beneficial effect on overall survival, this occurs following an earlier and larger effect on breast cancer recurrence.

9.2 The first cycle of the EBCTCG (1984 and 1985)

The first meeting of the nascent EBCTCG took place in London in October 1984 and preliminary analyses of data from two categories of trial were presented. Both were concerned with the evaluation of 'systemic' treatments—those involving drugs that would reach not just the breast and local tissues, but all parts of the body to which microscopic deposits of the cancer might already have spread. The first category included trials in which women in one treatment arm received only the standard treatment schedule at the centre involved in terms of the extent of surgery and whether or not radiotherapy was given, while women in the other treatment arm received the same standard treatment plus treatment with the anti-oestrogen agent tamoxifen, which can inhibit the growth of tumours with appreciable oestrogen receptor expression—so-called 'ER-positive' tumours. The second category of trials included patients in which the two trial arms differed only by the addition of some form of long-term cytotoxic chemotherapy, consisting of the administration of one or more drugs intended to kill cancer cells.

The data were analysed using standard statistical methods comprising significance tests and appropriately weighted estimates of treatment effects, based on log-rank analyses, together with life-table estimates of survival, which have been described elsewhere (EBCTCG 1990). Before these analyses, no generally agreed conclusions had emerged about the effects on mortality of either of these types of systemic therapy in early breast cancer, but it was apparent even from the preliminary results presented at the 1984 meeting that there were clearly significant reductions in short-term mortality among those receiving either tamoxifen or chemotherapy (Anonymous 1984). The final published data confirmed these preliminary findings (EBCTCG 1990, 1988). Individual data were available in 1985, when the EBCTCG was formally established, from a total of 28 trials of the effects of tamoxifen in which a total of 16,500 women had been randomized, of whom nearly 4000 had died by the end of the available follow-up. When all ages at diagnosis were combined, there was a highly significant reduction ($p < 0.0001$) in mortality for the women who had been allocated to tamoxifen compared with the women who had not. More detailed analysis indicated—misleadingly, as became apparent from later analyses of larger datasets—that the beneficial effect of tamoxifen was concentrated in women who were aged 50 or more at diagnosis, in whom the annual death rate from all causes combined was reduced by about one fifth. Furthermore, since not all patients complied with the treatment assigned, the true beneficial effect of tamoxifen is likely to be somewhat greater than this.

As regards the trials of cytotoxic chemotherapy, data were available from a total of 40 trials involving over 13,000 randomized women, of whom just over 4000 had died. There was a highly significant reduction in the overall death rate in trials of any chemotherapy versus no chemotherapy ($p = 0.003$) and also in trials of polychemotherapy—that is, chemotherapy with more than one drug for more than one month—versus single-agent chemotherapy ($p = 0.001$). In contrast to the tamoxifen trials, the beneficial effect of the chemotherapy appeared to be concentrated in women aged under 50 at diagnosis, in whom the annual death rate was reduced by about one quarter. The chemotherapy trials also suggested that administration of chemotherapy for 12–24 months might offer little survival advantage over administration of the same chemotherapy for about six months.

9.3 The second cycle (1990)

Breast cancer is unusual in that survival without apparent recurrence for the first five years after diagnosis is by no means a guarantee that cure has been achieved. Indeed, among women diagnosed with early breast cancer, mortality rates from the disease remain substantially elevated for at least the next ten to twenty years (Quinn *et al.* 2001). In the first cycle of the EBCTCG the 8000 or so deaths in the randomized women were approximately evenly distributed over years 1, 2, 3, 4, and 5+ of follow-up, but there was little useful information

TABLE 9.1. The main results for overall survival in the randomized controlled trials considered by the Early Breast Cancer Trialists' Collaborative Group. Standard errors (se) in percent are given in parentheses.

Cycle	Data included	Main results for overall survival and references
First	Trials started before 1985. Follow-up to 1985.	Tamoxifen (28 trials involving 16,500 randomized women): Highly significant ($p < 0.0001$) reduction in mortality in trials of 'tamoxifen versus no tamoxifen' over about five years of follow-up (EBCTCG 1988).
		Chemotherapy (40 trials involving over 13,000 randomized women): Highly significant ($p = 0.003$) reduction in mortality in trials of 'any chemotherapy versus no chemotherapy', and also ($p = 0.001$) in trials of 'polychemotherapy versus single-agent chemotherapy', both over about five years of follow-up. Chemotherapy for 12–24 months may offer little survival advantage over 6 months (EBCTCG 1988).
Second	Trials started before 1985. Follow-up to 1990.	Tamoxifen (40 trials involving 30,000 randomized women): Highly significant 17% (se 2; $p < 0.00001$) reduction in overall mortality rate in trials of 'tamoxifen versus no tamoxifen' over about 10 years of follow-up. Indirect comparisons suggest longer term treatment (∼2–5 years) better than shorter. Polychemotherapy plus tamoxifen clearly better than polychemotherapy alone at ages 50–69 (EBCTCG 1992).
		Chemotherapy (31 trials involving 11,000 randomized women): Highly significant 16% (se 3; $p < 0.00001$) reduction in overall mortality rate in trials of 'polychemotherapy versus no chemotherapy' over about 10 years of follow-up. No advantage in long-term treatment (∼12 months) over shorter term (∼6 months). Tamoxifen and polychemotherapy may be better than tamoxifen alone at ages 50–69 (EBCTCG 1992).
		Ovarian ablation (10 trials involving 3000 randomized women): Highly significant 25% (se 7; $p = 0.0004$) reduction in overall mortality rate for women treated at age < 50 over at least 10 years of follow-up. No significant effect for those aged 50+ when treated. (EBCTCG 1992).
		Immunotherapy (24 trials involving 6300 randomized women): No significantly favourable effects of immunotherapy found (EBCTCG 1992).
		Local therapies (64 trials involving 28,500 randomized women): Radiotherapy reduced rate of local recurrence by factor of three and breast conserving surgery involved some risk of recurrence in remaining tissue, but no definite differences in overall survival at 10 years (EBCTCG 1995).

Third	Trials started before 1990. Follow-up to 1995.	Tamoxifen: (55 trials involving 37,000 women): No significantly favourable effect in women with ER-negative tumours, but for 30,000 women with ER-positive or untested tumours highly significant effects with 12% (se 3), 17% (se 3) and 26% (se 4) reductions in the overall mortality rate in trials of 1, 2, and 5 years respectively of tamoxifen versus no tamoxifen, over about 10 years of follow-up. Proportionate benefit applies regardless of nodal status, age, menopausal status, daily tamoxifen dose, and whether or not chemotherapy was given (EBCTCG 1998*b*). Chemotherapy (69 trials involving 30,000 women): Highly significant reductions in overall mortality rate of 25% (se 5; $p < 0.00001$) in women aged < 50 and 11% (se 3; $p = 0.0001$) in women aged 50–69 in trials of "polychemotherapy versus no chemotherapy". Proportionate benefit similar regardless of nodal status, menopausal status (given age), ER-status and whether or not tamoxifen had been given. No advantage of more than about 6 months of treatment (EBCTCG 1998*a*). Ovarian ablation (12 trials involving 3500 women): No benefit for women aged over 50, but highly significant improvement in 15-year survival among those aged 50 or under when treated (15-year survival 52% versus 46%; $p = 0.001$) in trials of "ovarian ablation versus no ablation". Further evidence needed on effect of ablation in the presence of other adjuvant treatments (EBCTCG 1996). Radiotherapy (40 trials involving 20,000 women): Substantial reduction in breast cancer mortality largely offset by an increased risk of mortality from cardiovascular disease, so that overall 20-year survival was 37% with radiotherapy and 36% without ($p = 0.06$) in trials of "radiotherapy versus no radiotherapy". The ratio of benefit (from reduced mortality from breast cancer) to harm (from increased mortality from cardiovascular disease) was strongly affected by nodal status, age and decade of follow-up (EBCTCG 2000).
Fourth	Trials started before 1995. Follow-up to 2000.	Data on ∼80,000 women randomised in trials of tamoxifen, ∼50,000 women in trials of chemotherapy, 10 000 women in trials of ovarian ablation and ∼38,000 women in trials of local therapies have recently been published (EBCTCG 2005); see page 196.

on the effects of the treatments being compared after year 5. Therefore, the second cycle of the EBCTCG included trials that began before 1985, as in the first cycle, but the follow-up was now extended for a further five years, to 1990. This enabled the effects of treatment on mortality to be evaluated not just to five, but also to ten years after the diagnosis of breast cancer (EBCTCG 1992). Data were available for a total of 40 trials of the effect of tamoxifen versus the same standard treatments but without tamoxifen. These trials included nearly 30,000 women, comprising approximately 98% of all those randomized into eligible trials, and just over 8000 of them had died. A highly significant effect of tamoxifen was once again apparent ($p < 0.00001$), and women who had received the drug had 17% (standard error 2%—here and below we give standard errors in parentheses after the corresponding estimates) lower mortality rate over the entire period of follow-up than those who did not. It was also clear that tamoxifen substantially reduced—by 39% (9%), giving $p < 0.00001$—the risk of development of 'contralateral' breast cancer, that is, of a completely new cancer arising in the previously unaffected breast.

In the second cycle of the EBCTCG, data were available for 11,000 women randomized in a total of 31 trials of adjuvant polychemotherapy versus no chemotherapy—79% of all women randomized into eligible trials—of whom over 3500 had died. A highly significant effect of polychemotherapy was demonstrated ($p < 0.00001$) and women who had received polychemotherapy had mortality rate 16% lower than those who did not.

Treatment of pre-menopausal women with ovarian ablation, which destroys ovarian function, thus altering sex hormone levels and inducing an artificial menopause, may affect the progression of breast cancer and also survival. Data were available for just over 3000 women in ten randomized trials of the effect of ovarian ablation and these demonstrated a highly significant ($p = 0.0004$) reduction in mortality of 25% (7%) for the 1800 or so women treated under the age of 50. Curiously, this is the one EBCTCG result that did not prove durable. For the 1326 women randomized to ovarian ablation when aged over 50, ovarian ablation had no significant effect either on overall mortality or on recurrence-free survival. This is possibly due to the fact that the majority of such women would have been post-menopausal at the time they were randomized.

In the second cycle of the EBCTCG, data were also available on 6300 women randomized in 24 trials of immunotherapy given to increase the immune response of the woman's body to the tumour; eight trials of bacillus Calmette–Guérin, nine of levamisole, and seven of other agents. Neither in total, nor in any of the three subgroups, nor in any of the 24 separate trials was there any significantly favourable difference between treatment or control in either recurrence-free or overall survival—indeed, women given immunotherapy had 3% (4%) higher rates for both endpoints. Perhaps by chance, for bacillus Calmette–Guérin the adverse effect of 20% (8%) just reached a conventional level of statistical significance ($p = 0.02$). These results show that an overview can yield a strongly null result and, in particular, the results for bacillus Calmette–Guérin in the overview contrasted

with previous claims of a benefit from it in 'historically controlled' comparisons (EBCTCG 1992, Hortobagyi *et al.* 1978).

In the second cycle of the EBCTCG, the reduction in mortality following either tamoxifen or the polychemotherapy regimens tested in the trials available at that time was highly significant both during and after years 0–4, so the cumulative differences in survival are larger at ten than at five years after initial treatment. Both direct and indirect randomized comparisons indicate long-term polychemotherapy, over 12 months, for example, to be no better than shorter, for example, of six months. However, indirect comparisons suggested that longer-term tamoxifen, such as daily for two or for five years, is significantly more effective than shorter tamoxifen regimens, such as daily for only 1 year. This observation, together with promising preliminary findings from several trials, which randomly assign women to different durations of adjuvant tamoxifen therapy—such as two versus five years or five versus ten years (Peto 1996)—led in the 1990s to the establishment of the ATLAS and aTTom trials (`www.ctsu.ox.ac.uk/atlas/`) that are seeking to establish reliably the effects of prolonging adjuvant tamoxifen by an extra five years among women who have already received a few years—usually five or so—of tamoxifen prior to being enrolled in the trials. These two trials address the question of the appropriate duration of adjuvant hormonal therapy in general. Therefore, their results should be relevant not only to tamoxifen itself but also to other hormonal treatments as they become available.

In women aged over 70 at diagnosis, the second cycle of the EBCTCG showed the efficacy of tamoxifen, but few women in this age range had been included in the trials of polychemotherapy. Among women aged 50–69 not only were tamoxifen and polychemotherapy both demonstrated to have a beneficial effect when given individually, but a directly randomized comparison also demonstrated polychemotherapy plus tamoxifen to be better than polychemotherapy alone; a 20% (4%) reduction in mortality rate was seen ($p < 0.00001$). Directly randomized comparisons also suggested that polychemotherapy plus tamoxifen may be better than tamoxifen alone, but at that time the reduction in mortality of 10% (4%) was not highly significant. At ages below 50, although both polychemotherapy and ovarian ablation were demonstrated to have a beneficial effect when given individually, the numbers available for the examination of their effects when given in combination were small and the associated standard errors correspondingly large.

In addition to examining data on the effects of systemic treatments, the second cycle of the EBCTCG also considered trials of the effects of different local therapies (EBCTCG 1995). Data were available from 36 trials comparing radiotherapy plus surgery with the same type of surgery alone, ten comparing more-extensive surgery with less extensive surgery and 18 comparing more-extensive surgery with less-extensive surgery plus radiotherapy. Information was available on mortality for 28,500 women, over 97% of the women randomized to eligible trials. Some of these local therapies had substantially different effects on the

rates of local recurrence of the breast cancer: in particular, the addition of radiotherapy to surgery reduced the rate of local recurrence by a factor of three, and breast-conserving surgery involved some risk of recurrence in the remaining tissue. However, at least in the 1990 overview, these trials did not demonstrate any differences in overall survival at ten years.

9.4 The third cycle (1995)

In the third cycle of the EBCTCG, the number of eligible trials was expanded to include all those that began before 1990. Information was obtained on approximately 37 000 women who had been randomized in 55 trials of adjuvant tamoxifen versus no tamoxifen, comprising about 87% of all the women randomized into eligible trials (EBCTCG 1998*b*). Compared with the second cycle, the amount of evidence on events occurring more than five years after randomization was substantially increased and, in terms of numbers of deaths, the amount of evidence from trials of about five years of tamoxifen was doubled. Nearly 8000 of the randomized women had a low, or zero, level of oestrogen-receptor protein measured in their primary tumour; these are 'ER-negative' tumours. Among these women the overall effects of tamoxifen were small, with the annual mortality rate reduced by only 6% (4%), and there was no suggestion of any trend towards greater benefit with longer treatment. In contrast, among the remaining women, of whom there were 18 000 with ER-positive tumours and nearly 12,000 women with untested tumours, the results were striking: for trials of one year, two years, and five years of adjuvant tamoxifen, mortality was reduced by 12% (3%), 17% (3%), and 26% (4%), respectively, during ten years of follow-up. Not only were all these reductions highly significant individually, but there was some evidence of a greater effect with longer treatment ($p = 0.003$). The proportionate mortality reductions were similar for women with node-positive and node-negative disease, but in absolute terms the reductions were greater in node-positive women, in whom survival is generally poorer. In trials with the longest course of treatment, of about five years of tamoxifen, the absolute improvements in ten-year survival were 11% (2%) for node-positive (61% versus 50%; $p < 0.00001$) and 6% (1%) for node-negative (79% versus 73%; $p < 0.00001$). These benefits were largely irrespective of age, menopausal status, daily tamoxifen dose, and of whether or not the women in both arms of the trial had received chemotherapy. In terms of other outcomes, about five years of tamoxifen approximately quadrupled the incidence of endometrial cancer ($p = 0.0008$), and halved the incidence of cancer in the contralateral breast ($p < 0.00001$): in absolute terms, however, the decrease in the incidence of contralateral breast cancer was about twice as large as the increase in the incidence of endometrial cancer. Tamoxifen had no apparent effect on the incidence of colorectal cancer or, after exclusion of deaths from breast or endometrial cancer, on any of the other main categories of cause of death. About one extra death per 5000 woman-years of tamoxifen was attributed to pulmonary embolus but, based on the evidence available at that time, the excess was not statistically significant.

Information was available in the third cycle of the EBCTCG on about 18,000 women randomized in 47 trials of prolonged polychemotherapy versus no chemotherapy, about 6000 women randomized in 11 trials of longer versus shorter polychemotherapy, and about 6000 women in 11 trials of anthracycline-containing regimens versus cyclophosphamide, methotrexate, and fluorouracil (EBCTCG 1998*a*). In trials of polychemotherapy versus no chemotherapy there were highly significant reductions in mortality both for women aged under 50, for whom there was a 27% (5%) reduction ($p < 0.00001$), and for women aged 50–69 at randomization, who showed an 11% (3%) reduction ($p = 0.0001$), while few women aged 70 or over had been studied. After taking both age and time since randomization into account, the proportionate reductions in mortality were similar in women with node-negative and node-positive disease. These proportionate reductions suggest that, for women aged under 50 at randomization, the effect of polychemotherapy would be to increase a typical ten-year survival of 71% for those with node-negative disease to 78%, giving an absolute benefit of 7%, while for women with node-positive disease it would be to increase a typical ten-year survival of 42% to 53%, an absolute benefit of 11%. For women aged 50–69 at randomization, the corresponding increases would be from 67% to 69% for those with node-negative disease, an absolute benefit of only 2%, and 46% to 49% for those with node-positive disease, giving an absolute benefit of only 3%. At a given age, the benefits of polychemotherapy appeared largely independent of menopausal status at presentation, ER status of the primary tumour, and of whether or not adjuvant tamoxifen had been given. In addition, the directly randomized comparisons of polychemotherapy did not indicate any survival advantage with the use of more than about six months of polychemotherapy. In contrast, the directly randomised comparisons provided some evidence that, compared with cyclophosphamide, methotrexate, and fluorouracil alone, the anthracycline-containing regimens reduced mortality slightly, to a five-year survival of 69% versus 72% ($p = 0.02$). In terms of other endpoints, polychemotherapy reduced the incidence of cancer in the contralateral breast by about one-fifth and had no apparent adverse effect on deaths from causes other than breast cancer. Although the EBCTCG data show that polychemotherapy can improve long-term survival, it does have considerable short-term side effects, including leukopenia, nausea and vomiting, thromboembolic events, thrombocytopenia, anaemia, infection, mucositis, diarrhoea, and neurological toxicity (Pritchard *et al.* 1997, Fisher *et al.* 1990). The incidence of such events has not been reviewed by the EBCTCG, but clearly needs to be taken into account in treatment decisions.

Trials of the effect of ovarian ablation were also considered in the third cycle of the EBCTCG (EBCTCG 1996). Many of these trials began before 1980, and so 15 years of follow-up were available for analysis. Among the 1354 women aged 50 or over when randomized, there was no significant improvement of ovarian ablation on survival, as in the results obtained in the second cycle. However, among the 2102 women aged 50 or under when randomized, 15-year survival was highly significantly improved among those allocated ovarian ablation—52.4%

versus 46.1%, so 6.3% (2.3%) fewer deaths per 100 women treated—and the benefit was significant both for node-positive and for node-negative disease. In the trials of ablation plus cytotoxic chemotherapy versus the same chemotherapy alone, the benefit of ablation appeared smaller than in the trials in the absence of chemotherapy, and although there was no significant heterogeneity between these two subgroups, the benefit of ovarian ablation on survival was not significant when the trials in which both arms had received chemotherapy were considered on their own. It was concluded that further randomized evidence was needed on the additional effect of ovarian ablation in the presence of other adjuvant treatments and also on the relevance of hormone receptor measurements, which were only available for four of the 12 trials.

Many of the trials comparing radiotherapy plus surgery with the same type of surgery alone started even earlier than the trials of ovarian ablation. Therefore, in the third cycle of the EBCTCG, it was possible to examine the impact of radiotherapy at both ten and at twenty years (EBCTCG 2000). Data were available for a total of 40 trials, involving 20,000 women, half with node-positive disease. In these trials the radiotherapy fields included not only chest wall or residual breast, but also the axillary, supraclavicular, and internal mammary chain lymph nodes. Breast cancer mortality was reduced in the women who had received radiotherapy ($p = 0.0001$) but mortality from certain other causes, in particular cardiovascular disease, was increased, and overall 20-year survival was 37.1% with radiotherapy versus 35.9% without ($p = 0.06$). Nodal status, age and decade of follow-up strongly affected the ratio of breast cancer mortality to other mortality, and hence affected the ratio of absolute benefit to absolute hazard. It was estimated that, without the long-term hazard, radiotherapy would have produced an absolute increase in 20-year survival of about 2–4%, except for women at particularly low risk of local recurrence. The average hazard seen in these trials would, however, reduce this 20-year survival benefit in young women and reverse it in older women.

Until recently, it had been thought that an increased risk of cardiovascular disease occurred only following substantial doses of radiation, and improvements in radiotherapy techniques for breast cancer in recent years have tended to reduce radiation doses to the heart. However, there is now mounting evidence that doses that have traditionally been regarded by clinical oncologists as unimportant in terms of cardiovascular risk may, in fact, carry an appreciable long-term risk. The main evidence for this comes from the follow-up studies of the survivors of the atomic bombings of Hiroshima and Nagasaki, where significant dose-response relationships for heart disease and for stroke have been reported following whole body uniform doses (Preston *et al.* 2003). These data also suggest that if there is a threshold dose for non-cancer disease mortality then it cannot be greater than about 0.5 Gy and this suggests that, even with modern radiotherapy techniques, some cardiovascular risk may well remain. Further research is now being carried out, using data from cancer registries (Darby *et al.* 2003) together with detailed dosimetry data, to characterize more precisely the cardiovascular risk from radiotherapy for breast cancer.

9.5 The fourth cycle (2000)

The fourth cycle of the EBCTCG, whose results are currently being prepared for publication, has included even more data than the third round, with about 38,000 randomized women in trials of local therapies—including comparisons of radiotherapy plus surgery with the same type of surgery alone, more-extensive surgery with less extensive surgery, and more-extensive surgery with less-extensive surgery plus radiotherapy—and about 50,000 randomized women in trials of tamoxifen versus no tamoxifen, and 30,000 in the more interesting question of longer versus shorter durations of tamoxifen therapy, about 50,000 women involved in chemotherapy trials, and 10,000 in trials of ovarian ablation. In addition, for many of the women included in previous EBCTCG cycles, longer follow-up is available.

9.6 Recent trends in breast cancer mortality

During the period 1950–1960, the annual mortality rate for breast cancer in the age-range 35–69 years, calculated as the mean of the seven age-specific rates 35–39, 40–44, ... , 65–69 in the United Kingdom was around 58 per 100,000 women; see the left part of Figure 9.1. From about 1960, the rate started to rise, as in many other European countries, and this rise continued steadily until the late 1980s, by which time it was over 70 per 100,000 women. In 1990, however, it suddenly started to fall and it has fallen continuously since then, so that in 2000 it was only just over 50 deaths per 100,000, well below its value in the 1950s.

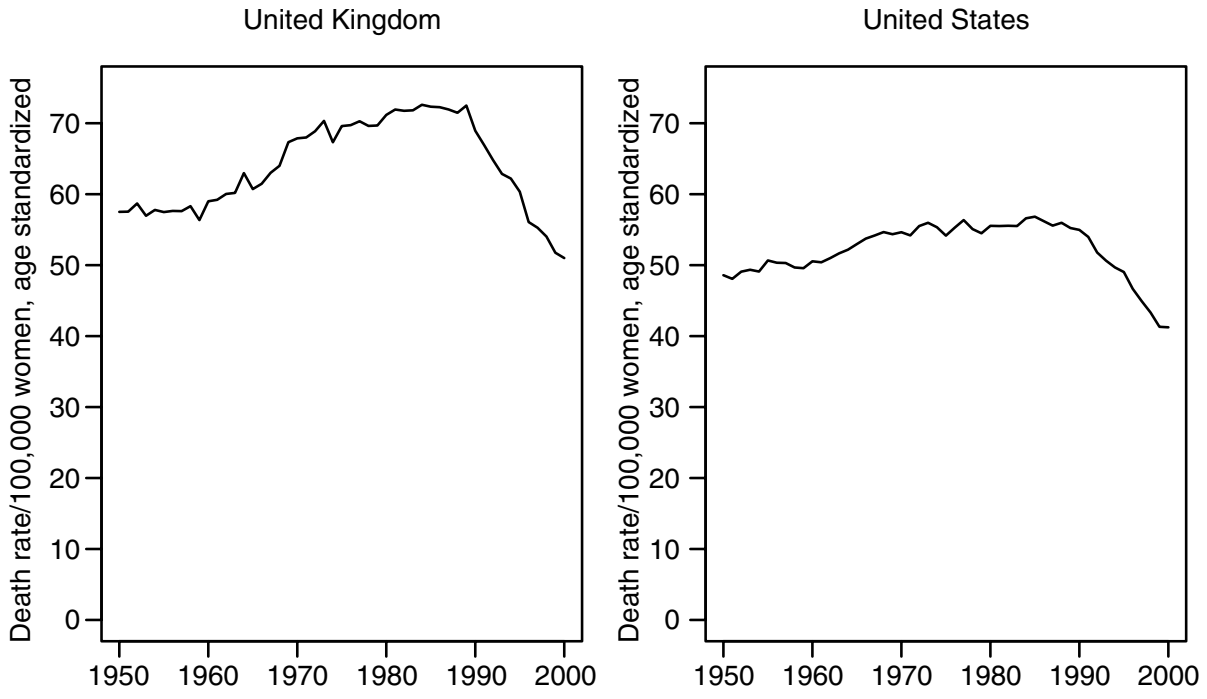

FIG. 9.1. Breast cancer mortality for women at ages 35–69 in the United Kingdom and United States, 1950–2000. The data are averaged annual rates in component five-year age groups, obtained using World Health Organization mortality and United Nations population estimates.

During the 1990s, lesser decreases have also occurred in several other countries, including the United States (Peto *et al.* 2000); see the right part of Figure 9.1. Recent data on breast cancer incidence, as opposed to mortality, are difficult to interpret as they are affected by screening. For example, in the UK the national screening program was introduced in 1987 for women aged 50–64, and has undoubtedly resulted in many cancers in this age range being diagnosed earlier than they would otherwise have been. However, there is no suggestion from the incidence rates at ages below 50 or above 65 of a sudden decrease in the underlying trend of breast cancer incidence rates that might be responsible for the recent decrease in mortality (Quinn *et al.* 2001). Some of the downward trends in mortality are likely to be the effect of the screening program, and detailed analyses have estimated that in the UK screening is responsible for 30–40% of the fall in mortality in age-groups 55–69 (Blanks *et al.* 2000, Sasieni 2003). The remaining 60–70% is likely to be explained partly by the tendency towards earlier presentation outside the screening program, but mostly by the increasing use of tamoxifen and chemotherapy from the mid-1980s, which has been helped by the EBCTCG analyses. In 2000, a United States National Institutes of Health Consensus Statement on adjuvant therapy for breast cancer (National Institutes of Health 2000) drew heavily on the findings of the EBCTCG for their recommendations on the use of tamoxifen, ovarian ablation and polychemotherapy. As a result of this and of similar treatment guidelines in other countries, further falls in breast cancer mortality worldwide can be expected in the future. At the same time new treatments for breast cancer that require rigorous assessment continue to be developed and provide further questions for assessment in future cycles of the EBCTCG.

Since this chapter was written, the report on the effects of chemotherapy and hormonal therapy of the fourth cycle of the EBCTCG has been published (EBCTCG, 2005). This shows that some of the widely practicable adjuvant drug treatments that were being tested in the 1980s, which substantially reduced 5-year recurrence rates, also substantially reduce 15-year mortality rates. In particular, for middle-aged women with ER-positive disease, the breast cancer mortality rate throughout the next 15 years would be approximately halved by 6 months of anthracycline-based chemotherapy followed by 5 years of adjuvant tamoxifen. For, if mortality reductions of 38% (age $<$ 50 years) and 20% (age 50–69 years) from such chemotherapy 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. Overall survival would be comparably improved, since these treatments have relatively small effects on mortality from the aggregate of all other causes. Further improvements in long-term survival could well be available from newer drugs, or better use of older drugs.

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