potentially valuable model to study the biologic differences within the ovaries of women at increased risk of developing ovarian cancer and the ovaries of women without increased risk. It is quite likely that the biologic mechanisms of the development of ovarian cancer in sporadic cases is similar to the mechanisms of development in women with genetic predisposition to develop the disease. The elucidation of these biologic mechanisms will allow rational approaches to the diagnosis, treatment, and, most important, prevention of this deadly disease.

References


Note

1Editor's note: SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

Five Years of Tamoxifen—or More?

Richard Peto*

Before 1990 there had been, for half a century, little evidence of any decrease in the U.S. age-standardized death rate from breast cancer. Chu et al. (1), however, have recently described a sudden decrease in breast cancer mortality during the 1990s, which they ascribe to the combined benefits of early detection and better treatment (particularly adjuvant chemotherapy and hormonal therapy) during the 1980s. A decrease during the 1990s relative to the previous pattern of U.S. breast cancer mortality is seen in each decade of age from 30-39 years to 70-79 years. In Britain, where there had been much less mammography during the 1980s but perhaps even more adjuvant hormonal therapy, a similarly sudden decrease in breast cancer mortality has also been seen during the 1990s, and at least some of this decrease is also attributable to better treatment of the disease, particularly with tamoxifen (2).

Although the absolute benefit produced by a few years of adjuvant tamoxifen therapy for patients with early breast cancer is not large (50% survival might, for example, be increased to 55% or 60%), the treatment is widely practicable and the disease is common. Since about one million women worldwide are now taking tamoxifen, this drug may well be preventing more cancer deaths than any other. But there is still widespread uncertainty as to how long such adjuvant therapy should usually continue. This question is being addressed directly by several trials that randomly assign women to different durations of adjuvant tamoxifen therapy (e.g., 2 versus 5 years or 5 versus 10 years). Last month and this month in the Journal, preliminary results have been reported from four of these trials (3-6). One of the reports, i.e., the one from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial (6), also includes some of the best evidence ever published on the advantages of 5 years of adjuvant tamoxifen versus no adjuvant tamoxifen, finding highly significant delays in disease recurrence both for women who were under 50 years of age when they were randomly assigned and for older women.

The original trials of adjuvant tamoxifen versus control that began in the 1970s quickly showed that both local and distant recurrences could be delayed. However, when distant recurrence occurred in those women who had not been allocated to adjuvant tamoxifen, then hormonal treatment would often be used to try to delay its progress. Since the additional recurrences in the control groups were those that could have been delayed if tamoxifen had been given initially, many of them could still respond to hormonal treatment. Thus, as far as survival is concerned, many of these studies should be thought of not as trials of tamoxifen versus no tamoxifen but rather as trials that compared two different strategies for using tamoxifen (i.e., as trials of adjuvant tamoxifen versus tamoxifen only when recurrence occurred). Hence, especially in the first few years after randomization in these studies, the effect of adjuvant tamoxifen on survival was less extreme than its effect on recurrence and was less quickly recognized. Indeed, in the early 1980s, it was widely, though mistakenly, believed that the previous trials had proved that adjuvant tamoxifen did not affect survival.

*Correspondence to: Richard Peto, FRS, Professor of Medical Statistics and Epidemiology, Clinical Trial Service Unit and Epidemiological Studies Unit, Imperial Cancer Research Fund, Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford OX2 6HE, U.K.
By 1984, however, a preliminary meta-analysis showed some effect on survival (7), and more detailed meta-analyses by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) in 1985 showed that 5-year survival could be improved (8). In 1985, however, it was only the overall results from the 28 trials then available (total at that time: 1762 deaths with adjuvant tamoxifen therapy versus 2020 without, two-sided P<.00001) that were statistically reliable. Although there was no significant heterogeneity in the results from the 28 trials in the 1985 overview, the play of chance meant that there was still, at that time, no apparent benefit in some of the studies (including, as it happened, the largest of them, which was the NSABP B-09 trial, then with 359 versus 363 deaths).

By the time of the 1990 EBCTCG overview (9), with more trials and longer follow-up, it had become apparent that the absolute survival advantage was greater after 10 years than after only 5 years of follow-up and that the benefit appeared to be greater with more prolonged tamoxifen treatment. Most of the trials of adjuvant tamoxifen versus control (again, “control” might well mean “no tamoxifen unless disease recurrence is diagnosed”) involved only 1, 2, or 5 years of adjuvant tamoxifen therapy. Within this range, more prolonged treatments appeared to be more effective at preventing or delaying recurrence and improving 10-year survival. Hence, when tamoxifen is being used as an adjuvant therapy for early breast cancer, many doctors now recommend that it should continue for about 5 years, and there have been suggestions that it should, for certain patients, continue for 10 years or even indefinitely.

But tamoxifen does have some adverse side effects that must be expected to be aggravated by longer treatment; perhaps the most important of these is an increased incidence of endometrial cancer (which, with only a few years of treatment, causes about one extra death per thousand women). Although, in terms of survival, the benefits of tamoxifen therapy are far greater than the hazards, there continues to be much debate as to whether a shorter duration of adjuvant tamoxifen (e.g., 2 years) might suffice and, conversely, as to whether a longer duration (e.g., 10 years) might generally be preferable. This question is important because, with about one million women now taking tamoxifen, even a small further improvement in long-term survival might prevent several thousand deaths a year.

It is, however, a surprisingly difficult question to answer directly because there is a substantial “carry-over” benefit from tamoxifen that lasts well beyond the treatment period. Thus, a few years of adjuvant tamoxifen therapy produces a reduction in the annual recurrence rate (and in the annual death rate) not only while treatment continues but also for some years after the treatment has ended (6,8). This persistent benefit was helpful in the trials of adjuvant tamoxifen therapy versus no adjuvant tamoxifen, since it increased the difference in 10-year survival between treatment and control groups. However, in trials that compare stopping after just a few years of tamoxifen versus continuing for several additional years, this carry-over benefit may initially be an obstacle, since a persistent benefit in the control (i.e., shorter duration) group may mean that, for the first few years of additional treatment, there is little additional benefit, even if later on a worthwhile additional benefit will emerge. Thus, trials of 2 versus 5 years of tamoxifen therapy may well need 10 years of follow-up rather than 5, and trials of 5 versus 10 years of therapy may well need 15 years of follow-up after the initial diagnosis rather than 10.

Even more than was the case with the trials of adjuvant tamoxifen versus control, what may be needed in the trials of a few versus several years of adjuvant tamoxifen therapy is randomization of a total (in all trials) of some tens of thousands of women, many years of follow-up, and, finally, worldwide collaboration in the interpretation of the overall findings. Nevertheless, the early results from the four newly published trials (3-6) are still of substantial interest (Table 1).

The two European trials (3,5) both compared 2 versus 5 years of adjuvant tamoxifen. Both trials involved substantial numbers of recurrences (British trial: 335; Swedish trial: 507) and of deaths (British trial: 204; Swedish trial: 294), both found significantly fewer recurrences with 5 years than with 2 years of tamoxifen therapy (British trial: two-sided P<.05; Swedish trial: two-sided P<.01), and both found somewhat fewer deaths with 5 years than with 2 years of treatment. These promising mortality differences, however, are not at present statistically convincing.

The two North American trials (4,6), one from the Eastern Cooperative Oncology Group (ECOG) and the one from the NSABP, both compared 5 versus about 10 years of adjuvant tamoxifen. The numbers of recurrences after these randomizations were relatively small (ECOG trial: 38; NSABP B-14 trial: 53), as were the numbers of deaths after recurrence (ECOG trial: 16; NSABP B-14 trial: 25). The NSABP results favor 5 years of

### Table 1. Results from four new trials of different durations of adjuvant tamoxifen therapy for early breast cancer*

<table>
<thead>
<tr>
<th></th>
<th>Swedish trial (5)</th>
<th>British trial (3)</th>
<th>NSABP B-14 trial (6)</th>
<th>ECOG trial (4)</th>
</tr>
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<tr>
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<td>2 y of therapy</td>
<td>5 y of therapy</td>
<td>2 y of therapy</td>
<td>5 y of therapy</td>
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<td>No. of women randomly assigned</td>
<td>1801</td>
<td>1744</td>
<td>1470</td>
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<td>No. of breast cancer recurrences</td>
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<td>228</td>
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<td>145</td>
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<tr>
<td>No. of deaths after recurrence or from an unknown cause</td>
<td>162</td>
<td>152</td>
<td>110</td>
<td>94</td>
</tr>
<tr>
<td>No. of deaths from a known cause before recurrence</td>
<td>92</td>
<td>78</td>
<td>14</td>
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<tr>
<td></td>
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*The women randomly assigned are those apparently free of breast cancer 2 years (3,5) or 5 years (4,6) after diagnosis, and the recurrences reflect the numbers of these women with a subsequent diagnosis of distant, local, or contralateral breast cancer. NSABP = National Surgical Adjuvant Breast and Bowel Project; ECOG = Eastern Cooperative Oncology Group.
but much larger numbers of patients still need to be randomly assigned. If the trials of different tamoxifen durations that are currently recruiting new patients can achieve really large-scale recruitment before the year 2000, then they will yield preliminary findings in 2005 and reliable findings in 2010.

Until then, the four new trial results (3-6) will tend to foster agreement with the statement in the summary of the NCI clinical announcement, “While we eagerly anticipate the results of ongoing trials of 5 years versus longer, all available evidence indicates that 5 years of tamoxifen is a reasonable standard for the adjuvant setting.” But they should also foster the continuing disagreement as to whether or not longer treatment is promising, which will probably be resolved only by long-term follow-up of substantially larger numbers of patients than those in the existing trials. This process is frustratingly slow, but eventually it is reliable, and it needs to be. Every year almost one million women develop breast cancer, and premature certainties as to whether adjuvant tamoxifen therapy should be stopped after 5 years could lead to many unnecessary deaths.

References