Coronary Heart Disease Mortality After 5 Years of Adjuvant Tamoxifen Therapy: Results from a Randomized Trial

Bo Nordenskjöld, Johan Rosell, Lars-Erik Rutqvist, Per-Olof Malmström, Jonas Bergh, Nils-Olof Bengtsson, Thomas Hatschek, Arne Wallgren, John Carstensen

From January 1, 1983, through December 31, 1992, a total of 4610 patients entered a randomized trial that compared mortality among patients receiving 2 years of adjuvant tamoxifen therapy with that in patients receiving 5 years of adjuvant tamoxifen therapy, 4175 of whom were recurrence free after 2 years of tamoxifen therapy. Among the 2046 patients randomly assigned to the 5-year group all-cause mortality, breast cancer–specific mortality, and the incidence of contralateral breast cancer were reduced, compared with those among 2129 patients randomized in the 2-year group, but the incidence of endometrial cancer was increased. In addition, mortality from coronary heart disease was statistically significantly reduced in the 5-year group, compared with that in the 2-year group (hazard ratio = 0.67, 95% confidence interval = 0.47 to 0.94; \( P = .022 \) [two-sided Wald test]). Ten years after surgery, 2.1% of the patients in the 5-year group and 3.5% of those in the 2-year group had died from coronary heart disease. No statistically significant increases in mortality from other heart diseases, cerebrovascular diseases, or other vascular diseases were observed. [J Natl Cancer Inst 2005;97:1609–10]

In 1996, we reported the first analysis of a randomized trial of postmenopausal women, younger than 75 years of age at surgery, who had early-stage breast cancer (1). We found increased disease-free survival and overall survival among patients assigned to 5 years of tamoxifen treatment compared with those among patients assigned to 2 years of tamoxifen treatment. After an additional 1 year of patient recruitment and a median follow-up of 10.6 years, we report an additional analysis of this trial that found reduced death rates from coronary heart disease and from breast cancer among patients in the 5-year group, compared with patients in the 2-year group.

The design and performance of the trial were described extensively in the first report (1). The study included data from five of the six Swedish health care regions; two of which used 20-mg daily doses of tamoxifen and three of which used 40-mg daily doses of tamoxifen. From January 1, 1983, through December 31, 1992, a total of 4610 patients were entered in the trial, 4175 of whom remained alive and recurrence free at 2 years and could thus contribute meaningful information to the comparison of outcomes associated with 2 years of tamoxifen treatment and with 5 years of tamoxifen treatment.

Information on deaths through December 31, 2000, was obtained from the Swedish Cause of Death Registry. In the analysis, the Ninth Revision of the International Classification of Diseases was used. Information on incidence of contralateral breast cancer and of endometrial cancer was obtained from the Swedish Cancer Registry.

We used a Cox proportional hazards model, with stratification by trial center. The validity of the proportionality assumption was assessed by repeating the Cox analyses in two time periods (the first 7 years from diagnosis and more than 7 years from diagnosis). For the analyses of mortality from cardiovascular diseases between the 2- and the 5-year groups, patients were censored at the date of diagnosis of distant metastasis, local recurrence, or contralateral breast cancer to avoid any interference from chemotherapy or radiotherapy of recurrent disease on cardiovascular mortality. Cumulative mortality from coronary heart disease was estimated by use of life-table methods. All \( P \) values were from two-sided Wald tests, obtained from the Cox regression models.

An intention-to-treat analysis revealed that 5 years of tamoxifen treatment compared with 2 years of tamoxifen treatment was associated with reduced all-cause mortality (hazard ratio [HR] = 0.81, 95% confidence interval [CI] = 0.73 to 0.90). Breast cancer mortality in the 5-year group was lower than that in the 2-year group (HR = 0.84, 95% CI = 0.73 to 0.96). The results from a subgroup analysis by estrogen receptor status suggested that this benefit was mainly restricted to patients with estrogen receptor–positive tumors (Table 1).

The incidence of contralateral breast cancer was reduced in the 5-year group compared with that in the 2-year group, but the incidence of endometrial cancer was increased (Table 1). Six patients in the 2-year group and seven patients in the 5-year group died from endometrial cancer.

Death from all cardiovascular diseases was statistically significantly lower in the 5-year group than in the 2-year group (HR = 0.79, 95% CI = 0.63 to 1.00). This reduction appeared to be mainly associated with a statistically significant reduction in mortality from coronary heart disease (Fig. 1 and Table 1). The reduction in mortality was still statistically significant when we restricted the analysis to the period beyond 7 years from diagnosis (HR = 0.58, 95% CI = 0.37 to 0.91; \( P = .02 \)); however, the reduction in coronary heart disease mortality was smaller and not statistically significant during the first 7 years (HR = 0.82, 95% CI = 0.47 to 1.41; \( P = .47 \)). No statistically significant increase in mortality from other heart disease, cerebrovascular disease, or other vascular diseases was observed (Table 1).

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See “Notes” following “References.”

DOI: 10.1093/jnci/dji342 © The Author 2005. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org.
Six deaths from pulmonary embolism have been recorded in the 5-year group, compared with five in the 2-year group.

Our data confirm previous findings of decreased death rates in patients receiving 5 years of postoperative tamoxifen therapy compared with 2 years of therapy (1). After a median follow-up of 10.6 years, this reduction was only partially explained by reduced breast cancer death. We now report that death from coronary heart disease was reduced. It should be pointed out that death from coronary heart disease is a late event, and we provide a long observation period. We have also studied postmenopausal patients who were up to 75 years of age at entry. In this population, coronary heart disease is an important cause of death.

![Graph of cumulative mortality from coronary heart disease](image)

Table 1. Number of events and hazard ratios in the 5 versus 2 years of adjuvant tamoxifen trial*

<table>
<thead>
<tr>
<th>No. of events</th>
<th>2-y group (n = 2129)</th>
<th>5-y group (n = 2046)</th>
<th>Hazard ratio (95% CI)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>809</td>
<td>671</td>
<td>0.81 (0.73 to 0.90)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Breast cancer mortality (174)‡</td>
<td>428</td>
<td>364</td>
<td>0.84 (0.73 to 0.96)</td>
<td>.013</td>
</tr>
<tr>
<td>ER (n = 2542)</td>
<td>259</td>
<td>213</td>
<td>0.77 (0.64 to 0.92)</td>
<td>.005</td>
</tr>
<tr>
<td>ER* (n = 603)</td>
<td>62</td>
<td>64</td>
<td>1.13 (0.79 to 1.62)</td>
<td>.50</td>
</tr>
<tr>
<td>Endometrial cancer mortality (n = 1030)</td>
<td>107</td>
<td>87</td>
<td>0.80 (0.61 to 1.07)</td>
<td>.13</td>
</tr>
<tr>
<td>Contralateral breast cancer incidence</td>
<td>83</td>
<td>55</td>
<td>0.68 (0.48 to 0.96)</td>
<td>.026</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>24</td>
<td>41</td>
<td>1.78 (1.08 to 2.95)</td>
<td>.025</td>
</tr>
<tr>
<td>Endometrial cancer incidence</td>
<td>6</td>
<td>7</td>
<td>1.16 (0.39 to 3.46)</td>
<td>.79</td>
</tr>
<tr>
<td>Coronary heart disease mortality (410–4)‡</td>
<td>78</td>
<td>54</td>
<td>0.67 (0.47 to 0.94)</td>
<td>.022</td>
</tr>
<tr>
<td>All cardiovascular mortality (390–459)‡</td>
<td>163</td>
<td>136</td>
<td>0.79 (0.63 to 1.00)</td>
<td>.047</td>
</tr>
<tr>
<td>Cerebrovascular disease mortality (430–8)‡</td>
<td>47</td>
<td>40</td>
<td>0.81 (0.53 to 1.23)</td>
<td>.32</td>
</tr>
<tr>
<td>Pulmonary embolism mortality (415.1)‡</td>
<td>5</td>
<td>6</td>
<td>1.20 (0.37 to 3.93)</td>
<td>.77</td>
</tr>
</tbody>
</table>

*CI = confidence interval; ER = estrogen receptor.
†Two-sided Wald test.
‡Ninth International Classification of Diseases code numbers.

There are, however, limitations to our study. The medical records from the Swedish Cause of Death Registry were not reviewed to confirm causes of death. Furthermore, the statistical power to detect rare events, such as mortality from endometrial cancer or pulmonary embolism, was small and is reflected in the wide confidence intervals in Table 1. Results from other investigations support our findings (2–5). Tamoxifen treatment alters the composition of lipids in the blood to a pattern that has been associated with reduced risk of heart disease (5). In their analysis of the Scottish adjuvant tamoxifen trial, McDonald et al. (2,4) found a reduced risk of coronary heart disease in their group of patients who were randomly assigned to receive 5 years of tamoxifen treatment compared with the risk in patients randomly assigned to no adjuvant tamoxifen therapy. Our results are also compatible with those of Reis et al. (6), who found no effect on coronary heart disease mortality during the initial years of follow-up of patients receiving 2 years of tamoxifen treatment or placebo in a prevention trial.

Our results strongly support the use of tamoxifen in the adjuvant treatment of breast cancer patients. When tamoxifen treatment is compared with other types of adjuvant therapy, such as aromatase inhibitor therapy (7), effects on both breast cancer and non-breast cancer mortality should be considered.

References


Notes

Editor’s Note: Dr. Rutqvist is currently conducting research sponsored by AstraZeneca. Dr. Bergh has participated in an advisory board arranged by AstraZeneca and has received honoraria for participating in courses by giving lectures and chairing meetings.

We thank the Swedish Cancer Society for support.

Manuscript received February 17, 2005; revised August 23, 2005; accepted August 25, 2005.