of 42 g, the relative risk was about 6 (2).

Breast and Bowel Project (NSABP) B-

trial, with an average cumulative dose

dosage of tamoxifen and the relative risk

relationship between the cumulative
doctorate of tamoxifen (e.g., the

short-term adjuvant tamoxifen therapy,

for instance, related to the

mean data for analysis.

Editor'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.

Curtis et al. (1) described the incidence of second cancers among 14,358 breast cancer patients reported to the Surveillance, Epidemiology, and End Results (SEER) Program who received adjuvant tamoxifen therapy. They found a significant excess of endometrial cancer in accordance with several previous reports but no excess of stomach and colon cancers as reported from three Scandinavian adjuvant tamoxifen trials.

Although the SEER data may provide relevant information on the effects of short-term adjuvant tamoxifen therapy, they appear to be of little value for judging the long-term effects of high cumulative doses of tamoxifen (e.g., the cumulative dose resulting from a 20-mg-daily schedule for 5 years, which now has become the standard treatment for most breast cancer patients).

In many studies of second cancer incidence after adjuvant tamoxifen therapy, there appears to be a direct relationship between the cumulative dose of tamoxifen and the relative risk of endometrial cancer. In the Stockholm trial, with an average cumulative dose of 42 g, the relative risk was about 6 (2). This excess was similar to that observed in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial with a protocol cumulative dose of 37 g (3). In trials using cumulative protocol doses of 11 g, the excess of endometrial cancer corresponded to a relative risk on the order of 2-3 (4,5).

In the study by Curtis et al. (1), there was no information on the tamoxifen doses actually received by the patients. However, the published figures indicate that the average cumulative dose was low. The ratio between the observed and the expected numbers of endometrial cancer cases among the tamoxifen-treated patients was 2.03. The corresponding ratio for those patients not treated with tamoxifen was 1.23. These figures suggest a relative risk of endometrial cancer of less than 2.0 associated with the use of tamoxifen in the SEER material. Given the mentioned results from previous trials, such a low figure is what one would expect with an average cumulative dose of less than 10 g. This is perhaps not surprising in view of the fact that the patients were treated during the period 1980 through 1992, when schedules of only 1 or 2 years of tamoxifen were common.

Thus, the SEER database does not appear to include many patients treated with tamoxifen doses that are relevant to current medical practice. In addition, as stated by the authors, few patients were followed for more than 10 years.

The mechanisms involved in tamoxifen carcinogenesis are not fully understood. It would appear that tamoxifen may have both tumor-initiating and tumor-promoting properties (2,6-9). Part of the promoting effect may be related to the estrogenic agonistic effects of tamoxifen. Such estrogenic effects may explain the early excess of endometrial cancer associated with tamoxifen therapy that has been observed in many studies. In contrast, tumor-initiating effects, for instance, related to the documented DNA-adduct-forming ability of tamoxifen, cannot be expected to show up until after several years of follow-up. Therefore, I agree with Curtis et al. that further studies of breast cancer survivors are needed to monitor site-specific risks of cancer over time in relation to duration and dose of tamoxifen.

LARS E. RUTQVIST

References


The mechanisms involved in tamoxifen carcinogenesis are not fully understood. It would appear that tamoxifen may have both tumor-initiating and tumor-promoting properties (2,6-9). Part of the promoting effect may be related to the estrogenic agonistic effects of tamoxifen. Such estrogenic effects may explain the early excess of endometrial cancer associated with tamoxifen therapy that has been observed in many studies. In contrast, tumor-initiating effects, for instance, related to the documented DNA-adduct-forming ability of tamoxifen, cannot be expected to show up until after several years of follow-up. Therefore, I agree with Curtis et al. that further studies of breast cancer survivors are needed to monitor site-specific risks of cancer over time in relation to duration and dose of tamoxifen.

LARS E. RUTQVIST

Note

Correspondence to: Lars E. Rutqvist, M.D., Ph.D., Oncologic Center, Karolinska Hospital, S-10401 Stockholm, Sweden.

Response

Dr. Atkins indicates that the risks we presented for gastrointestinal cancer following tamoxifen treatment of breast cancer are biased toward the null because we failed to consider induction time. Moreover, he maintains that our ability to detect increased risks among long-term survivors is limited because of the short follow-up in the Surveillance, Epidemiology, and End Results (SEER) Program database. The possibility of a minimum latency period for second cancers was explored in Table 2 of our brief communication (1). Al-
through the mean follow-up was 2.8 years, the number of tamoxifen-treated patients who survived 5 or more years (n = 2293) was close to the total number of tamoxifen-treated patients in the three Scandinavian trials (n = 2475) (2). Our results showed only a slight nonsignificant increase in risk of gastrointestinal cancer in the interval of 5 years or more among those treated with tamoxifen (observed/expected [O/E] = 1.29; 95% confidence interval [CI] = 0.83-1.92). However, we acknowledged that SEER currently has limited ability to evaluate risk among 10-year survivors. In response to Dr. Atkins' concern, we have analyzed separately 818 tamoxifen-treated patients in SEER who survived at least 7 years; no significant excess of gastrointestinal cancer was found (observed/expected [O/E] = 1.43; 95% CI = 0.65-2.71), although the risk of uterine corpus cancer remained elevated. In Scandinavia, Rutqvist et al. (2) reported a 1.9-fold increase in risk of gastrointestinal cancer associated with tamoxifen therapy (95% CI = 1.2-2.9), but they provided no information on risk among survivors of 5 or more or of 10 or more years.

Dr. Rutqvist notes that the current SEER data may be limited in judging the long-term effects of high cumulative doses of tamoxifen, especially the current tamoxifen schedule of 20 mg/day for 5 years. Actually, few studies have been able to evaluate risk of second cancers among long-term tamoxifen users, since 5-year regimens have only recently been widely used (3,4). In the Scandinavian study (2), more than 80% of the 2475 patients had 1-2 years of tamoxifen therapy, with maximum doses ranging from 11 to 29 g (45% had 30 mg/day for 1 year; 39% had 40 mg/day for 2 years; 16% had 40 mg/day for 5 years). Thus, the tamoxifen-related excesses of endometrial and gastrointestinal cancers observed in the Scandinavian trials appear to be based primarily on therapy given for fewer than 2 years. Further data on long-term tamoxifen use are provided by the large National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial, with 2639 patients receiving 20 mg/day for 5 or more years (5). The risks of endometrial cancer in the randomized, tamoxifen-treated group were 7.5 compared with the placebo group, 2.2 compared with population-based incidence rates, and 2.3 compared with data from the NSABP B-06 trial. The last two estimates resemble the twofold risk that we observed in the SEER database. The NSABP B-06 trial yielded no excess of colorectal or stomach cancer. Furthermore, two case-control studies (6,7) have found a significant trend of increasing risk of endometrial cancer with increasing duration of tamoxifen use, with threefold risks noted for users of 5 or more years.

Although information on duration of tamoxifen therapy is not available in SEER, it is possible to evaluate a subset of our cohort treated during a period when longer term tamoxifen therapy was gradually introduced (Table 1). The risks of cancers of the gastrointestinal tract and uterine corpus among patients receiving tamoxifen in the period 1985-1992 were similar to the risks among those treated during 1980-1984, whereas the risk of contralateral breast cancer fell to levels comparable to those of the general population. Estimation of risks of second cancers occurring beyond 5 years in the 1985-1992 period was limited by small numbers of person-years at risk.

Dr. Rutqvist suggests that the relative risk of uterine corpus cancer after breast cancer in our study is likely to be lower than the 2.03 risk observed in the tamoxifen group, since a 1.23 risk was seen in the no/unknown tamoxifen group. We did note in our brief communication (7) that at least part of the excess risk observed in the no/unknown tamoxifen group was related to tamoxifen therapy not reported to the SEER Program. Comparing the observed uterine corpus cancers incidence rates among tamoxifen-treated patients to that expected from the SEER population (O/E = 2.03) provides the most appropriate estimate, since breast cancer patients treated before the introduction of tamoxifen had a risk of uterine cancer similar to that of the general population.

In commenting on possible carcinogenic mechanisms, Dr. Rutqvist suggests that tamoxifen may have both tumor-promoting and tumor-initiating effects related to its capacity to form DNA adducts in laboratory animals. Although there is some evidence that humans may be less efficient in metabolizing the active compound a-hydroxytamoxifen (8-10), additional studies are needed on the possible genotoxic effects of tamoxifen. Most importantly, as noted by Drs. Atkins and Rutqvist, the risk of second cancers following tamoxifen therapy will be clarified only when large numbers of breast cancer patients are followed for long periods with detailed data on dose, duration of exposure, and potential confounders.

ROCHELE E. CURTIS
JOHN D. BOICE, JR.
DONNA A. SHRINER
BENJAMIN F. HANKEY
JOSEPH F. FRAUMENI, JR.

Table 1. Risk of selected second primary cancers among women treated with tamoxifen for breast cancer, aged 50 or more years, with localized or regional stage disease, who did not receive chemotherapy, by site and calendar year of initial breast cancer diagnosis

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
<td>O/E</td>
</tr>
<tr>
<td>All digestive cancers</td>
<td>1277</td>
<td>13 081</td>
</tr>
<tr>
<td>Stomach</td>
<td>7101</td>
<td>31 944</td>
</tr>
<tr>
<td>Colon, rectum</td>
<td>44 157</td>
<td>1.89-4.63</td>
</tr>
<tr>
<td>Breast (contralateral)</td>
<td>20 571</td>
<td>1.33-3.25</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>16 445</td>
<td>1.39-3.96</td>
</tr>
</tbody>
</table>

*O = observed number of second cancers; O/E = observed-to-expected ratio; CI = confidence interval.
Re: The p53 Gene in Breast Cancer: Prognostic Value of Complementary DNA Sequencing Versus Immunohistochemistry

Several papers published in the Journal have consistently shown the prognostic relevance of p53 protein expression detected by immunohistochemistry in large series of lymph node-negative breast cancers treated with local-regional therapy alone until early relapse (1-4). The findings in these papers have been recently contradicted by the findings of Sjögren et al. (5). Since p53 expression is an important product of translational research, controversial results do not inspire the confidence of physicians.

It is likely that alterations in the p53 gene (also known as TP53) detected by single-stranded conformation polymorphism analysis and mutational analysis provide prognostic information about tumor progression that is more accurate than that obtained with the simpler, quicker, and, in general, more feasible immunohistochemical detection using available monoclonal antibodies. However, the prognostic role of genomic alterations should be demonstrated in a series in which the authors reproduce previous immunohistochemical data.

For these reasons, my specific comments about the article by Sjögren et al. (5) are as follows:

1) The article deals with a mixed series of patients with lymph node-negative and lymph node-positive breast cancers who were given different treatments (regional or systemic), and this complexity may have interfered with the ability to determine the relevance of p53 expression as a prognostic variable or as a predictor of response to radiotherapy, hormonal therapy, or chemotherapy, as speculated by the authors in their discussion.

2) Details about histologic procedure are not reported. Fixation type and duration are known to strongly interfere with the results, even when microwave oven pretreatment is used (6).

3) The criteria employed to define p53 positivity (qualitative versus quantitative) are not generally used and not easily reproduced. In fact, there is a substantial difference between the 20% positive tumors reported by Sjögren et al. for 316 patients and the 45% positive tumors observed in our series of 1400 patients using the same criteria of positivity versus negativity. Moreover, in consideration of the "secondary analysis" reported in Table 4 (5), by which the predictive power of immunohistochemistry was similar to that of sequencing, the choice of cutoff values for the former determination appears to be crucial.

ROSELLA SILVESTRINI

References


Notes

Affiliations of authors: R. E. Curtis, J. D. Boice, Jr., D. A. Shriner, J. F. Fraumeni, Jr. (Division of Cancer Epidemiology and Genetics), B. F. Hankey (Cancer Statistics Branch), National Cancer Institute, Bethesda, MD.

Correspondence to: Rochelle E. Curtis, M.A., National Institutes of Health, Executive Plaza North, Suite 408, Bethesda, MD 20892.