Recent studies have indicated that the tamoxifen-related risk of uterine corpus cancer may be especially high for some uncommon cell types, although the magnitude of risk has not been quantified. We evaluated data from 39,451 breast cancer patients diagnosed from 1980 through 2000 who were initially treated with tamoxifen and found that the overall risk of subsequent uterine corpus cancer was increased more than twofold (observed-to-expected ratio [O/E] = 2.17, 95% confidence interval [CI] = 1.95 to 2.41) relative to the general SEER population. The relative risk was substantially higher for malignant mixed Mullerian tumors (MMMTs) (O/E = 4.62, O = 34, 95% CI = 3.20 to 6.46) than for endometrial adenocarcinomas (O/E = 2.07, O = 306, 95% CI = 1.85 to 2.32), although the excess absolute risk was smaller—an additional 1.4 versus 8.4 cancers per 10,000 women per year, respectively. Among those who survived for 5 years or longer, there was an eightfold relative risk for MMMTs and a 2.3-fold risk for endometrial adenocarcinomas, with patients developing MMMTs having a worse prognosis. These findings indicate that tamoxifen may have delayed effects, such as the increased risk of MMMTs, rare but aggressive tumors of unclear pathogenesis. [J Natl Cancer Inst 2004;96:70–4]

Risk of Malignant Mixed Mullerian Tumors After Tamoxifen Therapy for Breast Cancer

Rochelle E. Curtis, D. Michal Freedman, Mark E. Sherman, Joseph F. Fraumeni, Jr.

Tamoxifen has been shown to be effective in improving survival for women with breast cancer and appears to decrease the risk of estrogen receptor–positive breast cancer in high-risk populations of healthy women (1–4). Despite its benefits, tamoxifen has weakly estrogenic properties that can produce endometrial cell proliferation and, consequently, tamoxifen use increases the risk of endometrial cancer by approximately two- to threefold (5–12). Recent studies
In this report, we extend our previous clinical surveys from 1980 through 2000, when registries in the Surveillance, Epidemiology, and absolute risk of subsequent malignant mixed mullerian tumors (MMMTs) substantially higher for rare, aggressive tumors associated with tamoxifen may be substantially higher for tamoxifen users treated from 1973 through 1979 (for women with all stages of disease) or from 1980 through 1984 (for women with localized stage only). Women who received chemotherapy, endocrine therapy, endocrine surgery, or endocrine radiation therapy were excluded from the analysis. The patient groups designated as “tamoxifen users” and “non–tamoxifen users” were mutually exclusive.

We found that, from 1980 through 2000, breast cancer patients initially treated with tamoxifen had more than a twofold increased risk (O/E = 2.17, 95% CI 1.95 to 2.41) of developing a subsequent cancer of the uterine corpus when the observed number of subsequent cancers was compared with that expected from the SEER general population (Table 1). However, the relative risk among tamoxifen users was substantially higher for subsequent MMMTs (O/E = 4.62, 95% CI 3.20 to 6.46) than for endometrial adenocarcinomas (O/E = 2.07, 95% CI 1.85 to 2.32). Because MMMTs are rare, the large relative risk translates into a small excess absolute increased risk, with only an additional 1.4 tamoxifen-related MMMTs observed per 10 000 woman-years-at-risk, compared with an additional 8.4 tamoxifen-related endometrial adenocarcinomas. We found no evidence of an increased risk of leiomyosarcomas, although we observed a statistically nonsignificant 2.3-fold increase in risk for a combined group of stromal sarcomas and adenosarcomas among tamoxifen users. Among tamoxifen users who survived 5 or more years, the risk of MMMTs was eightfold compared with a 2.3-fold risk for endometrial adenocarcinomas. After the diagnosis of breast cancer, MMMTs tended to be detected later (median time to diagnosis = 7.5 years) than adenocarcinomas (median time to diagnosis = 4.5 years).

We found no increased risk for cancer of the uterine corpus overall (O/E = 0.99, 95% CI = 0.91 to 1.06) or for endometrial adenocarcinomas (O/E = 0.97, 95% CI = 0.90 to 1.06) specifically among non–tamoxifen users treated from 1973 through 1984 (Table 1). However, a statistically nonsignificant increased risk of MMMTs was seen among non–tamoxifen users (O/E = 1.38, 95% CI = 0.97 to 1.91).

We further assessed the risk among subgroups of subsequent endometrial adenocarcinomas. Analyses showed little difference in risk by stage and grade of endometrial adenocarcinoma among tamoxifen users (data not shown). The risk of clear-cell adenocarcinoma was similar among tamoxifen users and non–tamoxifen users. Analysis of serous adenocarcinomas was limited by infrequent reporting of this cancer to SEER before the early 1990s.

The risk of developing endometrial adenocarcinomas and MMMTs among tamoxifen users did not vary appreciably by age at diagnosis or stage of initial breast cancer, although the risk of MMMTs was greatest in women aged 60–69 years at the time of their initial treatment (Table 2). The risk of MMMTs appeared higher for black women (O/E = 8.55, 95% CI 3.43 to 17.62) than for white women (O/E = 4.11, 95% CI 2.68 to 6.02), although the difference was not statistically significant.

The cumulative mortality from uterine corpus cancer among tamoxifen users was very low (0.37%, 95% CI = 0.23% to 0.51%) 15 years after initial treatment. Prognosis was poor among patients who developed MMMTs, with 25 deaths among the 34 women diagnosed, including at least 15 deaths attributed to uterine cancer or sarcoma (Table 2). Nonetheless, death related to MMMTs was rare among tamoxifen users, with an estimated 0.8 deaths per 10 000 woman-years-at-risk or approximately 11–12 deaths among 10 000 breast cancer patients followed for 15 years.

Our results from the SEER population-based registries support previous evidence that tamoxifen users have an increased risk of MMMTs (13–16). In U.S. trials of more than 17 000 women, Wickerham et al. (15) found that 12 tamoxifen users developed MMMTs or uterine sarcomas (1.7/10 000 woman-years-at-risk) compared with none among non–tamoxifen users. In addition, a Dutch case–control study (13) reported that MMMTs and uterine sarcomas were
Table 1. Risk of uterine corpus cancer after breast cancer, by type of initial therapy, histologic type of uterine cancer, and time since breast cancer diagnosis*

<table>
<thead>
<tr>
<th>Time since breast cancer diagnosis</th>
<th>1–4 y</th>
<th>5–9 y</th>
<th>≥10 y</th>
<th>Total ≥1 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients entering interval*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen†</td>
<td>39,451</td>
<td>20,053</td>
<td>5,522</td>
<td>39,451</td>
</tr>
<tr>
<td>No tamoxifen‡</td>
<td>67,190</td>
<td>51,918</td>
<td>39,050</td>
<td>67,190</td>
</tr>
<tr>
<td>Woman-years at risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>116,191</td>
<td>60,454</td>
<td>11,926</td>
<td>188,571</td>
</tr>
<tr>
<td>No tamoxifen</td>
<td>236,596</td>
<td>224,642</td>
<td>336,526</td>
<td>797,764</td>
</tr>
<tr>
<td>Second uterine cancer/therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O/E</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All patients survived 1 or more years following an invasive breast cancer identified through the Surveillance, Epidemiology, and End Results (SEER) Program population registries. Patients who received initial therapy with chemotherapy, endocrine surgery, or endocrine radiation therapy were excluded from the analysis. O = observed number of subsequent (i.e., second and third) cancers; E = expected number of subsequent cancers; O/E = observed-to-expected ratio; tamoxifen group = patients who received tamoxifen as their initial therapy; no-tamoxifen group = patients who did not receive hormones as their initial therapy; CI = confidence interval; EAR = excess absolute risk per 10,000 woman-years-at-risk, ([O – E]/woman-years-at-risk) × 10,000.
†Patients included in the no-tamoxifen group were diagnosed from 1973 through 1979 (women with all stages of disease) or from 1980 through 2000.
‡Patients included in the tamoxifen group were diagnosed from 1980 through 2000.
§Statistically significant when 95% CI excludes 1.0.

<table>
<thead>
<tr>
<th>Group</th>
<th>Histologic type</th>
<th>No tamoxifen</th>
<th>Tamoxifen</th>
<th>No tamoxifen</th>
<th>Tamoxifen</th>
<th>95% CI</th>
<th>EAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Adenocarcinoma</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>0.00 to 2.85</td>
<td>0.07</td>
</tr>
<tr>
<td>II</td>
<td>Malignant mixed Mullerian tumors (MMMTs)</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>0.97 to 1.06</td>
<td>0.21</td>
</tr>
<tr>
<td>III</td>
<td>Leiomyosarcomas</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>0.97 to 1.06</td>
<td>0.21</td>
</tr>
<tr>
<td>IV</td>
<td>Endometrial stromal, adenosarcoma</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td>0.97 to 1.06</td>
<td>0.21</td>
</tr>
<tr>
<td>V</td>
<td>Other uterine corpus cancers</td>
<td>34</td>
<td>34</td>
<td>34</td>
<td>34</td>
<td>0.97 to 1.06</td>
<td>0.21</td>
</tr>
</tbody>
</table>

more common among long-term (≥2 years) tamoxifen users than among non–tamoxifen users (15.4% [eight case patients] versus 2.9% [five case patients]). Other studies with smaller numbers of subjects have also suggested that the risk of tamoxifen-related MMMTs is increased (8,14) and the time to diagnosis is longer than for tamoxifen-related uterine adenocarcinomas (17,20).

Although mechanisms underlying tamoxifen-related MMMTs are unclear, immunohistochemical and molecular analyses have suggested that MMMTs may originate as an adenocarcinoma that acquires sarcomatous differentiation over time (21). Despite limited epidemiologic evidence that MMMTs and
endometrial carcinomas may share re-
productive and hormonal risk factors
(22), the delayed time to diagnosis and
more aggressive behavior associated
with tamoxifen-related MMMTs rela-
tive to endometrial adenocarcinomas
in our study and other investigations
(13,16) suggest differences in patho-
genic mechanisms.

An advantage of our study was the
large number of breast cancer patients
treated with hormones in a population-
based setting. However, we were limited
by a lack of information regarding ta-
moxifen dose and duration of use, ther-
apy for recurrences, hysterectomy data,
use of postmenopausal estrogens, and
other risk factors for endometrial cancer.
In addition, our estimates of sec-
ondary cancer risk may be conservative
because cancer diagnoses are not avail-
able for those patients who migrate out of
SEER catchment areas. However,
risks may also be affected by increased
surveillance and detection bias among
tamoxifen users.

In conclusion, we provide population-
based evidence that use of tamoxifen is
associated with an overall fourfold rela-
tive risk for MMMTs, which rose to
eightfold among long-term breast cancer
survivors, compared with the twofold
risk for endometrial adenocarcinomas.
Although MMMTs are associated with a
poor prognosis, these tumors are rare
and the absolute risk of death is small.
These findings indicate that tamoxifen
may have delayed effects in some pa-
tients, such as the heightened risk of
MMMTs, aggressive tumors of unclear
pathogenesis.

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NOTES

Editor’s note: SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on an annual basis, and the NCI makes the data available to the public for scientific research.

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