Risk of endometrial cancer after tamoxifen treatment of breast cancer

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Summary
Since large trials have been set up to assess whether tamoxifen decreases the risk of breast cancer in healthy women, it has become important to investigate the drug's potential adverse effects, including occurrence of endometrial cancer. We undertook a case-control study in the Netherlands to assess the effect of tamoxifen on the risk of endometrial cancer after breast cancer.

Introduction
Since its introduction in the early 1970s, tamoxifen has been widely and effectively used to treat advanced breast cancer. Adjuvant tamoxifen therapy in early-stage breast cancer became common in the 1980s, and has been convincingly shown to improve disease-free survival as well as overall survival for women older than 50 years. Several large trials have suggested, furthermore, that tamoxifen reduces the risk of cancer in the contralateral breast. Based on these findings, chemoprevention trials have been set up in the USA and Europe to find out whether tamoxifen decreases the risk of breast cancer developing in healthy women judged to be at high risk of the disease.

Our knowledge of the long-term effects of tamoxifen is still limited. Tamoxifen's mixed oestrogen-agonist and oestrogen-antagonist properties have led to concern that the drug may increase the risk of endometrial cancer. The Stockholm trial found that women receiving 40 mg tamoxifen daily for at least 2 years had a more than six-fold excess risk of endometrial cancer in comparison with untreated controls. No significant increase in risk has been reported in other major adjuvant trials, although a non-significant excess of endometrial cancer after tamoxifen treatment was noted in an evaluation of Danish trials and in an unpublished Southwest Oncology Group Trial. The 10-year cumulative risk of endometrial cancer in postmenopausal women is estimated to be 0-3% or less. Thus, a follow-up study with sufficient power to settle the question of whether there is an excess risk of endometrial cancer after tamoxifen treatment would require long-term follow-up of many thousands of breast cancer patients. We therefore used a case-control design to investigate, in a nationwide study, whether tamoxifen, at different doses and for different durations, increases the risk of endometrial cancer.

Patients and methods
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Patients and methods
Since 1989, the Netherlands has had a population-based, nationwide cancer registry served by nine regional cancer registries. Most registries have been operating since 1986, the Eindhoven Cancer Registry since 1975, and the Middle Netherlands Breast Cancer Registry since 1973. Patients with endometrial cancer after breast cancer were identified from eight of the nine regional cancer registries; other cases (most with endometrial cancer diagnosed before 1986) were identified from the hospital tumour registries of two major cancer treatment...
controls were women with breast cancer in whom endometrial cancer had not been diagnosed. For each case patient, 3 controls were sought. They were individually matched to the patient for date of birth (within 3 years), date of diagnosis of breast cancer (within 2 years), and pathology laboratory where the breast cancer diagnosis was made. In addition, each control had to have survived, with an intact uterus, for at least as long as the time between the diagnosis of breast cancer and endometrial cancer in the corresponding case. Furthermore, we required that the control had not had a second primary cancer (other than carcinoma in situ of the cervix, basal-cell carcinoma of skin, or contralateral breast cancer) before the date the case patient developed endometrial cancer. When more than 3 controls per case met the above criteria, we selected those with the closest year of diagnosis of breast cancer, and then closest date of birth, to the case. For endometrial cancer patients whose breast cancer diagnoses were recorded in the cancer registries, controls were drawn through the registries. For those whose breast cancer registration records were not present in the registries (since they were not operating at the time), controls were selected through the Dutch Network and National Database for Pathology. This database contains records of all cytological and histological diagnoses made in the Netherlands, with computerised data submission by the individual pathology laboratories. The database was set up in 1977, and complete national coverage was achieved in 1989. Control selection through this database was allowed only if the breast cancer diagnosis of the case patient was also recorded in the pathology database. 3 controls were found for 28 case patients, 2 controls for 5 cases, and 1 control for 2 cases. For each case and her matched controls, full medical records were obtained for detailed data abstraction. Information was collected on stage of breast cancer, menopausal status at diagnosis of breast cancer, occurrence of contralateral disease, vital status, date of latest follow-up examination or date of death, and cause of death. We recorded for each period of tamoxifen treatment the starting date, the stopping date, and the dosage. The use of radiotherapy, chemotherapy, and hormonal treatment other than tamoxifen for breast cancer was also recorded. For each control, we checked extensively whether she had undergone hysterectomy (in which case she was excluded from the study). If necessary, information was obtained from the patient’s general practitioner. Complete information on all treatments, including periods of tamoxifen use and dosage, was eventually available for all women. For cases, we also sought information from the medical record on the endometrial cancer diagnosis (stage of endometrial cancer, full pathology report, treatment for endometrial cancer). All pathology reports of endometrial cancer were reviewed centrally by one of us (JB). If reports were incomplete or diagnosis uncertain, the slides were reviewed by the local pathologist. The relative risk of endometrial cancer associated with tamoxifen use was estimated by comparison of the case patient’s treatment history with that of her matched controls, by conditional logistic regression methods. Relative risk estimates, two-sided p values, and 95% CI were calculated with the microcomputer programme EGRET (SERC, Seattle, Washington, USA); comparisons between exposure categories were based on likelihood-ratio tests. For analysis, only the treatment of case patients during the time between the diagnoses of breast cancer and of endometrial cancer was included. For controls, treatment was studied for an equivalent time, starting with the date that breast cancer was diagnosed. Total duration of tamoxifen use and total dose were examined specifically as relevant factors in determining risk. The cumulative dose of tamoxifen was grouped into quartiles to calculate relative risks for each category in relation to the reference group of patients not treated with tamoxifen. Tests for trend in relative risk of endometrial cancer by duration (or cumulative dose) of tamoxifen were calculated by fitting the actual months (or mg) of use as a continuous variable in the logistic regression analyses. To assess the effect of dose intensity, duration-response slopes were estimated simultaneously for women who had received daily doses of 40 mg and 30 mg or less. Multivariate analyses were done to account for potential confounding effects of radiotherapy (yes/no), chemotherapy (yes/no), hormonal treatment other than tamoxifen, and breast cancer stage. For this purpose, hormonal treatment other than tamoxifen was classified according to the expected effect on the endometrium (oestrogen stimulation, yes/no; progestagenic protection yes/no). Results Most of the women were over 55 years old and postmenopausal when breast cancer was diagnosed (table 1). Date of birth was matched within 1 year for 78% of controls and within 2 years for 94%. Most (74%) of the endometrial cancers occurred in patients whose breast cancer had been diagnosed in the 1980s. 89% of controls matched cases within 1 year for diagnosis of breast cancer. The median time between the diagnoses of breast cancer and endometrial cancer was 34 (5–201) months. More cases than controls were diagnosed with advanced breast cancer (94% vs 74%, p<0.03, Fisher’s exact test). Controls were slightly more likely than case patients to have received
Table 2: Relative risk (RR) of endometrial cancer according to total duration of tamoxifen use and cumulative dose

<table>
<thead>
<tr>
<th>Duration (mo)</th>
<th>Cases</th>
<th>Controls</th>
<th>Matched RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>75</td>
<td>227</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;12</td>
<td>6</td>
<td>28</td>
<td>0.6 (0.2-1.7)</td>
</tr>
<tr>
<td>13-24</td>
<td>7</td>
<td>14</td>
<td>1.9 (0.6-5.8)</td>
</tr>
<tr>
<td>25-60</td>
<td>7</td>
<td>12</td>
<td>2.2 (0.8-6.5)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>3</td>
<td>4</td>
<td>3.0 (0.6-15.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cumulative dose (mg)</th>
<th>Cases</th>
<th>Controls</th>
<th>Matched RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>75</td>
<td>227</td>
<td>1.0</td>
</tr>
<tr>
<td>18670</td>
<td>3</td>
<td>17</td>
<td>0.7 (0.2-2.3)</td>
</tr>
<tr>
<td>14 681-14 800</td>
<td>3</td>
<td>17</td>
<td>0.8 (0.2-2.6)</td>
</tr>
<tr>
<td>14 681-31 720</td>
<td>8</td>
<td>12</td>
<td>2.5 (0.9-7.1)</td>
</tr>
<tr>
<td>&gt;31 720</td>
<td>7</td>
<td>13</td>
<td>2.1 (0.7-6.0)</td>
</tr>
</tbody>
</table>

24% of the case patients and 20% of controls had used tamoxifen at some time, and the relative risk of endometrial cancer for women who had ever been treated with tamoxifen compared with those who had not was 1.3 (95% CI 0.7-2.4). The median duration of tamoxifen use was higher for case patients than for controls (19 vs 13 months, p = 0.07). The risk of endometrial cancer increased with duration (table 2). Women who had used tamoxifen for more than 2 years had a 2.3 (0.9-5.9) times greater risk of endometrial cancer than never users and the risk rose to 3.0 (0.6-15.8) for those treated for more than 5 years. None of the risk estimates for categories of duration reached significance, but the inclusion of duration of tamoxifen use as a linear continuous variable in the logistic regression model produced a significant trend (p = 0.049). The cumulative dose of tamoxifen was also associated with the risk of endometrial cancer (table 2, p for trend = 0.046). The effect of tamoxifen was best fitted by including a binary term (ever/never use) and the log-transformed duration of tamoxifen use as a continuous variable in the model (p = 0.026). Similar duration and dose-response patterns were found when analyses were restricted to the 89 women (and their matched controls) in whom endometrial cancer was diagnosed more than 1 year after the initial breast cancer diagnosis. Adjustment for the variables chemotherapy, radiotherapy, hormonal treatment other than tamoxifen, and stage of breast cancer did not substantially alter the risk estimates in table 2.

Of the 81 tamoxifen users in our study, most (59%) had received daily doses of 40 mg, 17% received 30 mg, and 23%, received 20 mg or less. We attempted to separate the effects of dose intensity, duration of tamoxifen use, and cumulative dose. The average dose of tamoxifen taken daily did not affect the risk of endometrial cancer in a model accounting for total duration of use (p = 0.54). The inclusion of dose intensity in the model hardly affected the duration-response trend (0.05). To explore further the effect of dose intensity, duration-response slopes were fitted simultaneously for women who had received 40 mg daily and those who received 30 mg or less. The relative risk per year of tamoxifen use (with a multiplicative model, based on actual months of use) was 1.22 for a daily dose of 30 mg or less and 1.24 for 40 mg (tests for linear trend p = 0.18 and p = 0.10, respectively). The two doses did not differ in duration-response trends (p = 0.73).

Within the case group, we studied whether the endometrial cancers in women who had used tamoxifen had different characteristics from those diagnosed in women who had never been treated with the drug (table 3). The stage distributions and morphology of the endometrial cancers in these two groups showed no striking differences. During median follow-up of 15 months after the diagnosis of endometrial cancer, none of the tamoxifen-treated women died of this cancer. Median follow-up in never users was 29 months. 2-year actuarial survival after the diagnosis of endometrial cancer was similar for women who had received breast cancer treatment with tamoxifen and for those who had never received the drug (68% and 71%, respectively).

Discussion

Our results support the hypothesis that use of tamoxifen increases the risk of endometrial cancer. We found a significant trend in risk of endometrial cancer with total duration of tamoxifen treatment, whatever the dose intensity.

In interpreting our results we considered several potential sources of bias. Increased medical surveillance in tamoxifen users, as well as the presence of gynaecological symptoms due to tamoxifen treatment (eg, vaginal bleeding) might lead to earlier diagnosis of endometrial cancer in such women than in untreated patients, which might result in a spurious association between tamoxifen and endometrial cancer. We found no evidence for such bias. First, the stage distribution of the endometrial cancers did not differ between ever and never users. Furthermore, women who had used tamoxifen for a year or less did not have an increased risk of endometrial cancer, and in the (small) subgroup of endometrial cancers diagnosed within 1 year from the breast cancer diagnosis we found no association with tamoxifen use.

Since the Netherlands did not have a nationwide cancer registry in the 1970s and early 1980s, some patients with endometrial cancer after breast cancer were not eligible for our study, solely because there was no sampling frame for control breast cancer patients diagnosed in the same
It has been postulated that any increase of endometrial cancer risk due to the oestrogenic effects of tamoxifen would yield a high proportion of highly differentiated, prognostically favourable tumours, as has been observed with endometrial carcinomas associated with oestrogen replacement therapy.23-28 We found no substantial differences in histological features of the endometrial cancers diagnosed in tamoxifen-treated patients and in non-treated women. The only suggestion of a difference was in the proportion of well-differentiated tumours (52% in tamoxifen users and 32% in women not treated with tamoxifen). Since the histological slides of endometrial cancers were not reviewed centrally, this finding must be interpreted cautiously. In Magriples and colleagues' study26 of the clinical and histological features of endometrial cancers in breast cancer patients who had or had not received tamoxifen, there was a significant excess of poorly differentiated tumours in the tamoxifen-treated group.26 However, the number of tamoxifen users in that study, as well as in ours, was small (15 and 23, respectively), and in both studies the age distribution of the tamoxifen-treated group differed from that in the untreated patients. A much larger patient population would be needed to refute or confirm an association between tamoxifen use and specific histological characteristics of endometrial cancer.

Increased risk of endometrial cancer after tamoxifen use will cause some morbidity in breast cancer patients treated with the drug. However, the proven clinical benefit of tamoxifen in controlling breast cancer clearly outweighs the modest increase of endometrial cancer risk. Endometrial cancer has a more favourable prognosis than breast cancer, so no patient should be denied tamoxifen treatment of her breast tumour because of anticipated adverse effects on the endometrium.

The issue of whether tamoxifen should be used to prevent cancer in healthy women, who do not have a medical need for treatment, is different, however. Even if, at the population level, the postulated reduction in the incidence of breast cancer were to outweigh the apparently increased risk of endometrial cancer, it is debatable whether the use of a medical intervention can be justified when it prevents breast cancer in some women at the cost of inducing endometrial cancer in others. This issue will continue to provoke discussion in the medical community until more is known about tamoxifen's long-term benefits and adverse effects. Further studies are needed to quantify the risk for women taking 30 mg or 20 mg per day, to assess the effect of very long durations of use (5 years or more), and to determine the risk for ex-users.

Meanwhile, we believe that, on the basis of our results, physicians should be alert to the higher risk of endometrial cancer in all women using tamoxifen, both breast cancer patients and healthy participants in prevention trials. Regular gynaecological examinations may be worth while for long-term users.


References


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Short Report

α1-antitrypsin deficiency in intracranial aneurysms and cervical artery dissection

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The pathogenesis of ruptured intracranial aneurysms and spontaneous cervical artery dissections is not well understood but an underlying arteriopathy is usually suspected. Except for some patients with fibromuscular dysplasia or certain heritable connective tissue disorders, investigations into the nature of this arteriopathy have been unsuccessful.1 Deficiencies of α1-antitrypsin or other inhibitors of proteolytic enzymes may have a role in the development of abdominal arterial aneurysms.2 Such deficiency could undermine the integrity of the vascular extracellular matrix, predisposing the arterial wall to dissection or aneurysm formation. We report a group of patients with α1-antitrypsin deficiency who developed aneurysmal subarachnoid haemorrhage or spontaneous cervical artery dissection.

All patients with α1-antitrypsin deficiency, who were evaluated at the Mayo Clinic between 1976 and 1992, were identified through a computerised and coded diagnostic index. This group consisted of 168 women and 194 men (mean age 48.1 years). All had symptoms of α1-antitrypsin deficiency, which had been diagnosed with similar methods throughout the study period. During this time, about 140 patients with spontaneous carotid dissection and 1250 patients with aneurysmal subarachnoid haemorrhage were seen at our institution.

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