Minireview

Endometrial Carcinoma and Tamoxifen: Clearing Up a Controversy

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Abstract
During the past 5 years, a number of case reports and clinical trial results have associated tamoxifen therapy with an increased incidence of endometrial carcinoma. A review of the literature shows that there are over 200 cases of endometrial carcinoma reported in tamoxifen-treated women. Most cases are Stage I (82%), grade 1–2 disease (80%), which is consistent with the Surveillance Epidemiology and End Results Reporting data of 74 and 79% for Stage I and grade 1–2 endometrial carcinoma. We conclude that there is a modest increase in endometrial carcinoma incidence during tamoxifen therapy (i.e., 2/1000 tamoxifen treated women per year versus 1/1000 women per year for Surveillance Epidemiology and End Results Reporting), that there is no strong association with duration of therapy, and that tamoxifen is not associated with a high-grade, poor prognosis disease. The benefits of tamoxifen in lives saved exceeds the incidence of endometrial carcinoma.

Introduction
Tamoxifen is the endocrine therapy of choice for all stages of breast cancer (1). Each year about 80,000 women in the United States start a course of tamoxifen therapy which usually continues for at least 5 years. The strategic use of long-term adjuvant tamoxifen therapy is a concept, developed in the laboratory (2–5), that has been successfully translated through clinical trials (1) to improve the survival of women with breast cancer (6).

The clinical success of tamoxifen as a therapeutic agent (there are now 6,000,000 woman/years of experience) and the low incidence of serious side effects (1) were key to the decision to test tamoxifen as a preventive in women only at risk for breast cancer. Laboratory data that show tamoxifen inhibits mammary carcinogenesis (7, 8), the finding that contralateral breast cancer is reduced by tamoxifen (9), and the positive estrogen-like effects of tamoxifen that maintain bone density (10–12) and reduce fatal myocardial infarction (13, 14) all support the testing of tamoxifen as a preventive in double-blind, placebo-controlled, randomized clinical trials. Clinical trials that are recruiting 16,000–20,000 women volunteers are now proceeding in the United States, United Kingdom, and Italy (15).

The widespread use of tamoxifen as the only antiestrogen available for the treatment of breast cancer has naturally led to a close reexamination of both the laboratory and clinical toxicology of the drug. Close monitoring of clinical information is extremely important to ensure the safety of patients either on clinical trials or within the approved treatment community.

The past year has seen increased patient and physician awareness about the possibility of tamoxifen-induced carcinogenesis (16, 17). The primary cause for concern is the potential link between long-term tamoxifen therapy and the development or stimulation of endometrial carcinoma (18, 19) with poor prognosis (20).

Like the concept of long-term tamoxifen therapy to treat breast cancer, the idea that tamoxifen could be detrimental to breast cancer patients with preexisting endometrial cancer was based on laboratory evidence (21). The purpose of this review was to trace the origins of the concern linking tamoxifen and endometrial cancer and reevaluate the current information obtained from clinical observations.

Laboratory Investigations
There is no evidence that tamoxifen induces endometrial carcinoma in laboratory animals. Perhaps the most pertinent experiment would be to administer tamoxifen to mice, because in short-term tests the drug is classified as an estrogen in this species (22, 23). However, long-term tamoxifen administration only causes the vagina and the uterus to become quiescent and refractory to exogenous estrogen administration (24, 25).

Tamoxifen blocks the binding of [³H]estradiol to the estrogen receptor isolated from endometrial carcinomata (26). These data laid the foundation for clinical studies that demonstrated the value of tamoxifen in the treatment of advanced endometrial carcinoma (27, 28). However, tamoxifen is not a pure antiestrogen and shows estrogen-like properties in the human vagina (29). Studies of human endometrial carcinomas in athymic mice demonstrate that estrogen receptor-positive tumors grow more rapidly in estrogen-treated mice, whereas rapidly growing estrogen receptor-negative tumors are unaffected by estrogen (30). Therefore, there was no reason to believe that tamoxifen would not stimulate the growth of some endometrial tumors. Satyaswaroop and coworkers (31, 32) demonstrated that tamoxifen increases the level of progesterone receptors, an estrogenic response, in estrogen receptor-positive endometrial carcinoma and suggested that a combination of tamoxifen plus a progesterin might be a better treatment strategy for advanced endometrial carcinoma than either therapy alone (31).

However, their observation (31) that tamoxifen could encourage the growth of endometrial tumors in athymic animals prompted us to suggest "the possibility of an increasing incidence of endometrial tumors during prolonged tamoxifen therapy for breast cancer" (21). In a collaborative study with Dr. Satyaswaroop, we demonstrated the target site specificity of tamoxifen to block the estrogen-stimulated growth of a human breast cancer inoculated into athymic mice, but to encourage the growth of an endometrial carcinoma inoculated on the other side of the same mouse (21). We recommended that "A large cohort of patients under long-term tamoxifen therapy (/>5 years) needs

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to be monitored for the occurrence of tamoxifen-stimulated endometrial tumors" (21).

The laboratory evidence for our concerns about tamoxifen and endometrial carcinoma growth was presented to the clinical community in 1988 at an International Breast Cancer Symposium to celebrate the 900th anniversary of the University of Bologna (Bologna, Italy). Several clinicians in the audience responded by investigating the link between tamoxifen treatment and endometrial cancer.

**Clinical Response**

Hardell (33) reported the characteristics of 11 women who developed endometrial carcinoma during long-term tamoxifen therapy. However, only two of the patients had received 4–5 years of adjuvant tamoxifen and there was no information about the population data base; therefore, calculations of incidence could not be made. Hardell subsequently (34) suggested a link between an increase in endometrial carcinoma in patients who receive radiation therapy plus tamoxifen, but again calculations of incidence could not be made. In contrast, the Stockholm group (18) reported the incidence of second primary cancers in their clinical trial of adjuvant tamoxifen versus control. The group noted a significant and increasing risk of endometrial carcinoma in the group randomized to 5 years of adjuvant tamoxifen treatment, but a significant overall decrease in second primary breast cancers. Thus, the target site specificity of tamoxifen demonstrated in the laboratory (21) appears to be true for the patient. Nevertheless, the idea that long-term tamoxifen treatment may be inappropriate and cause an unacceptable risk of endometrial cancer became the focus of clinical concern.

Since 1988 there has been a growing number of reports linking tamoxifen with endometrial carcinoma (34); however, two studies are particularly important because their publication created additional concern among the patient and clinical communities. The first study, reported by Magriples et al. (20), surveyed patients in the Yale/New Haven data base for the decade 1980–1990 to identify women with breast cancer who subsequently developed endometrial cancer. The Yale group surveyed 3457 patient records and found 53 patients with both breast and endometrial cancer. Only 15 patients with both breast and endometrial cancer were identified who had taken tamoxifen at any time. However, the authors concluded, "it appears that women receiving tamoxifen as treatment for breast cancer who subsequently develop uterine cancer are at risk for high-grade endometrial cancers that have a poor prognosis" because the tumors from tamoxifen-treated patients were in general (67%) poorly differentiated carcinomas. This conclusion was completely justified from their data base and their publication naturally created an incentive to determine the grade and staging of endometrial carcinoma observed during tamoxifen therapy.

The second study that caused concern was published by the NSABP in 1994 (19). In adjuvant study B14, 20 mg tamoxifen was administered daily to 1419 of 2834 randomly assigned node-negative breast cancer patients. In addition, 1220 patients were registered to receive tamoxifen and were followed up for at least 5 years. Overall, 15 cases of endometrial cancer were reported in the group randomized to tamoxifen, giving an approximate incidence rate of 1.3/1000 woman years for 8 years of follow-up (our calculation). There were seven cases of endometrial carcinoma (one reported sarcoma is excluded in our calculations) in the registered group, giving an approximate incidence rate of 1.1/1000 women years with 5 years of follow-up. Although these incidence rates for endometrial cancer in tamoxifen-treated patients compare favorably with rates for endometrial carcinoma from SEER data (approximately 1/1000 woman years), the concern centered on the three deaths from endometrial cancer in the patients treated with tamoxifen. These women, plus the three women who died of endometrial cancer in the Stockholm study (35), implied that the conclusion from Magriples et al. (20) that tamoxifen-induced endometrial cancer "with a poor prognosis" was correct. In response to these clinical concerns, we had surveyed the literature to address the questions: Does long-term tamoxifen therapy induce endometrial cancer? Does tamoxifen induce high-grade endometrial carcinoma with poor prognosis?

### Analysis of Endometrial Carcinoma and Tamoxifen

We have updated our initial survey (36) and found 209 cases of endometrial cancer associated with tamoxifen treatment (Table 1). We have also noted eight mixed Müllerian tumors and seven sarcomas (37). In 133 cases the menopausal status was given and all but one patient was postmenopausal. Of the 209 patients with documented endometrial carcinoma, 46 (22%) did not have details of daily dosage, but the remainder received doses ranging from 10- to 60-mg daily. Initial concerns that the higher dose (40 mg tamoxifen) used in the Stockholm study (18) was responsible for the apparently high incidence of endometrial cancer is not supported by our analysis (37). Only 51 patients (24%) had used 40 mg tamoxifen daily, whereas 100 patients (48%) had used 20 mg tamoxifen daily. Indeed, the reports on the duration of tamoxifen treatment in our analysis did not support the hypothesis that long-term tamoxifen treatment causes a dramatic increased incidence of endometrial cancer. Endometrial cancer was reported for 97 patients who received more than 2 years of tamoxifen treatment, but 79 patients received 2 years or less of tamoxifen treatment.

#### Table 1

<table>
<thead>
<tr>
<th>Patients</th>
<th>Duration of tamoxifen treatment</th>
<th>Endometrial cancer</th>
<th>Mixed Müllerian tumors</th>
<th>Sarcomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤2 years</td>
<td>79 patients</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>&gt;2 years</td>
<td>97 patients</td>
<td></td>
<td></td>
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</tbody>
</table>

Note: These data are from reports in the literature as case reports or statistics from clinical trials (37).

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[2] The abbreviations used are: NSABP, National Surgical Adjuvant Breast and Bowel Project; RT, radiotherapy; SEER, Surveillance Epidemiology and End Results Reporting.
with 4 women who developed endometrial cancer if they continued and one in the tamoxifen-treated arm (40).

Added another case of endometrial carcinoma to the untreated arm $n=539$; Ref. 39). A more recent update of the study added another case of endometrial carcinoma to the untreated arm and one in the tamoxifen-treated arm (40).

It is now appropriate to answer the posed questions and reconsider the interpretation of the links between tamoxifen and endometrial cancer.

Does Long-Term Tamoxifen Therapy Induce Endometrial Cancer?

To address this question we will examine the data provided in the literature from three clinical trials of 5-year adjuvant tamoxifen treatment and two clinical trials that incorporate a 1-year treatment arm.

The individual data (35) for the 16 endometrial carcinomas that developed during tamoxifen treatment in the Stockholm trial (18) have been plotted as months of tamoxifen therapy versus the appearance of endometrial cancer after breast cancer (Fig. 1). Although the original article (18) concluded that the women randomized to the 5-year treatment arm had a higher risk of developing endometrial cancer, examination of Fig. 1 demonstrates that 12 women who received 2 years or less of tamoxifen treatment developed endometrial cancer compared with 4 women who developed endometrial cancer if they continued tamoxifen therapy up to 5 years.

Fig. 1 shows that twice as many endometrial cancers were reported for women who stopped tamoxifen therapy at 2 years as compared to those women who continued the drug. While it would be inappropriate to suggest that long-term tamoxifen treatment prevents endometrial cancer, it also seems unreasonable to suggest that these data support the position that long-term tamoxifen therapy causes an increase in endometrial cancer.

An increase in endometrial carcinoma with long-term tamoxifen was not found in the Scottish trial of 5 years of tamoxifen therapy (38). Not a single case of endometrial carcinoma (but 3 sarcomas) was reported initially in the tamoxifen-treated arm ($n=539$) while two cases appeared in the untreated group ($n=531$; Ref. 39). A more recent update of the study added another case of endometrial carcinoma to the untreated arm and one in the tamoxifen-treated arm (40).

In contrast, the NSABP study B14 (19) found 15 cases of endometrial carcinoma in patients randomized to receive 20 mg tamoxifen for at least 5 years ($n=1419$) and 7 cases (1 sarcoma) in patients registered to receive at least 5 years of tamoxifen treatment ($n=1420$). The average time on study is 8 years for randomly assigned patients and 5 years for registered patients. The incidence of endometrial cancers in the 2639 women receiving different durations of tamoxifen therapy does not differ (Fig. 2). Nine women developed endometrial cancer after at least 2 years of tamoxifen treatment, whereas only six women had developed endometrial cancer after 4–6 years of tamoxifen treatment. The Stockholm study (18) estimated approximately a 5-fold increase in the relative risk for endometrial carcinoma for women allocated to 5-year tamoxifen versus 2-year tamoxifen treatment. One would, therefore, predict a much higher incidence of endometrial carcinoma (30+) in the 4–6-year tamoxifen treatment group in the NSABP study if the principle derived from the Stockholm study (18) was correct.

Instead of considering whether long-term tamoxifen treatment causes an increase in endometrial cancer, one could take the position that even a short course of tamoxifen treatment causes an increase in endometrial carcinoma. The Christie Hospital study (41) of 1 year of adjuvant tamoxifen (20 mg daily) treatment detected the same incidence, i.e., one endometrial carcinoma in both treated ($n=282$ patients) and untreated ($n=306$ patients) groups after 13 years of follow-up.

In contrast, a Danish trial (42) of 1 year (48 weeks) of adjuvant tamoxifen (30 mg daily) treatment detected 2 endometrial carcinomas in patients ($n=846$) who received RT alone but 7 endometrial carcinomas in patients who received both RT and tamoxifen ($n=864$). A graph in the publication by Anderson et al. (42) clearly indicates that after 8 years of follow-up, the cumulative incidence of endometrial cancer for the RT group was 0.27%, but this increased to 1% if tamoxifen was added to the treatment regimen. However, unlike the Stockholm study (18), tamoxifen did not prevent the development of second primary breast cancers. Clearly, these are disturbing conclusions.
Endometrial Carcinoma and Tamoxifen

Tamoxifen as a Carcinogen

Large oral doses of tamoxifen cause adducts to the DNA in rat liver (45, 46). Similarly, the daily feeding of large doses (>3 mg/kg) starting at 6 weeks of age for half the life of a rat produces a dose-related increase in rat liver tumors (47–49). These data would be a major concern about the toxicology profile of any new drug about to go into clinical trial, but since tamoxifen has been in clinical practice for about 20 years, it is important to reassess the laboratory evidence in light of clinical experience.

The experiments in the laboratory are both dose, duration, and species specific. The doses used range between 10 and 30 times the doses used in clinical practice, i.e., the doses used to produce tumors in rats range from 5 to 45 mg/kg, whereas the daily dose of tamoxifen given to patients is about 0.25–0.4 mg/kg, depending on patient weight. The duration of therapy used in the clinical situation is about 5 years, or 6% of a postmenopausal patient’s life. In contrast, the animal studies use high doses for 50% of the rat’s life but start at 6 weeks of age (or the equivalent of a 14-year-old patient). The design of the carcinogenesis experiment in rats is, therefore, very different than the use of tamoxifen in patients (for a review, see Ref. 17). In the clinical situation, no increase in hepatocellular carcinoma has been noted during the first 10 years of tamoxifen usage (1977–1987; Ref. 50); however, it must be pointed out that a 10-fold increased risk of hepatocellular carcinoma is known to occur with the use of 5–8 years of oral contraceptives (51). This risk is considered to be acceptable by regulatory authorities; therefore, at least this elevation in risk must be permitted for tamoxifen should the statistics show a rise in future decades. It therefore, at least this elevation in risk must be permitted for tamoxifen should the statistics show a rise in future decades. It must be stressed that the fact that tamoxifen causes liver carcinogenesis in rats is an indicator of the possibility, but not the certainty, of carcinogenesis in humans. The rat seems particularly susceptible to liver carcinogenesis, whereas the mouse is not (17). It is, therefore, possible that metabolic differences (52–56) are responsible for carcinogenesis in the rat, so it is important to document these carefully to determine whether

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Table 2 Staging and grades of endometrial carcinoma in the Magriples series (20) compared with a summary of literature (37) and data accumulated by SEER

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survey</th>
<th>SEERa (%)</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>7/9 (78%)</td>
<td>91/111 (82%)</td>
</tr>
<tr>
<td>II–IV</td>
<td>2/9 (22%)</td>
<td>20/111 (18%)</td>
</tr>
<tr>
<td>Grade</td>
<td>SEER (%)</td>
<td>SEER (%)</td>
</tr>
<tr>
<td>Good (Grade 1–2)</td>
<td>5/13 (38%)</td>
<td>90/113 (80%)</td>
</tr>
<tr>
<td>Poor (Grade 3)</td>
<td>8/13 (62%)</td>
<td>23/113 (20%)</td>
</tr>
</tbody>
</table>

a Percentages for the SEER data are derived from 12,717 endometrial carcinoma patients in the United States.

about the activity of tamoxifen, but a close examination of the presented data in their tables reveals an accumulated incidence of endometrial cancers of 11 in the true control, a group of patients (n = 1828) who received no further treatment. Thus, the accumulated incidence of endometrial cancer per 1000 women for the true control would be 6, and the group receiving RT plus tamoxifen would be 8/1000 women. It is, in fact, the RT alone accumulated incidence of endometrial cancer per 1000 women (n patients of endometrial cancers of 1 in the true control, a group of presented data in their tables reveals an accumulated incidence about the activity of tamoxifen, but a close examination of the

The analysis performed by Magriples et al. (20) identified 8 (62%) of 13 women treated with tamoxifen (40 mg daily) with high-grade (Grade 3) endometrial carcinoma. In our review of the literature (37) we identified 111 patients who developed endometrial carcinoma during tamoxifen treatment where disease stage was noted (Table 2). Similarly, 113 patients had information concerning tumor grade. If we compare the information given in the Magriples series (20) with our series, we find 22% of patients distributed in Stage II–IV disease for the Magriples series (n = 2) and 18% for our survey (n = 20; Table 2). In contrast, we found that only 20% of patients in our survey had high-grade (Grade 3) endometrial carcinoma which contrasts with the Magriples series (20) of 62%. It is, however, pertinent to point out that the distribution of disease stage and grade for our survey is almost identical to information collected from the SEER data bank (Table 2). The Stockholm (35), the NSABP (19), and a recent retrospective study from the Memo-
selected patients may be at risk for carcinogenesis because of pharmacogenetic traits.

Summary and General Conclusions

During the past 5 years, there has been intense interest in documenting the occurrence of endometrial carcinoma during tamoxifen therapy, but it is now possible to estimate the benefits and risks of therapy. Since 1989 the use of tamoxifen as an adjuvant has been expanded to include patients with node-negative disease and estrogen receptor-positive tumors. Therefore, if there are 182,000 new cases of invasive breast cancer annually in the United States, there will be at least 80,000 women who will start a minimum of 5 years of adjuvant tamoxifen therapy annually. This would produce a conservative estimate of about 500,000 women in America who are currently taking tamoxifen. If one argues that women who have estrogen receptor-positive breast cancer will receive tamoxifen at some time during their treatment plan, the estimate of tamoxifen users could rise to 1,000,000. Furthermore, tamoxifen is used worldwide so the actual number of women taking tamoxifen annually becomes enormous. The benefits of tamoxifen to improve survival and reduce second primary breast cancers is demonstrated in an overview of clinical trials (6) and current research is documenting benefits for the postmenopausal patient in preserving bone and reducing the risk of fatal myocardial infarction (10–14). The benefits produced by tamoxifen for women’s health will result in an increased longevity for tens of thousands of breast cancer patients in America alone.

In the deficit column, there are published reports of over 200 endometrial carcinomas worldwide, mainly in postmenopausal patients. There appears to be very little association with the duration of tamoxifen therapy, and the concerns about the development of high-grade tumors (20) have not been confirmed by the majority of investigators (19, 36, 37, 44). However, the question of the true incidence of endometrial carcinoma during tamoxifen therapy is complex because it is already known that there is at least a 5-fold higher incidence of occult disease compared to clinically evident disease in the general population (57). This has been established for the general population without cancer by an analysis of autopsy information. Tamoxifen is known to produce estrogen-like effects in the uteri and vaginas of some women (29, 58–60), and this can lead to discharge and, in some cases, spotting and bleeding (1). Obviously, these symptoms can lead to a detection bias as the prudent physician will make a detailed gynecological examination, especially in light of the knowledge that tamoxifen can be associated with endometrial carcinoma.

Overall, a conservative estimate of 2/1000 women/year could be made for the incidence of endometrial carcinoma during any duration of tamoxifen therapy, compared with 1/1000 women reported by SEER in the general population. However, 80% of these tumors will be early stage and low grade. For the woman with breast cancer, who regrettably already has an elevated risk for endometrial cancer (relative risk 1.7, Ref. 61), the additional risks of long-term tamoxifen therapy are extremely small compared to the known benefit of therapy for increased survival. Physicians should educate postmenopausal patients taking tamoxifen to report any suspicious spotting or bleeding so that a thorough gynecological examination can be performed.

References


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