The Effect of Tamoxifen on the Endometrium

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Tamoxifen (Nolvadex), a nonsteroidal antiestrogen, was first approved by the FDA for the treatment of patients with breast cancer in 1978. Large clinical trials have demonstrated a recurrence-free and overall survival benefit.

Introduction

Tamoxifen (Nolvadex), a nonsteroidal antiestrogen, has been widely used for the management of patients with breast cancer since the 1970s. It is believed to exert its main effect by blocking the binding of estrogen to the estrogen receptor. Although primarily an antiestrogen, tamoxifen may also exhibit some mild estrogenic effects. Since the initial report by Killackey et al [1] suggesting a possible link between tamoxifen use and the development of endometrial carcinoma in three patients, approximately 133 additional cases of tamoxifen-associated uterine cancer have been reported [2-13]. Most recently, the results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial were published [12]. This randomized trial of tamoxifen versus placebo in women with estrogen receptor (ER)-positive breast cancer confined to the breast with negative axillary nodes revealed a 7.5-fold increase in the risk of developing endometrial cancer in the tamoxifen-treated group.

The indications for tamoxifen use have broadened to include long-term adjuvant therapy as well as preventive therapy for selected high-risk women. Consequently, a large number of women, including healthy young patients with no history of cancer, will be subjected to the long-term effects of tamoxifen. This review evaluates the current literature regarding tamoxifen use in breast cancer patients and associated uterine neoplasia, and discusses the role of screening for endometrial cancer in tamoxifen-treated breast cancer patients.

Laboratory Data

Several preclinical studies have indicated that tamoxifen may indeed exert an estrogenic effect on the endometrium. Satyaswaroop et al [14] transplanted both ER-positive and ER-negative human endometrial cancer cell lines into nude mice and evaluated the effect of both tamoxifen and 17-beta-estradiol on tumor growth. Although the ER-negative tumor grew rapidly, there was no difference in the rate of tumor growth between tamoxifen- and estrogen-treated animals, compared with controls. In contrast, the rate of growth of the ER-positive cell line was significantly accelerated in the tamoxifen-treated animals, compared with controls, although to a lesser degree than was seen with estrogen treatment. In addition, tamoxifen increased the levels of functional progesterone receptors, providing further evidence for the estrogenic potential of tamoxifen.

Gottardis et al [15] demonstrated in athymic mice the contrasting actions of tamoxifen on the growth of ER-positive breast and endometrial cancer cell lines. While stimulating the growth of the endometrial tumor, tamoxifen had no effect on breast tumor growth and had an antagonistic action on the estradiol-stimulated growth of breast tumors.

Clinical Studies

The estrogenic effect of tamoxifen on the female genital tract has also been demonstrated clinically. Boccardo et al [16] investigated the estrogen-like effect of tamoxifen on the vaginal epithelium. Hormonal evaluation of the female patient can be determined by means of exfoliative vaginal cytology using the karyopyknotic index (KPI), which is the relation of mature superficial cells to intermediate cells. Postmenopausal estrogen replacement therapy generally induces increased cellular maturity and, consequently, increases the KPI. After at least 8 weeks of tamoxifen treatment, treated patients had a significantly higher KPI than did untreated patients, suggesting an estrogenic effect of tamoxifen on the vaginal epithelium.
Endometrial Polyps and Hyperplasia

Several recent reports have implicated tamoxifen treatment in the development of endometrial polyps and hyperplasia (Table 1). Lahti et al [9] performed transvaginal sonography, hysteroscopy, and endometrial curettage on 103 postmenopausal breast cancer patients; 51 had received tamoxifen at 20 to 40 mg/day for a median of 30 months, while 52 had received no hormonal treatment. The patients were matched with respect to age, parity, time since menopause, body mass index, and concomitant medical conditions. Compared with control subjects, the tamoxifen-treated patients had a significantly thicker mean endometrial width (10.4 mm versus 4.2 mm) and a larger uterine volume, as determined by transvaginal sonography. However, they also had a higher incidence of uterine fibroids.

The percentage of endometrial polyps was significantly higher in the tamoxifen-treated group, compared with controls (36% vs 10%). Of the 43 patients in the tamoxifen-treated group who had an endometrial thickness of 5 mm or more, 17 (39.5%) had endometrial polyps; however, 22 (51.2%) had no abnormal pathologic findings. Two patients in the tamoxifen group had endometrial hyperplasia, and one patient had endometrial cancer at the time of curettage. Two patients in the control group also had endometrial cancer. All significant endometrial pathology was found in asymptomatic patients with an endometrial width greater than 5 mm on transvaginal sonography. If transvaginal sonography were used as a screening method for endometrial cancer with the abnormal cutoff limit set at 5 mm, approximately 50% of patients would undergo endometrial sampling unnecessarly.

Since endometrial polyps often contain hyperplastic endometrial glands, their etiology is thought to be the presence of endogenous or exogenous estrogenic activity. The authors therefore concluded that long-term tamoxifen use is associated with estrogenic side effects manifested by an increased occurrence of polyps. This study failed to demonstrate any increase in precancerous or cancerous endometrial lesions associated with tamoxifen treatment.

Other Studies—Other authors have also reported a higher incidence of endometrial polyps and hyperplasia in tamoxifen-treated breast cancer patients. Corley et al [17] reported on four tamoxifen-treated patients who developed unusual endometrial polyps characterized by cystically dilated glands and stromal decidualization. These findings were not confirmed in the 17 cases of endometrial polyps reported by Lahti et al [9].

Gal et al [18] reported an 18% incidence of endometrial hyperplasia in random endometrial biopsies obtained from 38 breast cancer patients who had received tamoxifen at a dosage of 20 mg/day for at least 12 months. Thirty-two patients (46%) who were initially eligible for study could not participate, as endometrial samples could not be obtained due to atrophic changes. In the second phase of the study, the authors performed endometrial biopsies prospectively on 11 patients at 4- to 6-month intervals. Three (28%) of these patients developed endometrial hyperplasia following 6, 10, and 12 months of tamoxifen use. Again, 40% of the patients initially eligible for study could not participate due to inability to undergo an endometrial biopsy. The 20% overall incidence of endometrial hyperplasia reported by Gal et al [18] was higher than the 4% incidence noted by Lahti et al [9] in 51 tamoxifen-treated breast cancer patients.

Gibson et al [19] recently reported the results of a retrospective review of endometrial pathology found at dilatation and curettage (D&C) performed in 240 breast cancer patients. Seventy-five (31%) of these patients had received tamoxifen, 20 mg/day, for a mean duration of 26 months as therapy for their breast cancer. Patients in this study were stratified as symptomatic (abnormal bleeding) or asymptomatic (curettage performed as part of another procedure or due to the presence of a thickened endometrial stripe on ultrasound examination).

Among tamoxifen users who were symptomatic at the time of D&C, the incidence of endometrial polyps was 15%; hyperplasia, 2%; and adenocarcinoma, 11%; compared with an incidence of 13%, 4%, and 11%, respectively, for nonusers. Among asymptomatic patients receiving tamoxifen, the incidence of polyps, hyperplasia, and adenocarcinoma was 9%, 0%, and 0%, while nonusers had an incidence of 5%, 4%, and 0%, respectively. All of the cases of endometrial carcinoma were associated with abnormal vaginal bleeding. The 11% incidence of endometrial carcinoma in this study was comparable to what has been reported for all patients presenting with postmenopausal bleeding in the general population [20].

The mean duration of tamoxifen use in those patients found to have adenocarcinoma was 44 months, compared with 18 months in those patients with polyps, and 19 months in the patient with hyperplasia. This difference was not statistically significant, possibly due to small numbers. The authors concluded that short-term tamoxifen use at the 20 mg/day dosage level was not associated
with a higher incidence of abnormal pathology, as detected at the time of D&C in breast cancer patients.

**Breast Cancer Prevention Trials**—Recently, large-scale randomized trials of tamoxifen as a chemopreventive agent have been initiated in England and the United States for women considered to be at high risk for developing breast cancer based on family history. Kedar et al [21] recruited a randomized cohort of 111 postmenopausal women from the Pilot Breast Cancer Prevention Trial at the Royal Marsden Hospital, to study the effect of tamoxifen on the uterus and ovaries. Sixty-one patients had received tamoxifen at 20 mg/day for a median of 22 months, while 50 had received placebo for a median of 24 months. Eight patients in each group were receiving estrogen replacement therapy at the time of study. All patients underwent endovaginal sonography with color Doppler imaging, after which an endometrial biopsy was performed. The tamoxifen group was found to have a significantly larger uterine volume and a lower impedance to blood flow in the uterine arteries. Patients were not, however, stratified as to the presence of uterine fibroids. In addition, the tamoxifen-treated group had a significantly thicker mean endometrial diameter (9.1 mm versus 4.8 mm). On endometrial biopsy, 10 patients (16%) in the tamoxifen-treated group were found to have atypical endometrial hyperplasia, while five (8%) had endometrial polyps. None of the patients in the control group had hyperplasia on endometrial biopsy, and only one patient had an endometrial polyp. No patient in either group had evidence of endometrial carcinoma. The predictive value of an endometrial thickness 8 mm or larger for atypical hyperplasia or polyps was 100% (16/16), suggesting a possible screening role for transvaginal sonography in breast cancer patients receiving tamoxifen.

**Endometrial Carcinoma**

As mentioned previously, since 1985, nearly 140 cases of tamoxifen-associated uterine cancers have been reported. [1-13] The anecdotal nature of many of these small series, while suggesting an association between tamoxifen treatment for breast cancer and the development of endometrial cancer, fails to provide conclusive evidence for its occurrence. Perhaps the strongest data initially implicating tamoxifen use and the subsequent development of endometrial cancer were published in 1989 by Fornander et al. [4] The authors reviewed the frequency of new primary cancers as recorded in the Swedish Cancer Registry for a group of 1,846 postmenopausal women with early breast cancer who were included in a randomized trial of adjuvant tamoxifen. They noted a 6.4-fold increase in the relative risk of endometrial cancer in 931 tamoxifen-treated patients, compared with 915 patients in the control group. The tamoxifen dosage in this study was 40 mg/day, and the greatest cumulative risk of developing endometrial cancer was after 5 years of tamoxifen use.

**NSABP B-14**—Fisher et al [12] recently published the most compelling data to date regarding the association between tamoxifen use and the development of endometrial cancer when they reported the findings of the NSABP B-14 trial. Data regarding the rates of endometrial and other cancers were analyzed on 2,843 patients with node-negative, ER-positive, invasive breast cancer randomly assigned to placebo or tamoxifen (20 mg/day), and on 1,220 tamoxifen-treated patients registered in NSABP B-14 subsequent to randomization. Two of the 1,424 patients assigned to receive placebo developed endometrial cancer; however, both had subsequently received tamoxifen for treatment of breast cancer recurrence. Fifteen patients randomized to tamoxifen treatment developed endometrial cancer. One of these patients never actually accepted tamoxifen therapy. Eight additional cases of uterine cancer occurred in the 1,220 tamoxifen-treated patients, with women age 60 or older accounting for 76% of cases. The mean duration of tamoxifen therapy was 35 months, with 36% of the endometrial cancers developing within 2 years of therapy, and six occurring less than 9 months after treatment was initiated, suggesting that some of the cancers may have been present prior to starting tamoxifen therapy.

The average annual hazard rates for endometrial cancer were 0.2/1,000 in the placebo group and 1.6/1,000 in the randomized tamoxifen-treated group. The relative risk of an endometrial cancer occurring in the randomized, tamoxifen-treated group was 7.5. Similar results were seen in the 1,220 registered patients who received tamoxifen.

**Caveats**—Although the findings indicate that the average annual and cumulative hazard rates of occurrence of endometrial cancer are greater in tamoxifen-treated patients than in those receiving placebo, the authors point out several caveats.

First, there may have been a bias in detection, as tamoxifen-treated patients are more often symptomatic and more likely, therefore, to seek gynecologic consultation.

Second, the rate of endometrial cancer in the placebo-treated group appeared to be unusually low.
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Survival, Epidemiology, and End Results (SEER) data [22] would predict that 6.9 cancers would occur in the placebo group. Using SEER data as a comparison, the relative risk of endometrial cancer in the randomized tamoxifen-treated group would be 2.2. In addition, findings from the NSABP B-06 trial noted seven endometrial cancers occurring in 1,159 breast cancer patients with negative lymph nodes who did not receive systemic therapy. This yielded an average annual hazard rate for endometrial cancer of 0.7/1,000. Comparing this with the rate of 1.6/1,000 for endometrial cancer in the randomized tamoxifen-treated group from the B-14 trial, the relative risk for endometrial cancer with tamoxifen use is 2.3, similar to that obtained using SEER data.

Finally, any conclusions regarding the risks of tamoxifen treatment inducing endometrial cancer must weigh the benefits of tamoxifen in reducing breast cancer recurrence and new contralateral breast cancers. In the B-14 trial, the cumulative rate of breast cancer relapse was reduced from 227.8/1,000 in the placebo group to 123.5/1,000 in the randomized tamoxifen-treated group. In addition, the cumulative rate of contralateral breast cancer was reduced from 40.5 to 23.5/1,000, respectively, in the two groups. Taking into account the increased cumulative rate of endometrial cancer, there was a 38% reduction in the 5-year cumulative hazard rate in the tamoxifen-treated group. These results led the authors to conclude that the benefit of tamoxifen therapy for breast cancer outweighs the potential increase in endometrial cancer being reported.

**Histology of Tamoxifen-Associated Uterine Cancer**

The etiology of tamoxifen-associated endometrial neoplasia has not been established. There are, however, some metabolites of tamoxifen that may act primarily as estrogen agonists, and some investigators favor this mechanism as a possible hypothesis for the development of endometrial neoplasia. Metabolite E is formed by the removal of the aminoethane side chain from tamoxifen. This compound is a weak estrogen agonist that binds the estrogen receptor with low affinity [23]. The presence of a hydroxyl group in this compound destabilizes the ethylene bond, allowing isomerization of the compound to its E isomer, a potent estrogen agonist. The clinical significance of metabolite E is controversial, as it has not been detected in the serum of tamoxifen-treated breast cancer patients, and its role in endometrial neoplasia remains speculative.

It is well established that unopposed estrogen administration is associated with an increased risk of developing endometrial carcinoma. These tend to be predominantly early-stage, low-grade, minimally invasive lesions that have a favorable prognosis [24]. If the effect of tamoxifen on the endometrium is that of a weak estrogen agonist, one could expect associated endometrial cancers to have clinical characteristics comparable to those associated with unopposed estrogen.

**The Yale Study**—A recent report from the Yale Tumor Registry by Magriples et al [8] suggested that uterine cancers occurring in breast cancer patients on tamoxifen may behave more aggressively and carry a worse prognosis. The authors identified 53 patients with invasive or in situ breast cancer who subsequently developed uterine cancer. Fifteen of the patients had received adjuvant tamoxifen at a dosage of 40 mg/day for a mean of 4.2 years, while 38 had not received tamoxifen. The mean patient age was 72.3 years for tamoxifen users, which was not statistically different from those not receiving tamoxifen (68.5 years). The interval between the diagnosis of breast and endometrial cancer was significantly lower in the tamoxifen-treated group, compared with those not receiving tamoxifen (5.3 vs 12.3 years). In the tamoxifen-treated group, 67% of the uterine cancers were high-grade lesions (grade 3 adenocarcinoma) or had high-risk histologies (papillary serous, clear cell, mixed mesodermal tumor), compared with 28% of those developing in the 38 breast cancer patients who had not received tamoxifen. In addition, patients in the tamoxifen-treated group were statistically more likely to die of endometrial cancer (33.3% versus 2.6%).

These findings led the authors to conclude that “women receiving tamoxifen as treatment for breast cancer are at risk for high-grade endometrial cancers that have a poor prognosis.” In addition, the presence of a high percentage of poor-prognosis histologies, including poorly differentiated adenocarcinoma, papillary serous, and clear cell cancers, along with mixed mesodermal tumors, in the tamoxifen-treated group led the authors to speculate that the mechanism of tamoxifen-induced endometrial neoplasias may be different from that of neoplasias induced by exogenous estrogen, which are associated with more favorable histologies.

**Lack of Confirmation**—Several recent studies [11-13,25], however, have not been able to confirm the findings of Magriples et al [8] (Table 2). Barakat et al [13] reported the Memorial Sloan-Kettering Cancer Center experience in 73 patients with a history of breast cancer who subsequently developed uterine cancer. Twenty-three (32%) had received tamoxifen for at least 1 year, with a median duration of use of 4.5 years, while 50 (68%) did not receive tamoxifen. There was no significant
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difference in age, mean weight, or median survival following hysterectomy between the two groups of patients. The median interval between the diagnosis of breast and uterine cancer was less in those receiving tamoxifen (4.6 vs 6.7 years), but this was not statistically significant. There was no significant difference in the FIGO stage of the uterine cancers occurring in those patients who had received tamoxifen, compared with nonusers.

In the tamoxifen-treated group, 74% of the corpus cancers were endometrial adenocarcinomas, while 26% were high-risk histologic subtypes, including papillary serous and clear cell carcinomas, as well as uterine sarcomas. This distribution was identical to that seen in the group not receiving tamoxifen. Five women (22%) from the tamoxifen group died of uterine cancer, as did 13 (26%) of those who did not receive tamoxifen. The authors concluded that there was no difference in the stage, grade, or histologic subtype of corpus cancers that develop in breast cancer patients using tamoxifen, compared with nonusers.

Other authors have reported similar results. Fornander et al [25] recently reported the clinicopathologic findings of endometrial cancers occurring as second primaries in 931 tamoxifen-treated patients with early breast cancer from the Stockholm Adjuvant Tamoxifen Trial [4]. The median duration of tamoxifen use was 24 months, and the drug was given at a dosage of 40 mg/day. On histologic review of these cancers, 82% were FIGO stage I, and all were histologic grade 1 or 2. Three deaths (18%) were attributable to endometrial cancer.

VanLeeuwen et al [11] recently reported the results of a case-control study from the Netherlands Cancer Registry. There was no difference in the FIGO stage or histologic distribution of endometrial cancers that occurred in 23 breast cancer patients who received tamoxifen, compared with 75 who did not. None of the tamoxifen-treated patients died of endometrial cancer, compared with four of those who did not receive tamoxifen.

Finally, the results of the NSABP B-14 trial [12] also confirmed that uterine cancers occurring in tamoxifen-treated breast cancer patients are not associated with a higher incidence of adverse histologic features. Eighty-eight percent of the tamoxifen-associated endometrial cancers were FIGO stage I. In addition, 71% were endometrioid adenocarcinomas and 78% were low-grade lesions. Four deaths (16%) were due to endometrial cancer.

The Role of Screening

The published data would appear to support an association between tamoxifen and the development of both benign and malignant endometrial neoplasia. The increased risk of endometrial cancer associated with tamoxifen use will lead to increased morbidity in breast cancer patients, but this does not appear to outweigh the significant advantage that tamoxifen confers by controlling breast cancer. This issue is clear for the patient with a diagnosis of breast cancer. Of greater concern is the possible implication of using tamoxifen in healthy women considered to be at high risk for developing breast cancer based on family history. Large-scale trials of tamoxifen as a chemopreventive agent are currently underway in England and the United States. Whether the postulated reduction in breast cancer outweighs the risk of endometrial cancer in this population remains to be determined.

Additional studies are also required to evaluate the issue of dose and duration of tamoxifen use. In a meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer, Steinberg et al [26] noted an increased risk of breast cancer based on dosage and duration of tamoxifen use. Whether the dose level of tamoxifen or duration of use is important remains to be determined. In the study by Magriples et al [8] and in the Swedish trial [4], the tamoxifen dosage was 40 mg/day, twice the conventional dosage used in this country. Fornander et al [4], noted that the greatest cumulative frequency of uterine cancer was seen among the patients who were allocated to 5 years of tamoxifen treatment. VanLeeuwen et al [11] noted that women who used tamoxifen for more than 2 years had a 2.3 (range, 0.9 to 5.9) times greater risk of endometrial cancer than nonusers, and the risk rose to 3.0 (range, 0.6 to 15.8) for those treated for more than 5 years. None of the risk estimates for duration of use reached statistical significance, however.

Recommendations Regarding Screening

What, if any, recommendations can be made at this point regarding screening for endometrial cancer in breast cancer patients on tamoxifen? To begin with, the expected annual risk of endometrial cancer is approximately 2/1,000, as defined by the B-14 trial [12]. A screening program may detect premalignant endometrial precursors, such as atypical hyperplasia or benign endometrial conditions including polyps, the incidence of which will be higher than 2/1,000. The best
method for screening, however, remains to be determined. Some have proposed annual endometrial sampling, although this is not without its difficulties. Gal et al [18] were unable to perform office endometrial biopsies with a Novak curette in 44% of 89 postmenopausal patients, due to atrophic changes. Should these patients be subjected to the inherent morbidity of a fractional D&C under general anesthesia?

**Suction Biopsy**—Perhaps larger screening studies such as the one that is currently being performed at Memorial Sloan-Kettering Cancer Center, which uses an endometrial suction biopsy device (Pipelle, Unimar, Wilmington, Conn), may help answer this question. Certainly, all patients with abnormal bleeding should seek immediate gynecologic evaluation. As reported by Gibson et al [19], all cases of endometrial carcinoma detected by D&C in tamoxifen-treated breast cancer patients occurred in women who presented with abnormal bleeding.

**Sonography**—Transvaginal sonography may provide a noninvasive means of screening for endometrial pathology in tamoxifen-treated breast cancer patients. The definition of an abnormal endometrial stripe remains to be determined. As reported by Lahti et al [9], if a cutoff of 5 mm or more were used to define an abnormal endometrial echo, about 50% of patients undergoing endometrial sampling on that basis would be found to have no abnormal pathology. Kedar et al [21] reported a predictive value of 100% (16/16) for atypical hyperplasia or polyps with an endometrial stripe of 8 mm or more. These findings suggest that premalignant changes can be detected with transvaginal sonography; however, the use of ultrasound and/or endometrial sampling to screen for endometrial neoplasia needs to be evaluated in large prospective trials before screening recommendations can be made.

Care must be taken not to overinterpret the ultrasonographic findings of the endometrium in tamoxifen-treated patients. Goldstein [27] recently reported five postmenopausal tamoxifen-treated patients who, on routine surveillance with vaginal probe ultrasonography, were described as having heterogeneous, bizarre-appearing endometria with multiple sonolucent areas suggestive of a polyp. Because of concerns regarding tamoxifen use and endometrial neoplasia, the first patient was referred for a curettage and hysteroscopy. Minimal tissue was obtained, and hysteroscopic evaluation revealed a smooth atrophic endometrium. When the abnormal sonographic appearance persisted, the patient underwent a sonohysterogram, which involves the instillation of 3 to 10 mL of saline at the time of sonography. The fluid enhancement revealed that the changes originally interpreted as endometrial were actually subendometrial in origin. Four additional patients with similar abnormal sonographic findings were also found to have subendometrial abnormalities on sonohysterogram. It is unclear what these abnormal areas represent, as none of the patients have undergone hysterectomy, although it was speculated that they may represent adenomyomatous-like changes. Further studies regarding the sonographic appearance of the endometrium in tamoxifen-treated patients are warranted.

**A Recommendation for All Women With Breast Cancer**

For now, all women with breast cancer, whether or not they are receiving tamoxifen, should be encouraged to undergo annual gynecologic evaluation, which should include endometrial sampling in the presence of abnormal vaginal bleeding.

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