Endometrial Carcinoma Associated with Breast Carcinoma

Low Incidence with Tamoxifen Use

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Presented at the Society of Surgical Oncology's 48th Annual Meeting, Boston, Massachusetts, March 23, 1995.

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Received June 30, 1995; revisions received November 21, 1995, and February 12, 1996; accepted February 12, 1996.

BACKGROUND. Women treated with tamoxifen for breast cancer are at increased risk of endometrial cancer. This study examines the experience at Roswell Park Cancer Institute (RPCI) with women diagnosed with both endometrial carcinoma (EC) and breast carcinoma (BC) to determine the risk and stage of endometrial carcinoma among women treated with tamoxifen.

METHODS. The tumor registry was searched for women with diagnoses of both BC and EC between 1980 and 1993. Systemic therapy was classified for all analytic cases of breast carcinoma (women who received primary BC treatment at RPCI). Medical records of all women with both BC and EC were reviewed, including all analytic and nonanalytic cases.

RESULTS. There were 1947 analytic and 1534 nonanalytic BC cases and 877 analytic and 239 nonanalytic EC cases. Thirty-six women in the nonanalytic breast cancer group also had endometrial carcinoma. Fifteen had endometrial carcinoma before breast carcinoma, and 20 of 21 women with breast cancer first had no record of tamoxifen use. Thirty-seven women in the analytic breast carcinoma group had endometrial carcinoma. Endometrial carcinoma preceded breast carcinoma in 29 women. Breast carcinoma preceded endometrial carcinoma in eight women, and two of these developed endometrial carcinoma during or after tamoxifen therapy. Therefore, a total of three women developed endometrial cancer during or after tamoxifen therapy (two analytic and one nonanalytic). The EC was classified as International Federation of Gynecology and Obstetrics (FIGO) Stage IA (1 patient) and IB (2 patients) with one patient each with histologic Grade I, II, and III after 1, 2, and 5 years of tamoxifen therapy, respectively. No patients had recurrence or died from endometrial carcinoma. The risk of endometrial carcinoma with tamoxifen was determined from the number of women in the breast cancer analytic group receiving tamoxifen. Hormonal therapy was coded as part of systemic treatment in 652 of 1947 analytic patients (33%; 510 as adjuvant therapy and 142 for metastatic cancer). Of these patients, 172 of 652 women (26%) had undergone hysterectomy prior to breast cancer diagnosis, and another 71 women (11%) received nontamoxifen hormone therapy (e.g., prednisone). Tamoxifen therapy was documented in 402 women in the analytic group. (The median age of these women at BC diagnosis was 63 years). Therefore, the maximum estimate of endometrial carcinoma risk is 2 of 402 cases (0.5%).

CONCLUSIONS. The risk of endometrial carcinoma with tamoxifen use is low. The value of routine invasive screening for endometrial carcinoma for women receiving tamoxifen should be determined by prospective study. ***Cancer* 1996; 77:2058–63.**

KEYWORDS: breast carcinoma, tamoxifen, tamoxifen adverse effects, endometrial carcinoma, endometrial carcinoma risk, incidence.

Tamoxifen is widely used in breast cancer treatment. Adjuvant tamoxifen therapy lengthens disease free survival, increases overall survival, and reduces the risk of developing breast carcinoma in the contralateral breast.[1-5] Tamoxifen also is widely used in the treatment of women with metastatic breast cancer.

Tamoxifen is generally considered a safe drug whose benefits far outweigh its risks. However, one risk of tamoxifen is an increased risk of endometrial carcinoma. Tamoxifen's mixed estrogen antagonist and agonist effects on the endometrium may be responsible, but the exact mechanisms of tamoxifen's effect on the endometrium are unclear.[6-14] Estimates of the relative risk of endometrial carcinoma with tamoxifen therapy range from 1.3–7.5.[8,15,16]

The outcome for tamoxifen-associated endometrial carcinoma is probably the same as that for endometrial carcinoma in women who have not received tamoxifen. However, a recent report from the Yale/New Haven Hospital tumor registry by Magriples et al. showed a higher than expected incidence of poorly differentiated and deeply invasive endometrial carcinomas among women treated with tamoxifen for breast carcinoma.[7] The results of the Yale study prompted us to review our tumor registry to assess the stage and outcome of tamoxifen-associated endometrial carcinoma at the Roswell Park Cancer Institute (RPCI). We extended this review to include all women with diagnoses of both endometrial and breast carcinoma, and to estimate the incidence of tamoxifen-associated endometrial carcinoma by determining the number of women at risk during the study period from breast cancer treatment data.

METHODS

The RPCI American College of Surgeons (ACoS) tumor registry was searched for women with a breast or endometrial carcinoma diagnosis between 1980 and 1993. These cases were then searched for women who also had the other cancer diagnosis in any year. Each case was classified as analytic or nonanalytic by the ACoS guidelines. Analytic cases are those who received the major treatment of the primary cancer at RPCI. Nonanalytic cases are those for whom there was minimal contact at RPCI (such as those seeking a second opinion), one aspect of treatment (such as radiation), or treatment of recurrence but not of the primary disease. The RPCI tumor registry maintains annual follow-up on 98% of all analytic and nonanalytic cases.

The medical record and tumor registry record on all women with both endometrial and breast carcinoma diagnoses from both the analytic and nonanalytic groups were reviewed in detail independently by two authors. The information cataloged included demographics, endometrial cancer staging and treatment data, and cancer outcome. Hormone receptor information could not be located for a significant proportion of women, precluding its use in analysis. All women who had endometrial carcinoma after breast carcinoma had a full review of breast carcinoma treatment to identify use of tamoxifen in relation to endometrial carcinoma. Dose and duration of tamoxifen use was recorded.

The incidence of endometrial carcinoma among tamoxifen users was estimated from the tumor registry analytic cases. Systemic treatment is classified in the tumor registry as none, chemotherapy, chemohormonal therapy, hormonal therapy, surgical hormonal ablation, and others. The medical records of all analytic breast carcinoma cases classified as receiving hormonal therapy or chemohormonal therapy were reviewed. The type and duration of hormonal therapy used was recorded. In addition, the rate of hysterectomy prior to breast cancer diagnosis was also determined from a review of medical record data to determine the number of breast carcinoma cases at risk of developing endometrial carcinoma while on tamoxifen. A similar review of the nonanalytic group would not be useful because of the paucity and variability in the medical record information on the treatment of the primary cancer.

RESULTS

From 1980 to 1993, there were 1534 nonanalytic cases with breast carcinoma and 239 nonanalytic cases with endometrial carcinoma. Of the nonanalytic breast carcinoma cases, 36 had both breast and endometrial carcinoma. Breast carcinoma preceded endometrial carcinoma in 21 women. The median age at breast carcinoma diagnosis was 51 years (range, 21-92 years). There was no record of tamoxifen use in 20 of these women. Of these 20 women, 5 had breast cancer staging characteristics for which tamoxifen might have been recommended. Further inferences about the incidence of endometrial carcinoma with tamoxifen use in the nonanalytic group are not reasonable because of the paucity of treatment data.

There were 1947 analytic breast carcinoma cases and 877 analytic endometrial carcinoma cases. The median age at breast cancer diagnosis was 56 years (range, 15–97 years). Thirty-seven of the analytic breast carcinoma cases also had endometrial carcinoma (Table 1). Breast carcinoma was the first cancer in eight women. Tamoxifen was not used in breast cancer treatment in six women, none of whom had breast cancer staging characteristics for which the investigators believe tamoxifen should have been employed.

Three women developed endometrial carcinoma during or after tamoxifen use (two analytic and one nonanalytic breast cancer patients). The women were age 42,

TABLE 1
Characteristics of Analytic Breast Carcinoma Patients Roswell Park Cancer Institute, 1980-93 (n = 1947)

Total number with both breast and endometrial carcinoma	37
Number with EC before BC	29
Number with BC before EC (no tamoxifen)	6
Number with BC before EC (tamoxifen used)	2
Median age, yr (range) (tamoxifen users)	63 (23-97)
Percent older than age 50 (tamoxifen users)	88%
Median duration tamoxifen use (adjuvant therapy) (mo)	36 (1-125)
Median duration tamoxifen use (metastatic disease) (mo)	12 (1-72)
Median follow-up (all tamoxifen users) (mo)	46 (1-167)

EC: endometrial carcinoma; BC: breast carcinoma.

61, and 62, respectively, at time of endometrial carcinoma diagnosis (Table 2). They all developed endometrial carcinoma during tamoxifen therapy. The duration of tamoxifen use prior to the development of endometrial carcinoma was 1, 2, and 5 years, respectively. The tamoxifen dose was 20 mg/day for 2 patients, and 40 mg/day for one case. Two women presented with abnormal vaginal bleeding, and one woman presented with pelvic pain. All three women had International Federation of Gynecology and Obstetrics (FIGO) Stage I disease (one case, IA; two cases, IB, FIGO corpus cancer staging. *Int J gynecolobstet* 1989;28:190). One case each was histologic grade I, II and III (FIGO as above). None of the women developed recurrent endometrial carcinoma, or died from endometrial cancer. Two died from metastatic breast carcinoma 2 and 3 years, respectively, after treatment of endometrial carcinoma.

To estimate the incidence of endometrial carcinoma for women receiving tamoxifen, the prior hysterectomy rate and actual use of tamoxifen among the analytic breast cancer group was determined. The tumor registry listed hormone therapy with or without cytotoxic chemotherapy as an element of treatment in 652 of 1947 cases (33%). Because of documented prior hysterectomy prior to breast cancer diagnosis, 172 cases (26%) were not at risk for endometrial carcinoma. Of the remaining 480 cases, 402 had documented use of tamoxifen. Drugs other than tamoxifen that were classified as hormonal therapy were used in 66 cases (prednisone as part of adjuvant chemotherapy in 63 cases, other hormones in 3 cases). No hormone therapy could be documented in five cases. The medical records could not be located for seven women. Tamoxifen was used as treatment for metastatic breast cancer in 75 women, and as adjuvant therapy in 327 women. Tamoxifen was the sole systemic agent in 325 cases, and was combined with chemotherapy in 77 cases. The median duration of documented tamoxifen use was 28 months (12 months for metastatic disease, and 36 months for adjuvant therapy) and median follow-up was 46 months (Table 1). The majority of women receiving tamoxifen were postmenopausal as defined by age older than 50 years (88%). The median age at breast carcinoma diagnosis of women receiving tamoxifen was 63 years (range, 23-97 years).

Tamoxifen use was documented for 402 analytic cases at risk for endometrial carcinoma. Therefore, the incidence of endometrial carcinoma estimated from the analytic patients is 2 in 402 patients (0.5%). For women treated with adjuvant tamoxifen, the incidence was 1 in 327 cases (0.3%).

DISCUSSION

A number of studies in recent years have shown that women who take tamoxifen for breast carcinoma treatment are at increased risk for endometrial carcinoma. The initial report of the Swedish trial was followed by similar reports from single institutions, case-control series, and other randomized trials.[6-8,15,17,18]

The Yale tumor registry review raised alarm because it showed a high frequency of high grade endometrial carcinoma among tamoxifen users, which translated into poor outcome.[7] Five of 15 women died of endometrial carcinoma, and another 3 had recurrence. However, whereas the Yale study showed tumors of higher grade and stage, in virtually every other series the majority of endometrial cancers were early stage and low grade, with high expected cure rates.[6-8,15,17-19]

The review reported here was undertaken to examine the RPCI experience with endometrial carcinoma and tamoxifen. Like the Yale review, it is a retrospective tumor registry survey. It is thorough because the RPCI tumor registry maintains 98% follow-up on all patients in the registry. To avoid missing cases because of misclassification as analytic or nonanalytic, we reviewed the medical records of all women with both diagnoses. We extended the tumor registry review method of the Yale study to estimate the incidence of tamoxifen-associated endometrial carcinoma. We determined the number of women exposed to tamoxifen and the number not at risk by virtue of prior hysterectomy. In performing this chart review, we relied upon the tumor registry classification of systemic therapy. The charts of the 1295 analytic breast carcinoma cases not coded as receiving hormone therapy were not reviewed for use of tamoxifen or prior hysterectomy. Had this been done and the women found to have received tamoxifen but inaccurately coded, the denominator of at-risk women would have increased, with no effect on the numerator of women who developed endometrial carcinoma while receiving tamoxifen. All cases of endometrial carcinoma in the analytic breast carcinoma group were

TABLE 2
Characteristics of Breast Carcinoma Stage, Tamoxifen Use, and Endometrial Cancer Stage in Tamoxifen-Associated Endometrial Carcinomas

Case no.	Age at BC yr	BC stage	Reason for TAM	Tam dose (mg/day)	Duration Tam Use before EC	Presenting symptoms	FIGO Stage/Grade	Outcome
1	41	T2 N1 M0	BC mets at 4 yr	20 mg	1 yr	Bleeding	IB/I	Dead, BC
2	59	T1 NX M0	Adjuvant	20 mg	2 yr	Pelvic pain	IA/II	Alive, NED
3	51	T2 N0 M0	BC mets at 6 yr	40 mg	5 yr	Bleeding	IB/III	Dead, BC

BC: breast carcinoma; EC: endometrial carcinoma; NED: no evidence of disease; mets: metastastes; Tam: Tamoxifen.
Cases 1 and 2 are analytic breast cancer cases. Case 3 is a non-analytic breast cancer case.

detected and reviewed regardless of systemic therapy code. The risk estimate is 0.5% (2 of 402 cases).

In this study, all three tamoxifen-associated endometrial carcinomas were early stage, with one patient each with histologic Grade I, II, and III. All endometrial carcinomas were effectively treated with no sequelae.

We did not examine the incidence of other uterine malignancies in this population. The development of other uterine malignancies in women receiving tamoxifen has been reported with small numbers.[10,19,20] The rarity of these lesions makes it difficult to address the incidence and the mechanism of tamoxifen causation of these lesions is unexplained.

Factors that influence endometrial carcinoma risk with tamoxifen may include dose of tamoxifen, patient age, and duration of tamoxifen use. The highest risk of tamoxifen therapy among all reports is in the Swedish trial with a dose of 40 mg/day.[6] Endometrial carcinoma developed among 17 patients in the tamoxifen-treated arm and in only 3 patients in the control arm for a relative risk of about 6.[6] The cumulative incidence of uterine malignancy was 6% after 5 years of tamoxifen. A Danish case–control study evaluated the incidence among matched populations of women treated with 30 mg/day tamoxifen, and found a relative risk of 1.9.[17,18] The National Surgical Adjuvant Breast Project (NSABP) B-14 trial of adjuvant tamoxifen (20 mg/day) in lymph node negative breast carcinoma patients found a relative risk of 7.5, but using population–based estimates as a control reduced the relative risk to 2.2.[8] The cumulative incidence of endometrial carcinoma was less than 1% (23 endometrial carcinomas among 2639 tamoxifen-treated women).[8] A recent review by Jaiyesimi et al. concluded that the cumulative incidence of endometrial carcinoma in all women treated with tamoxifen in major trials is 0.9% versus 0.2% in controls.[21]

The majority of cases of tamoxifen-associated endometrial carcinoma are in postmenopausal women.[21] An association between duration of tamoxifen therapy and endometrial carcinoma risk has not been fully established. The optimal duration of tamoxifen therapy to maximize breast carcinoma benefit is not yet defined, although there is no apparent benefit in continuing adjuvant tamoxifen after 5 years.[16,21,22] The risk of endometrial carcinoma may therefore strengthen the position that tamoxifen should be discontinued after 5 years.

The low incidence and excellent outcome for tamoxifen-associated endometrial carcinoma raises the question about the appropriate level of endometrial screening necessary. All women receiving tamoxifen should be warned of this risk. The majority of patients with endometrial carcinoma present with abnormal vaginal bleeding. Careful history plus annual pelvic examination with cervical cytology should be an integral part of breast cancer follow-up surveillance. Abnormalities on examination or symptoms should prompt immediate evaluation, including examination and sampling of the endometrium.[23]

Screening with periodic aspiration biopsy, hysteroscopy, or transvaginal ultrasound has been proposed. Abnormal findings may be noted in a significant proportion of women receiving tamoxifen. Lahti et al. noted an increase in the endometrial thickness and uterine volume among tamoxifen users when studied by ultrasound and hysteroscopy.[24] A number of authors reported increased endometrial thickness, uterine size, volume, and blood flow by ultrasound in tamoxifen users.[12,24-27] As many as 80–90% of postmenopausal women who are receiving tamoxifen have endometrial thickness greater than 5 mm, the standard upper limit of normal.[24] A cutoff of 5 mm for endometrial thickness to require endometrial biopsy would result in biopsy in 84% of tamoxifen-treated women and only 20% of controls.[24] Biopsies of women receiving tamoxifen reveals hyperplastic changes in a significant proportion of patients.[10,12,19,24-26] The

Royal Marsden group performed endometrial biopsy and transvaginal ultrasound in 111 postmenopausal women randomized on their tamoxifen breast cancer prevention trial.[26] The placebo group and tamoxifen groups respectively had 90% and 61% atrophic endometrium, 6% and 13% proliferative endometrium, 0% and 16% atypical hyperplasia, and 2% and 8% polyps. None had endometrial carcinoma. There was a significant correlation between ultrasound-determined endometrial thickness and histologic abnormalities. All women with atypical hyperplasia or polyps had endometrial thickness greater than 8 mm.

Aggressive screening of women receiving tamoxifen carries potential risk. Although the presence of increased endometrial thickness or hyperplasia leads to cancer in only a small fraction of women, it is likely that many women identified with these findings will be withdrawn from treatment with tamoxifen. These women are then denied the proven benefits of tamoxifen. If this affects a significant proportion of women receiving tamoxifen, it is possible that more women will die of recurrent breast carcinoma than will be saved from endometrial carcinoma, and certainly from endometrial carcinoma death. It is possible that strategies such as periodic progesterone therapy for all women receiving tamoxifen, or selectively for those who demonstrate endometrial abnormalities, will be worthwhile. However, it is necessary for such strategies, and for endometrial screening itself, to be tested by prospective study.

This study estimates the risk of endometrial carcinoma in women treated with tamoxifen to be 0.5%. Cancers that develop are mostly early stage and do not result in death because the large majority of endometrial carcinomas in women receiving tamoxifen present with symptoms while the cancer is at an early stage. The risk of endometrial carcinoma death from an endometrial carcinoma diagnosed at advanced stage is extremely low. The role of invasive screening to detect the rare asymptomatic patient with endometrial carcinoma who presents at an advanced stage has yet to be established and should be the subject of prospective study. At this time, women with breast carcinoma who are receiving tamoxifen should undergo careful periodic history and annual pelvic examination with a Papanicolaou smear. Because there is clear survival advantage with its use in breast carcinoma, tamoxifen remains an important treatment for breast carcinoma and its use and benefits should not be overshadowed by endometrial carcinoma risk.[16,21]

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