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Gynecologic Oncology 94 (2004) 256–266

Gynecologic Oncology

www.elsevier.com/locate/ygyno

Review

Endometrial pathologies associated with postmenopausal tamoxifen treatment

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Received 20 August 2003
Available online 19 June 2004

Abstract

Objective. To evaluate various endometrial pathologies described in association with postmenopausal tamoxifen treatment, as well as the clinical aspects of these endometrial pathologies.

Methods. A search was made in PUB MED for all studies published in English, up to the end of 2003, reporting on endometrial pathologies in association with postmenopausal tamoxifen treatment. Overall 106 studies were available, and all are included in this review. The types of studies included were mostly randomized clinical trials, non-randomized cohort studies, prospective and retrospective case controlled studies.

Results. Endometrial polyps represent the most common endometrial pathology associated with postmenopausal tamoxifen exposure. A high rate of malignancy was reported in these polyps. Endometrial hyperplasia, endometrial polyps, endometrial cancer and malignant mixed mesodermal tumors and sarcoma are more commonly diagnosed in postmenopausal breast cancer tamoxifen-treated patients as compared to non-treated patients. Long-term tamoxifen users are more likely to succumb to endometrial cancer and endometrial sarcomas than non-users, due to the unfavorable histology of the endometrial malignancy, and an advanced stage of diagnosis.

Conclusions. The clinician should be alerted to these pathologies, which, in some cases, may potentially increase the mortality of these patients. Consequently, it is suggested that their supervision is of importance, especially if the patients experience any gynecological symptoms, including pelvic pain or pressure.

Keywords: Tamoxifen; Endometrial pathologies; Menopause

Introduction

Tamoxifen is the antihormonal treatment of choice for postmenopausal breast cancer patients with positive estrogen receptors. One of the most significant and deleterious side effects of postmenopausal TAM treatment appears to be its proliferative effect on the endometrium. Overall endometrial pathologies, including hyperplasia, polyps, carcinoma and sarcoma have been identified in up to 36.0% of postmenopausal breast cancer TAM-treated patients [1–93].

Very abundant literature is available on this subject, providing conflicting results and can be quite confusing for the clinician. Moreover, the last ACOG Committee Opinion on TAM and endometrial cancer [94] found the prospective trials on proper follow-up of asymptomatic postmenopausal breast cancer TAM-treated patients as insufficient to give definitive guidelines [25,26,29,95].

In an attempt to locate all available studies reporting on endometrial pathologies in association with postmenopausal TAM treatment, a search was made in PUB MED for all studies published in English under the category of: tamoxifen, endometrial pathology, uterus and menopause. All these studies are included in this review. The types of studies included are mostly randomized clinical trials, non-randomized cohort studies, prospective and retrospective case controlled studies.

This review will evaluate the various endometrial pathologies described in association with postmenopausal TAM treatment, as well as the clinical aspects of these endometrial pathologies. It will further evaluate the differences between the various results and will attempt to raise clinical conclusions.

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doi:10.1016/j.ygyno.2004.03.048

Clinical considerations of tamoxifen-induced endometrial pathologies

The frequency of endometrial pathologies was found to be significantly higher among postmenopausal breast cancer TAM-treated patients, compared with postmenopausal breast cancer nontreated patients [1,5,7,45] (Tables 2, 4). It was also found to be more common among healthy women who received preventive TAM treatment, compared to healthy nontreated women (control group) [10].

However, it was impossible to predict which postmenopausal breast cancer patients would develop endometrial pathologies during TAM treatment, as no significant statistical differences of various clinical features tested were found between patients with or without endometrial pathologies [4], though some clinical features may be associated with an increased risk for the appearance of endometrial pathologies following postmenopausal TAM treatment.

Duration of TAM treatment

It has been suggested that long-term administration of TAM may cause notable endometrial side effects [2,16,19,31,33,34,36–38,56]. Tamoxifen therapy for >48 consecutive months was associated with an increased frequency of endometrial lesions, especially endometrial polyps [12]. Others have found that there is no increased risk of developing endometrial pathologies following an additional 18 months of continuous TAM therapy, nor is there any aggravation of already existing endometrial pathologies [8]. However, this study was performed on a relatively small number of patients.

Based on their review of the literature summarizing studies published through 1995, on the association between postmenopausal TAM treatment and endometrial cancer, Jordan and Assikis [41] suggested that twice as many endometrial cancers were reported in women who stopped TAM therapy at 2 years, compared to those who continued to take the drug [41]. However, in one of the major studies published on this issue, patients allocated to receive 5 years of TAM had raised frequency throughout the entire observation period. The differences in the frequency of endometrial cancer between the 2-year and the 5-year groups was significant ($P < 0.01$) [39]. Moreover, many other reports published in recent years have demonstrated a significant association between longer duration of TAM treatment and the appearance of endometrial cancer [43–45,58,64,68] as well as uterine sarcoma [58,86,87,95], increasing relative risk (RR) for endometrial cancer, as compared to nontreated patients, with gradual increase in duration of TAM treatment, up to 60 consecutive months [40] (Tables 7, 8).

Greater clinical awareness of endometrial cancer in recent years, and the prospective gynecological follow-up of patients performed in recent studies, may contribute to the increased diagnosis of endometrial cancer cases following longer duration of TAM treatment (Table 7).

Cumulative TAM dose

It has been synonymously reported that endometrial pathologies are associated with high cumulative doses of TAM administered to postmenopausal breast cancer patients [19]. An increased frequency of endometrial hyperplasia and neoplasia, but not of endometrial polyps, was found in patients who were treated with more than 15 g of TAM compared with those who received lower cumulative doses [3]. All five cases of primary endometrial cancer that were diagnosed in another study occurred in women who received a cumulative dose of >35 g [9]. The women who received 20 mg of TAM daily developed endometrial pathologies after longer periods of treatment than those who were treated with 40 mg of TAM daily [9].

Vaginal bleeding

A high incidence of overall endometrial pathologies (75–92.9%), as well as of endometrial hyperplasia, endometrial polyps and endometrial carcinoma were reported in postmenopausal breast cancer TAM-treated patients complaining of vaginal bleeding or spotting [11,13,14,16,20–22,40,45,83]. The above rate was significantly higher compared to that diagnosed in similar patients without these symptoms (24.6%; $P = 0.0001$) [20]. Moreover, the endometrial pathologies appeared considerably earlier in patients suffering vaginal bleeding, compared to those not showing this symptom ($P = 0.0002$) [20] (Tables 3, 5).

Increased endometrial ultrasonographic thickening

A significant increase (>50%) in secondary endometrial thickening, measured ultrasonographically in postmenopausal TAM-treated patients, has been associated with a high rate of endometrial pathologies, including endometrial cancer [31].

Pretreatment endometrial lesions

Long-term hysteroscopic and histological follow-up of the endometrium, performed before and during TAM treatment, revealed the appearance of new endometrial pathologies, especially of endometrial polyps, in 25–26.9% of postmenopausal breast cancer patients treated with TAM as compared to postmenopausal breast cancer nontreated patients [2,33,34,36,37]. Others demonstrated that the prevalence of endometrial pathologies before and after TAM therapy remained the same (10%), showing a nonsignificant variation [35]. Nevertheless, a high-risk group of patients was identified in whom endometrial pathologies were diagnosed before commencement of TAM therapy. These patients had a significantly higher rate of endometrial pathologies following 3 years of TAM treatment, compared to similar patients who had no endometrial pathologies before TAM therapy [34].

Table 1
Distribution of endometrial hyperplasia in postmenopausal breast cancer patients treated with tamoxifen

Authors	Simple endometrial hyperplasia	Complex endometrial hyperplasia
	No. (%)	No. (%)
Gal et al. [2]	2 (2.2)	7 (7.9)
Lahti et al. [5]	1 (2.0)	1 (2.0)
Zarbo et al. [32]	11 (9.6)	5 (4.3)[a]
Barakat et al. [51]	2 (1.89)	1 (0.9)

[a] Two cases contained atypical tissue.

Finally, it has been shown that the endometrium of postmenopausal breast cancer patients treated with TAM may possess different responses to TAM exposure [15].

To conclude: The frequency of overall endometrial pathologies was higher among postmenopausal breast cancer TAM-treated patients, compared with nontreated patients. These endometrial pathologies may be associated with longer duration of TAM treatment, higher cumulative TAM dose, complaint of vaginal bleeding and the existence of pretreatment endometrial pathological lesions.

Endometrial hyperplasia

A high rate of simple and complex endometrial hyperplasia [2,5,32,45,51], with or without atypia, was identified in specimens collected from postmenopausal TAM-treated patients [1–7,9–16,19–22,24–26,28–34,36,37,45–52] (Tables 1–3), as compared to nontreated patients [4,5,7,11,13,16,23,25,36,37,46] (Table 2) and compared to healthy controls [1]. Endometrial hyperplasia was also found to be more common among healthy women who received preventive TAM treatment, compared to healthy nontreated women (control group) [10].

Simple and complex endometrial hyperplasia was described in endometrial polyps recovered from postmenopausal breast cancer TAM-treated [15,45,47,50] and nontreated patients [15]. Endometrial hyperplasia was also reported in 49% of TAM-associated malignant tumors compared with 26% of those patients not taking TAM [52].

Table 3
Distribution of endometrial hyperplasia in postmenopausal breast cancer tamoxifen-treated patients with and without vaginal bleeding

Authors	Patients with vaginal bleeding	Patients without vaginal bleeding	Endometrial hyperplasia in symptomatic patients	Endometrial hyperplasia in asymptomatic patients	*P* value
			No. (%)	No. (%)	
Cohen et al. [20]	14	224	5 (35.7)	12 (5.6)	<0.0001
Marconi et al. [22]	23	78	3 (13.0)	6 (7.7)	NS

NS = nonsignificant.

Most studies [1,5,7,16,37] have shown a higher rate of endometrial hyperplasia in TAM-treated patients as compared to nontreated patients (Table 2). All are case controlled studies. Cohen et al. [15] and McGonigle et al. [46] showed different results (Table 2). The differences in the results may be attributed to the fact that not all endometrial specimens were collected by hysteroscopy in these two studies [15,46].

Some were collected by diagnostic curettage [15,46] or by blind endometrial sampling [46]. It has been suggested that in postmenopausal TAM-treated patients, hysteroscopy should be the method of choice, when endometrial sampling is needed (i.e., in symptomatic patients or when ultrasonographic evaluation revealed thick endometrium or an endometrial echognic mass [1,2,33,34,36,37,47,54]), as endometrial pathologies, even other than polyps, may be localized in the endometrium of these patients. Thus, sampling methods, other than hysteroscopy, may leave some endometrial pathologies undiagnosed, especially in the TAM-treated patients, as potentially they are more prone to endometrial pathologies.

The differences in the results may also be attributed to the presence or absence of vaginal bleeding [16,46], as a

Table 2
Distribution of endometrial hyperplasia in postmenopausal breast cancer tamoxifen-treated patients and in postmenopausal breast cancer nontreated patients

Authors	Tamoxifen-treated patients	Nontreated patients	Endometrial Hyperplasia in tamoxifen-treated patients	Endometrial Hyperplasia in nontreated patients	*P* value
			No. (%)	No. (%)	
Neven et al. [1]	30	29	1 (3.3)	0 (0.0)	Not indicated
Lahti et al. [5]	51	52	2 (4.0)	1 (2.0)	NS
Cohen et al. [7]	93	20	2 (2.15)	0 (0.0)	Not indicated
Cohen et al. [15]	175	27	21 (12.0)[a]	3 (11.0)	NS
Cheng et al. [16]	33	23[b]	10 (30.3)[a,b,c]	1 (4.3)[b]	Not indicated
Maugeri et al. [37]	124	104	17 (13.7)	0 (0.0)	<0.00001
McGonigle et al. [46]	58[b]	68[b]	4 (6.9)[b]	5 (7.4)[b]	NS

NS = nonsignificant.
[a] Simple and complex hyperplasia.
[b] Some tamoxifen-treated and nontreated patients had vaginal bleeding.
[c] Some patients had atypical features (Lahti et al. [5]).

Table 4
Distribution of endometrial polyps in postmenopausal breast cancer tamoxifen-treated patients and in postmenopausal breast cancer nontreated patients

Authors	Tamoxifen-treated patients	Nontreated patients	Endometrial polyps in tamoxifen-treated patients	Endometrial polyps in nontreated patients	*P* value	Sampling method
			No. (%)	No. (%)		
Neven et al. [1]	30	29	7 (23.3)	1 (3.4)	<0.05	case control study
Lahti et al. [5]	51	52	17 (36)	5 (10)	0.004	prospective case control study
Cohen et al. [7]	93	20	5 (5.38)	0 (0.0)	Not indicated	prospective case control study
Cohen et al. [15]	175	27	14 (8.0)	2 (7.4)	NS	prospective case control study
Cheng et al. [16]	33	23	7 (21.2)[a]	0 (0.0)	0.025	prospective case control study
Maugeri et al. [37]	124	104	17 (13.7)	0 (0.0)	<0.00001	prospective case control study
McGonigle et al. [49]	58[a]	68[a]	10 (17.2)[a]	11 (16.2)[a]	NS	case control study

NS = not significant.
[a] Sixty-three percent of tamoxifen-treated patients and 86% of nontreated patients suffered vaginal bleeding.

high incidence of overall endometrial pathologies (75–92.9%) as well as of various endometrial pathologies were recovered from postmenopausal breast cancer TAM-treated patients complaining of vaginal bleeding or spotting [11,13,14,16,20–22,40,45,83]. This rate was significantly higher compared to that diagnosed in similar patients without these symptoms (24.6%; $P = 0.0001$) [20]. Thus, the considerably high rate of endometrial hyperplasia diagnosed among TAM-treated patients in Cheng et al.'s [16] study may be, at least, partially attributed to the presence of vaginal bleeding [16].

It is demonstrated synonymously that endometrial hyperplasia is significantly more common among postmenopausal breast cancer TAM-treated patients with vaginal bleeding as compared to patients without this symptom [20,22] (Table 3). Both studies are case controlled.

To conclude: Endometrial hyperplasia is more commonly diagnosed in TAM-treated patients as compared to nontreated patients, and among postmenopausal breast cancer TAM-treated patients with vaginal bleeding as compared to patients without this symptom.

Endometrial polyps

Endometrial polyps represent the most common endometrial pathology associated with postmenopausal TAM exposure, with a rate of 8–36.0% [1,3–22,24–37,45–51,53–56] (Table 4).

Endometrial polyps recovered from TAM-treated patients are more translucent and are distinguished, microscopically, from typical polyps by higher fibrotic content [45], a combination of proliferative activity and focal periglandular stromal condensation [18,50], extensive glandular hyperplasia [17] and by stromal fibrosis and cellularity [45]. Mucinous metaplasia also occurs more frequently, usually in association with larger polyps and longer duration of TAM therapy [50]. Endometrial polyps may also be composed of a mixture of simple endometrial hyperplasia, complex endometrial hyperplasia (with or without atypia) and a small focus of endometrial carcinoma [54].

The polyps are often multiple and larger in postmenopausal TAM-treated patients (median size = 2.9 cm; range = 0.3–11.0 cm), than are seen in healthy, postmenopausal women on hormone replacement therapy (median size = 1.05 cm; range = 0.3–2.0 cm) or in healthy, postmenopausal, untreated controls (median size = 1.35 cm; range = 0.2–3.6 cm) [50].

Endometrial polyps were nearly always found to be significantly more common among postmenopausal breast cancer TAM-treated patients as compared to nontreated patients [1,5,16,17] (Table 4), as well as compared to healthy controls [1]. All studies were case controlled. In a randomized, double-blind controlled trial, endometrial polyps were found to be more common among healthy women who received preventive TAM treatment, compared to healthy nontreated women (control group) [10].

Endometrial polyps were synonymously found to be significantly more common among postmenopausal breast cancer TAM-treated patients with vaginal bleeding as compared to patients without this symptom [11,20,22] (Table 5). All studies were case controlled.

Table 5
The distribution of endometrial polyps in gynecologically asymptomatic postmenopausal breast cancer tamoxifen-treated patients and in similar gynecologically symptomatic patients

Authors	Symptomatic patients	Asymptomatic patients	Endometrial polyps in symptomatic patients	Endometrial polyps in asymptomatic patients	*P* value	Sampling method
			No. (%)	No. (%)		
Cohen et al. [20]	14	224	5 (35.7)	30 (13.4)	<0.0111	prospective case control study
Marconi et al. [22]	23	78	31 (52.5)	13 (59.1)	NS	case control study
Borenstein et al. [11]	7	15	2 (28.6)	0 (0.0)	NS	prospective case control study

NS = not significant.

Some risk factors have been identified for endometrial polyps in postmenopausal breast cancer TAM-treated patients: older age at menopause, longer duration of breast disease, heavier body weight and thicker endometrial thickness, measured by transvaginal ultrasonography, compared with similar patients without endometrial polyps [56].

Recently, it has been found that previous use of hormone replacement therapy, shorter duration of TAM exposure and additional years of TAM treatment may significantly increase the risk of developing recurrent endometrial polyps in such patients [96]. Interestingly, all recurrent polyps were benign [96].

Saline infusion sonography should be performed in all postmenopausal TAM-treated patients in whom transvaginal ultrasonography revealed thick endometrium, as it has been suggested to be the best diagnostic method for identification of endometrial polyps in these patients [47]. It has also been suggested that operative hysteroscopy should be used for removal of endometrial polyps, since blind endometrial biopsy may often yield no tissue, especially in the presence of large endometrial polyps [47].

To conclude: Endometrial polyps represent the most common endometrial pathology associated with postmenopausal TAM exposure. They are significantly more common among postmenopausal breast cancer TAM-treated patients as compared to nontreated patients, and are significantly more common among postmenopausal breast cancer TAM-treated patients with vaginal bleeding as compared to patients without this symptom.

Malignant endometrial polyps

It has been suggested that endometrial polyps may form an intermediate stage between simple endometrial hyperplasia and endometrial malignancy [9]. There is an evidence of an association between postmenopausal TAM treatment for breast cancer and an increased risk of endometrial cancer [57]. Thus, postmenopausal TAM exposure also may contribute to the development of a higher number of malignant endometrial polyps [54].

Malignant transformation was reported in 3.0–10.7% of endometrial polyps recovered from postmenopausal breast cancer TAM-treated patients [34,45,50,53,54] (Table 6). This malignancy rate is higher than that reported in healthy controls as well as that reported in the general female population [54]. A high grade of malignancy (0.0–53.3%) was reported in these malignant endometrial polyps [34,45,50,53,54] (Table 6).

In spite of the severity of this endometrial entity, only about 50.0% of the patients complained of vaginal bleeding [45,53,54] (Table 6).

There is no correlation between malignant polyps and polyp size and treatment duration [34,45,50,53,54].

It was impossible to predict which polyps would contain malignant tissue, as none of the various clinical features, including duration of TAM treatment and mean endometrial thickness (as detected by transvaginal ultrasonography), compared between patients with malignant endometrial polyps and those with benign endometrial polyps were found to be significantly different [54].

It was suggested that endometrial polyps, ultrasonographically diagnosed in postmenopausal breast cancer TAM-treated patients, should be resected, due to the potentially high rate of malignancy [45,50,54], the high percentage of high-grade malignancy in these polyps [45,50,54], and to the fact that large endometrial polyps may precede the formation of malignant mixed mesodermal tumors [58,59].

This procedure should be performed in both gynecologically symptomatic and gynecologically asymptomatic patients, as nearly 50% of these malignant endometrial polyps were diagnosed in gynecologically asymptomatic patients [53,54].

Operative hysteroscopy should be used for the removal of endometrial polyps, since blind endometrial biopsy may yield no tissue, especially in the presence of large endometrial polyps [47]. Since in most of the malignant endometrial polyps described [34,45,50,53,54], only a small focus of the polyps contained malignant tissue [54], it is imperative to extract these polyps entirely and, thus, it is recommended to use operative hysteroscopy for such cases [47,54].

To conclude: A high rate of malignant transformation with a high grade of malignancy was reported in endometrial polyps recovered from postmenopausal breast cancer TAM-treated patients. Vaginal bleeding was associated with only 50.0% of the cases. There is no correlation between malignant polyps and polyp size or treatment duration.

Endometrial cancer

Abundant number of reports on endometrial cancer in postmenopausal breast cancer TAM-treated patients have

Table 6
Clinical and histological features of malignant endometrial polyps recovered from postmenopausal breast cancer tamoxifen-treated patients

Authors	Overall endometrial polyps in the study	Malignancy	High-grade malignancy	Vaginal bleeding	Duration of tamoxifen treatment (years)
		No. (%)	No. (%)		
Berliere et al. [34]	46	2 (4.3)	0 (0.0)	not indicated	1–3
Deligdisch et al. [45]	252	15 (5.9)	8 (53.3)	(31) 52%	Mean 3.2, median 3.0
Schlesinger et al. [50]	28	3 (10.7)	1 (33.3)	not indicated	not indicated
Ramondetta et al. [53]	5	not indicated	not indicated	3 (60%)	1.5–5
Cohen et al. [54]	67	2 (3.0)	1 (50.0)	1 (50.0%)	10.0 ± 8.0

Table 7
Relative risk of endometrial cancer in association with postmenopausal tamoxifen use

Authors	No. of patients	No. of controls	No. of endometrial cancers in patients	No. of endometrial cancers in controls	RR	95% CI	Tamoxifen dose (mg)	Type of study
Fornander et al. [39]	931	915	13 (1.4%)	2 (0.2%)	6.4	1.4–28	40	randomized
Fisher et al. [43]	1419	1424	15 (1.1%)	2 (0.1%)	7.5	1.7–32.7	20	randomized
van Leeuwen et al. [44]	–	–	98	–	1.3	0.7–2.4	–	case control study
Ribiero et al. [60]	481	480	1 (0.2%)	1 (0.2%)	–	–	20	randomized
Castiglion et al. [61]	167	153	0 (0.0%)	0 (0.0%)	–	–	20	randomized
Fornander et al. [62]	–	–	10	3	2.7	0.9–8.1	40	randomized
Ryden et al. [64]	483	236	9 (1.9%)	2 (0.8%)	2.0	–	30	randomized
Andersson et al. [65]	864	2674	7 (0.8%)	13 (0.5%)	1.9	0.8–3.9	30	case control study
Boccardo et al. [66]	168	165	0 (0.0%)	0 (0.0%)	–	–	30	randomized
Stewart et al. [67]	374	373	1 (0.3%)	1 (0.3%)	–	–	20	randomized
Cummings et al. [68]	85	83	1 (1.2%)	1 (1.2%)	–	–	20	randomized
Rutquist et al. [74]	–	–	23	4	5.6	1.9–16.2	20	randomized
Cook et al. [75]	–	–	33	66	0.6	0.2–1.9	–	case control study
Robinson et al. [76]	108	478	4	4	15.2	2.8–84.4	20	case control study
Curtis et al. [77]	14,358	72,965	73 (0.5%)	384 (0.5%)	2.0	1.59–25.5	–	nonrandomized cohort
Peters-Ingl et al. [85]	701	1408	8 (1.1%)	17 (1.2%)	1.1	0.71–1.80	20–40	retrospective cohort

been published [9,31,39,40,42–45,50,52–54,60–87], most of which demonstrate evidence of an association between postmenopausal TAM treatment for breast cancer and an increase in relative risk (RR) for endometrial cancer when compared to patients nontreated with TAM [39,40,44,45,52,62,63,65–77,79,81–87].

Relative risk

The risk does not decrease after cessation of TAM treatment, as the effect of TAM can last several years beyond discontinuation of exposure [86]. Therefore, it is important to emphasize that breast cancer patients could experience escalating endometrial proliferation over time, irrespective of TAM use, as the incidence of endometrial cancer after a breast cancer has shown a slight increased risk compared with the general population [97,98].

Different types of studies are reported in Table 7: randomized studies, case controlled studies as well as in retrospective reviews studies. Similar proportions of these types of studies found positive or negative RR of endometrial cancer with postmenopausal TAM treatment, when compared to nontreated patients. The impact and the power of the different studies may be attributed to the type of the study, but also to the total number of study patients. All studies reporting on a positive RR, except one, were based on a considerably higher study population [39,42,43,62,64,74,76,77,85], as compared to the studies reported on a negative RR [60,61,64–68,75]. Of course, it may be inappropriate to compare results obtained from different types of studies. However, in spite of the diversity of the various studies, one may get some impression from the overall data presented on the overall risk of endometrial cancer in postmenopausal breast cancer TAM-treated patients.

An increased rate of endometrial cancer was also reported in healthy postmenopausal TAM-treated women with a high risk for breast cancer, predominantly in women aged 50 years or older, who participated in a randomized, double-blind, TAM chemoprevention trial, compared to similar, healthy, nontreated women (RR = 2.53; 95% CI = 1.35–4.97) [88].

All patients reported in Table 7 were symptomatic [39,43,44,60–62,64–68,74–77,85].

Table 8
Relative risk of endometrial cancer in association with duration of postmenopausal tamoxifen use

Authors	RR* (95% CI)	Duration of tamoxifen treatment (years)
Sasco et al. [78]	1.5 (0.4–4.9)	<2
van Leeuwen et al. [44]	2.3 (0.9–5.9)	>2
Sasco et al. [78]	1.5 (0.4–5.6)	2–5
Bergman et al. [86]	2.0 (1.2–3.2)	2–5
Bergman et al. [86]	6.9 (2.4–19.4)	≥5
van Leeuwen et al. [44]	3.0 (0.6–15.8)	>5
Sasco et al. [86]	3.5 (0.94–12.7)	>5
Bernstein et al. [84]	4.06 (1.74–9.47)	>5

*Relative risk was compared to nontreated patients.

Duration of tamoxifen treatment

Longer duration of TAM use was associated with an increased risk of endometrial cancer [44,78,84,86] (Table 8), when compared to nontreated patients ($P < 0.001$) [86] ($P = 0.0002$) [84]. The RR was considerably higher with TAM treatment of ≥5 years, as compared to shorter durations of treatment.

Cumulative tamoxifen dose

There is also an association between high cumulative TAM dose and an increase in endometrial cancer risk, as compared to nontreated breast cancer patients. A RR of 6.4 (95% CI = 1.4–28), 7.5 (95% CI = 1.7–33) and 3.3 (95% CI = 0.6–32.4) for endometrial cancer have been associated

with a cumulative TAM dose of approximately 29.2, 36.5 and 10.9 g, respectively [39,42,43].

Cumulative doses of less than 14.68 g were not associated with an increased risk of endometrial cancer, whereas cumulative doses above 14.68 g were associated with approximately a 2-fold increase in risk [44]. The relative risk of endometrial cancer gradually increased with higher cumulative TAM doses up to ≥45 g (RR = 1.4 for 1–7.4 g, and RR = 16.7 for ≥45 g) [40]. A higher daily dose was also associated with an increased risk of endometrial cancer (20 mg = RR 9.3; 40 mg = RR 12.6) [40].

Histological types of endometrial cancer

Most of the endometrial cancers diagnosed were either endometrioid [43,72] or adenocarcinomas [40,73]. A lower frequency of endometrioid carcinoma and a higher frequency of clear cell carcinoma and of serous carcinoma were identified among TAM-treated patients, compared to nontreated patients [73].

Other types of endometrial malignancies are discussed later in this review.

Malignancy of endometrial cancer

Many studies have shown a lack of evidence to indicate that endometrial cancers resulting from TAM therapy are likely to be more aggressive tumors [39,40,43,44,66,67,72,73,77,79,85]. Most cases were of low grade and stage, with no differences in the stage, grade or histologic subtype of endometrial cancers occurring in TAM-treated patients, compared to nontreated patients [40,43,44,72,85].

All endometrial cancers reported in healthy postmenopausal TAM-treated women, at high risk for breast cancer, who participated in the TAM chemoprevention trial, were also stage I [88].

In recent years however, other studies have reported findings of endometrial cancers diagnosed in postmenopausal breast patients treated with TAM which were more advanced and had poorer prognoses than endometrial cancers found in nontreated patients [40,45,52,69,86,87]. Two-thirds of endometrial cancers diagnosed in such patients were associated with poorly differentiated endometrial carcinoma compared with carcinomas cases diagnosed in patients not treated with TAM ($P = 0.01$) [69].

Another study showed that stage III and IV endometrial cancers occurred more frequently in long-term TAM users (≥5 years) than in nonusers (17.4% vs. 5.4%, $P = 0.006$). Long-term users were more likely than nonusers to have malignant mixed mesodermal tumors or sarcomas of the endometrium (15.4% vs. 2.9%, $P \geq 0.02$) [86]. Other investigators [52,87] have reported similar results. Adverse histologies (papillary serous, malignant mixed mesodermal tumors or clear cell carcinomas) were found in 21.4% of TAM-treated patients, compared with only 1.5% diagnosed in nontreated patients (OR = 17.7; $P = 0.0002$) [52].

Increased clinical awareness for endometrial cancer in recent years, and the prospective long-term gynecological follow-up of patients performed in recent studies, may contribute to the increased diagnosis of endometrial cancer cases, especially following longer duration of TAM treatment.

Prognosis of endometrial cancer

Long-term TAM users are more likely to succumb to endometrial cancer than nonusers, due to the unfavorable histology of the endometrial malignancy and an advanced stage at diagnosis [40,45,52,69,80,86]. Endometrial cancer mortality rate among TAM-treated patients was significantly higher compared to nontreated patients (33.3% vs. 2.6%; $P = 0.005$) [69]. The 3-year endometrial cancer-specific survival rate was significantly worse for long-term users than for nonusers (76% for ≥5 years, 85% for 2–5 years and 94% for nonusers, $P = 0.02$). Furthermore, the 5-year overall endometrial cancer survival rate was significantly worse for TAM users compared with nonusers (40% vs. 64%; $P = 0.01$) [86]. In the report of 133 randomized trials, involving 75,000 breast cancer patients mentioned previously, a total of 27 cases of endometrial cancer mortality were reported in the TAM-treated patients (21.85% of the affected cases and 0.07% of overall patients in the study) and only five cases in nontreated patients. The overall cumulative risk was two deaths per 1000 [82]. Others, however, could not find such an association [44,72,81].

Higher fatality rate was reported in studies performed on a considerably higher study population [40,45,52,86,87]. It may well be that extension of the studies reporting on low mortality rate may reveal higher rate of endometrial malignancy, and ultimately higher mortality results [44,72,81].

No death from endometrial cancer was reported among healthy postmenopausal TAM-treated women with a high risk for breast cancer who participated in the TAM chemoprevention trial [88].

Risk factors for endometrial cancer

Some risk factors (other than those mentioned earlier in this review) for the appearance of endometrial cancer in postmenopausal breast cancer TAM-treated patients were reported: prior use of estrogen replacement therapy (ERT) [84], older age and longer duration of breast disease [83].

To conclude: There is evidence of an association between postmenopausal TAM treatment for breast cancer and an increase in relative risk for endometrial cancer when compared to nontreated patients. Most patients reported were symptomatic, having a longer duration of TAM use and a high cumulative TAM dose. Most endometrial cancers diagnosed were either endometrioid or adenocarcinomas. Long-term TAM users are more likely to succumb to endometrial cancer than nonusers, due to the unfavorable

histology of the endometrial malignancy, and an advanced stage at diagnosis.

Malignant mixed mesodermal tumors and uterine carcinosarcoma

The association between postmenopausal TAM treatment and malignant mixed mesodermal tumors (MMMT), including uterine carcinosarcoma, has been extensively described in the literature [9,40,45,58,59,71,73,86,89–93,99,100], mostly as case reports.

Some clinical observations described

There may be an association between long-term TAM treatment (>5 years) and the development of MMMT [58,59], and of carcinosarcoma formation [92], the age distribution of affected patients is similar to that reported for endometrial carcinoma [58,59], and an advanced stage of the disease was found in most of the patients and the outcome usually fatal [58,59]. Deligdisch et al. [45] reported on 33 cases of endometrial cancer diagnosed in histological specimens collected from 700 patients treated with TAM. Approximately two-thirds were moderately or poorly differentiated, including two cases of MMMT [45].

Bergman et al. [86] performed a nationwide case-control study on the risk and prognosis of endometrial malignancies after TAM use for breast cancer, comparing data obtained from 309 women with endometrial cancer after breast cancer and 860 matched controls with breast cancer but without endometrial cancer, and found that long-term TAM users were more likely than nonusers to have had MMMT or sarcoma of the endometrium (15.4% vs. 2.9%; $P \leq 0.02$).

Bouchardy et al. [99] observed in the Geneva Cancer Registry a 2.8-fold increased risk of corpus uteri cancer among TAM-treated patients (95% CI = 1.4–5.0, $P < 0.01$) as compared to 1.6-fold increase in nontreated patients (95% CI = 0.8–2.8, $P = 0.10$). Based on their results the authors calculated that in their cohort of women, a 29.0-fold increased risk (95% CI = 3.5–104.9, $P < 0.01$) compared with that expected in the general population [99].

A review of all available data on TAM from the global drug safety database through July 2001, for the occurrence of uterine malignancy, revealed 942 cases of uterine malignancies: 802 (85%) endometrial adenocarcinoma and 140 (15%) uterine sarcoma, of which 73% were MMMT, one-third having a fatal outcome.

Bernstein et al. [84] performed a population-based series of 324 women diagnosed with endometrial cancer after breast cancer, identified by four SEER registries, and found in the TAM-treated patients 11 out of 146 (7.5%) with sarcoma and 12 out of 178 (6.7%) among the nontreated patients. The endometrial cancer-specific survival rate was poorer in women with sarcoma as compared to those with adenocarcinoma ($P < 0.0001$). However, the prognosis of women with uterine sarcoma or adenocarcinoma who had taken TAM was no worse than that of women not exposed to TAM.

The NSABP study [44] revealed that 10% of uterine malignancies identified in TAM-treated patients were sarcomas.

In the Breast Cancer Prevention Trial studies (NSABP), a small number of sarcoma (predominantly MMMT) was identified in healthy women at increased risk for breast cancer (0.17%) [88].

However, Silva et al. [73] could not find significant differences in the rate of MMMT, adenosquamous carcinoma or leiomyosarcoma between TAM-treated and nontreated patients [73]. The discrepancy between this latter study, and the results described by all other reports may be attributed to the relatively small number of patients in this report [73]. It might well be that extending the number of patients will reveal similar results.

Based on their findings, Bouchardy et al. [99] concluded that there was strong increased risk of MMMT uteri cancer among TAM-treated patients and their close supervision was important [99], especially if the patients experienced any gynecological symptoms, including pelvic pain or pressure [100].

To conclude: Most studies reported on a higher rate of MMMT and sarcoma among postmenopausal breast cancer TAM-treated patients compared to nontreated patients, especially those exposed to long-term TAM treatment. An advanced stage of the disease was found in most of the patients and the outcome usually fatal.

Conclusions

Different types of endometrial pathologies are reported in association with postmenopausal TAM treatment, including endometrial cancer and sarcoma. However, the last ACOG Committee Opinion on TAM and endometrial cancer found the prospective trials on proper follow-up of asymptomatic postmenopausal breast cancer TAM-treated patients as insufficient to give definitive guidelines [94]. As screening tests have not been effective in increasing the early detection of endometrial cancer in women using TAM, they are not recommended [94]. Investigation should be performed only in case of any abnormal vaginal bleeding, bloody vaginal discharge, staining or spotting [94].

However, many investigators recommended that postmenopausal women who receive TAM for breast cancer should warrant closer gynecological surveillance for endometrial cancer during treatment [33,37,40,101–106], especially those with positive ERT histories, those obese when prescribed TAM [84], as well as long-term TAM users [86].

Moreover, in view of the latest findings, that two-thirds of endometrial cancers diagnosed in postmenopausal breast cancer TAM-treated patients are poorly differentiated and prognoses poorer than endometrial cancers found in nontreated patients [40,45,52,69,86,87,99], the clinician should

be alerted to these pathologies, especially by endometrial cancer and MMT, which may, in some cases, potentially increase the mortality rate of these patients. Consequently, it has been suggested that their close supervision is of importance [99], especially if the patients experience any gynecological symptoms, including pelvic pain or pressure [100].

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