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Tamoxifen use as a malignancy risk factor in postmenopausal women with endometrial polyps

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Abstract

Objective: We analyzed tamoxifen use as a malignancy risk factor in women with endometrial polyps.

Methods: This retrospective study included 675 women who underwent hysteroscopic polypectomy in 2010 to 2015 at the University of Campinas. Women were divided into tamoxifen use (n = 169) and no tamoxifen use (n = 506) groups. The primary outcome was endometrial cancer prevalence. Dependent variables included age, parity, years since menopause, presence of abnormal uterine bleeding, endometrial pattern on hysteroscopy, and endometrial thickness.

Results: There were seven cases of endometrial cancer in the tamoxifen use group (4.14%) and 41 in the no tamoxifen use group (8.1%; $P = 0.083$). On performing multivariate analysis, tamoxifen use was not a risk factor for endometrial cancer (prevalence ratio 0.51, 95% confidence interval [CI] 0.23-1.14, $P = 0.101$). The no tamoxifen use group had an increased prevalence of malignancy when women presented with abnormal uterine bleeding (prevalence ratio 3.9, 95% CI 2.08-7.29, $P < 0.001$), age >60 years (prevalence ratio 2.1, 95% CI 1.12-3.93, $P = 0.021$), or nulliparous status (prevalence ratio 3.13, 95% CI 1.55-6.35, $P = 0.002$). The tamoxifen use group had increased prevalence of malignancy when women were >60 years (prevalence ratio 7.85, 95% CI 1.05-58.87, $P = 0.006$) or nulliparous (prevalence ratio 8.36, 95% CI 2.32-30.11, $P < 0.001$).

Conclusion: Tamoxifen use was not related with a higher prevalence of endometrial cancer in women with endometrial polyps. Abnormal uterine bleeding, age > 60 years, and nulliparous status were associated with malignancy.

Key Words: Endometrial cancer – Endometrial polyps – Hysteroscopy – Tamoxifen.

Endometrial polyps are benign nodular protrusions of glands, stroma, and typical vessels on the endometrial surface.[1-4] Their actual incidence is unknown, but studies have shown their occurrence in 7.8% to 34.9% of women and that they are more common in postmenopausal women and frequently associated with abnormal uterine bleeding .[5-9]

The exact cause of their development is unknown, but it may be related to the imbalance between estrogen and progesterone receptors; other markers that regulate cell proliferation and apoptosis[10]; monoclonal proliferation; chromosome 6 and 12 alterations that could increase endometrial growth; and mutations in *HMGIC* and *HMGIY* genes that would increase aromatase expression in the endometrium and, consequently, increase estrogen exposure.[11,12] However, the emergence of polyps appears to be more closely related to the inhibition of apoptosis and possibly related to a higher estrogen/progesterone ratio.[6,10,13]

Risk factors for its development include increasing age,[5] obesity, hypertension, and tamoxifen use.[6,14] Women who use tamoxifen are at increased risk for the development of polyps (prevalence of 30%-60%), and a greater association has been shown between these polyps and carcinomas.[15-17]

Although most polyps are benign, they may contain premalignant or malignant lesions in up to 23.8% of cases.[17-19] The main risk factors for malignant polyps are advanced age, menopausal status, and abnormal uterine bleeding.[19]

Tamoxifen—a selective drug that binds to the estrogen receptor and has a non-steroidal antiestrogenic action—has been used since the 1970s for the adjuvant treatment of breast cancer. In the endometrium, it can have a proliferative effect, resulting in the appearance of polyps, hyperplasia, and endometrial cancer.[20] Tamoxifen use increases a woman's relative risk of endometrial cancer by 4 to 6 times, especially after 5 years of use.[16]

The mechanism of oncogenicity of tamoxifen is not fully understood, but it may be related to increased *TFF3* expression in endometrial tumor cells, leading to decreased apoptosis, cell cycle progression, angiogenesis, and metastatic

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potential.[21] Expression of the AGR2 protein appears to be linked to cell proliferation and myometrial invasion.[22]

Although it is well established that the use of tamoxifen increases the prevalence of endometrial cancer, the prevalence of malignant polyps in women using the medication remains to be elucidated, although it seems low. Thus, this study aimed to evaluate the real prevalence of malignant endometrial polyps in women using tamoxifen.

METHODS

This retrospective cohort study included medical record reviews of 675 women who attended the Women's Health Hospital of the University of Campinas (UNICAMP).

The inclusion criteria were endometrial polyps diagnosed by surgical hysteroscopy (rigid hysteroscope based on a 4.0-mm rod-lens system with a 308 forward oblique view; Karl Storz GmbH, Tuttlingen, Germany) and confirmed by anatomopathology. After that, the participants were divided into two groups: tamoxifen users (n = 169) and tamoxifen nonusers (n = 506). The 20-mg tamoxifen tablets used were manufactured by Sandoz (Cambe, PR, Brazil).

The exclusion criteria were impossible polyp resection, polyp not confirmed pathologically, and data missing from the medical records.

The variables analyzed were: tamoxifen use; duration of tamoxifen use; age; body mass index (BMI) classified as underweight ($<20\,kg/m^2$), adequate (20-25 kg/m^2), overweight ($>25\,kg/m^2$), or obese ($>30\,kg/m^2$); vaginal bleeding; menopausal status (amenorrhea for at least 12 months); parity; systemic arterial hypertension (pressure levels above 140/90 mm Hg); diabetes mellitus (glycemia above 126 mg/dL); polyp size; smoking status; use of hormonal therapy; and diagnosis of breast cancer.

The present study was approved by the Research Ethics Committee of the Faculty of Medical Science of University of Campinas (No. 13329713.0.0000.5404).

Statistical analysis

The sample size calculation was based on the malignant polyps in users and nonusers of tamoxifen obtained in previous studies of 0.98% and 5.71%, respectively. The sample size was calculated according to the methodology described by Hulley et al in the use of the chi-square test for independent samples considering a significance level of 5% and test power of 80% with a 3:1 weighting. We obtained n = 167 for tamoxifen users and n = 501 for nonusers for a total sample size of 668 women. SAS for Windows version 9.3 was used for statistical analyses.[23]

Descriptive statistics were calculated for women with endometrial polyps. Continuous values are summarized as mean and standard deviation, whereas categorical variables are summarized as percentages.

The chi-square test was used to compare categorical variables between groups. The Mann-Whitney test was used to compare numerical variables due to the absence of normal distribution.

TABLE 1. *Clinical characteristics of tamoxifen users (n = 169) versus nonusers (n = 506)*

Clinical characteristics	Users Mean ± SD, n (%)	Nonusers Mean ± SD, n (%)	*P*
Age (y)[a]	60.0 ± 10.0	56.9 ± 10.7	0.002
Nulliparous[b]	14.0 (8.28)	59.0 (11.66)	0.221
BMI (kg/m^2)[a]	29.5 ± 5.2	29.8 ± 5.5	0.330
Time of menopause (y)[a]	11.0 ± 8.8	9.29 ± 8.7	0.006
Postmenopausal bleeding[b]	62.0 (36.69)	252.0 (49.80)	0.002

BMI, body mass index; SD, standard deviation.
[a]Mann-Whitney test.
[b]Chi-square test.

Poisson univariate and multivariate regression analyses with stepwise criteria of variable selection and estimation of prevalence ratio (PR) and 95% confidence interval (CI) were used to analyze factors related to endometrial cancer. The significance level adopted for the statistical tests was 5%.

RESULTS

The mean age was 60.0 ± 10.2 years in the tamoxifen users and 56.9 ± 10.79 years in the tamoxifen nonusers ($P = 0.002$). Nulliparous status was slightly less common in the users (8.28%) than in the nonusers (11.66%; $P = 0.221$). The tamoxifen users had a mean BMI of 29.5 ± 5.2 kg/m^2 and were at 11.0 ± 8.8 years since menopause, whereas the nonusers had a BMI of 29.8 ± 5.5 kg/m^2 and were at 9.2 ± 8.7 years since menopause ($P = 0.330$ and $P = 0.006$, respectively). Bleeding affected 36.69% of the tamoxifen users versus 49.80% of the nonusers ($P = 0.002$) (Table 1).

Endometrial cancer affected 7 of the 169 (4.14%) tamoxifen users and 41 of the 506 (8.1%) nonusers ($P = 0.083$). The mean tamoxifen use duration was 2.8 ± 1.58 years (data not shown).

The mean endometrial thickness was 13.35 ± 6.93 mm in the tamoxifen use group versus 10.68 ± 6.84 mm in the tamoxifen nonuse group ($P < 0.001$) (Table 2).

On multivariate analysis using a stepwise variable selection criterion, tamoxifen use was not a risk factor for endometrial cancer (PR 0.51, 95% CI 0.23-1.14, $P = 0.101$) (Table 3). Among tamoxifen users, being older than 60 years increased the prevalence of endometrial cancer by 7.85 times (95% CI 1.05-58.87, $P = 0.006$), whereas being nulliparous increased the risk by 8.36 times (95% CI 2.36-30.11, $P < 0.001$). Among the tamoxifen nonusers, being over 60 years old increased the prevalence of cancer by two times (95% CI

TABLE 2. *Characteristics of the diagnostic examinations (transvaginal ultrasound and hysteroscopy) of tamoxifen users (n = 169) versus nonusers (n = 506)*

Characteristics of the diagnostic examinations	Users Mean ± SD	Nonusers Mean ± SD	*P*
Endometrial thickness (mm)	13.35 ± 6.93	10.68 ± 6.84	<0.001
Number of lesions	1.30 ± 0.81	1.37 ± 0.73	0.200
Lesion size (cm)	2.27 ± 1.35	1.95 ± 1.32	0.004

Mann-Whitney test.
SD, standard deviation.

TABLE 3. *Association of risk factors for endometrial cancer in women with endometrial polyps (n = 675)*

Factors risk	PR	95% CI	*P*
Age >60 y	2.49	1.36-4.53	0.003
Nulliparous	3.33	1.76-6.29	<0.001
BMI >30 kg/m^2	1.70	0.96-3.00	0.070
Without symptoms	0.44	0.24-0.80	0.007
Arterial hypertension	1.20	0.67-2.16	0.535
Diabetes mellitus	1.02	0.51-2.06	0.946
Breast cancer	0.54	0.25-1.15	0.109
Use of hormonal therapy	0.16	0.01-2.61	0.075
Use of tamofixen	0.51	0.23-1.14	0.101
Endometrial thickness >10 mm	1.37	0.48-3.89	0.560
Abnornal uterine bleeding	3.10	1.75-5.48	<0.001

Poisson regression analysis multivariate with stepwise criteria of variable selection.
95% CI, 95% confidence interval; BMI, body mass index; PR, prevalence ratio.

1.12-3.93, $P = 0.021$), abnormal uterine bleeding increased the prevalence by 3.9 times (95% CI 2.08-7.29, $P < 0.01$), and being nulliparous increased the prevalence of cancer by three times (95% CI 1.55-6.35, $P = 0.002$) (Table 4).

DISCUSSION

The frequency of endometrial cancer was 4.14% for tamoxifen users and 8.1% for nonusers; age >60 years old, abnormal uterine bleeding, and nulliparity were risk factors for malignancy. Endometrial thickness, abnormal bleeding, and a BMI >30 kg/m^2 were not associated with a higher prevalence of endometrial cancer in the tamoxifen users.

The literature shows similar rates of endometrial cancer of 3% in women using tamoxifen and up to 10% of malignancy without tamoxifen use.[16,24] A review of 46 studies evaluating the risk of malignancy in endometrial polyps showed a malignancy rate of 0.2% to 6.5%, with only one study showing a risk of 23.8%.[19]

In our study, most women took tamoxifen for 2 to 3 years. Studies have shown that the use of tamoxifen for 2 consecutive years increases the incidence of endometrial polyps. However, studies have also shown that the incidence of endometrial cancer increases as tamoxifen use increases (5 years).[16,24-26]

In the analyzed sample, more cases of cancer were found when the endometrial thickness on ultrasonography exceeded 12.5 mm. Smith-Bindman et al[27] showed that the risk of endometrial cancer increased from 0.002% to 6.7% in asymptomatic postmenopausal women with an endometrial thickness >11 mm. Cohen et al[24] pointed out that the risk of malignancy with endometrial thickness >8 mm should be considered and suggests complementary investigations using hysterosonography or hysteroscopy.

Clinical conditions such as hypertension, diabetes, and obesity were not statistically significant risk factors for malignancy in this study, although other studies state otherwise.[14]

On the contrary, conditions such as age >60 years and abnormal uterine bleeding were related to a higher incidence of endometrial cancer in women with endometrial polyps, data consistent with that of other studies in the literature.[19] The literature recommends that the endometria of women using tamoxifen should only be evaluated if abnormal bleeding is present because this factor is associated with a greater presence of endometrial lesions, especially endometrial cancer[16,28]; however, in the present study, abnormal bleeding was not a risk factor for endometrial cancer in tamoxifen users. Of the seven cases of endometrial cancer among tamoxifen users, only two women presented abnormal bleeding.

Tamoxifen use did not increase the prevalence of malignancy in women with endometrial polyps. A review by Cohen containing 106 studies evaluating uterine pathologies caused by tamoxifen indicated malignant and premalignant lesions in 3.0% to 10.7% of the polyps[16]—a higher frequency than that in nonusers.[16,24] An explanation for such a discrepancy may be the difference between the samples evaluated in the different studies, as most had smaller cohorts than that in our study.[16] However, it may also be warranted by tamoxifen usage time since the highest incidence occurred in women who use tamoxifen for 5 years, whereas in our population, women used tamoxifen for 2 to 3 years.

The limitations of this study include its retrospective model, small sample of tamoxifen users, 3:1 ratio to the control group, few cases of cancer, and statistical parameters.

Few studies have evaluated the prevalence of malignant polyps caused by tamoxifen, and the majority of the studies

TABLE 4. *Association of risk factors for endometrial cancer in tamoxifen users (n = 169) versus nonusers (n = 506)*

	Users			Nonusers		
Risk factors	PR	95% CI	*P*	PR	95% CI	*P*
Age >60 y	7.85	1.05-58.87	0.006	2.10	1.12-3.93	0.021
Nulliparous	8.36	2.36-30.11	<0.001	3.13	1.55-6.35	0.002
BMI >30 kg/m^2	3.81	0.74-19.62	0.110	1.45	0.79-2.69	0.232
Without symptoms	1.45	0.28-7.47	0.658	0.37	0.19-0.74	0.005
Arterial hypertension	4.04	0.49-33.53	0.196	1.04	0.56-1.94	0.895
Diabetes mellitus	1.53	0.30-7.89	0.611	0.95	0.44-2.05	0.893
Breast cancer	0.18	0.01-2.16	0.835	0.82	0.11-5.95	0.843
Use of hormonal therapy	1.56	0.10-24.70	0.605	0.17	0.01-2.67	0.078
Endometrial thickness >10 mm	1.25	0.07-21.16	0.461	1.41	0.49-4.09	0.522
Abnornal uterine bleeding	0.88	0.17-4.51	0.874	3.89	2.08-7.29	<0.001

Poisson regression analysis multivariate with stepwise criteria of variable selection
95% CI, 95% confidence interval; BMI, body mass index; PR, prevalence ratio.

were conducted with fewer participants. Thus, although the sample of patients using tamoxifen was relatively small, it was significantly larger than those of other studies. To ensure more precise results, future prospective studies with larger groups of women are required.

CONCLUSIONS

Tamoxifen use was not a risk factor for endometrial cancer in women with endometrial polyps. Risk factors for endometrial cancer in women with endometrial polyps included advanced age, abnormal uterine bleeding, and nulliparity.

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