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ORIGINAL REPORT

Impact of Raloxifene or Tamoxifen Use on Endometrial Cancer Risk: A Population-Based Case-Control Study

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ABSTRACT

Purpose
Raloxifene reduces breast cancer risk in women with osteoporosis, and both tamoxifen and raloxifene prevent breast cancer in high-risk women. However, in vitro, raloxifene does not share the pro-estrogenic effects of tamoxifen on the endometrium. Randomized trials of these agents have provided limited information about endometrial cancer risk in the general population. We sought to compare endometrial cancer risks associated with raloxifene, tamoxifen, and nonusers of a selective estrogen receptor modulator (SERM) in the general population and characterize the endometrial tumors occurring in these groups.

Methods
We performed a case-control study of white and African American women age 50 to 79 years in the Philadelphia area. Patients were diagnosed with endometrial cancer between July 1999 and June 2002. Controls were identified through random-digit dialing.

Results
We analyzed 547 cases and 1,410 controls. Among cases, 3.3% had taken raloxifene; 6.2% had taken tamoxifen. Among controls, 6.6% had taken raloxifene; 2.4% had taken tamoxifen. After adjustment for other risk factors, the odds of endometrial cancer among raloxifene users was 50% that of nonusers (odds ratio [OR] = 0.50; 95% CI, 0.29 to 0.85), whereas tamoxifen users had three times the odds of developing endometrial cancer compared with raloxifene users (OR = 3.0; 95% CI, 1.3 to 6.9). Endometrial tumors in raloxifene users had a more favorable histologic profile and were predominantly International Federation of Gynecology and Obstetrics stage I and low grade.

Conclusion
Raloxifene users had significantly lower odds of endometrial cancer compared with both tamoxifen users and SERM nonusers, suggesting a role for raloxifene in endometrial cancer prevention and individualization of SERM therapy.

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INTRODUCTION

Endometrial cancer is the most common gynecologic cancer in the United States, with approximately 40,000 incident cases and 7,500 deaths annually.[1] Estrogen exposure seems to play a significant role in endometrial cancer development. Tamoxifen, a selective estrogen receptor modulator (SERM), has been associated with endometrial cancer[2] via direct stimulation of endometrial estrogen receptors.[3,4] Raloxifene is similar to tamoxifen in imparting antiestrogenic effects in the breast (ie, reducing breast cancer incidence)[5,6] and pro-estrogenic effects in bone (ie, reducing or reversing osteoporosis),[7] but in vitro studies suggest that raloxifene does not share the pro-estrogenic effects of tamoxifen on the endometrium.[8,9]

Because raloxifene and tamoxifen seem to confer similar breast cancer prevention benefits, other risks and benefits of these drugs are critically important to physicians and patients in individualizing treatment decisions. Clinical trials of raloxifene for osteoporosis and breast cancer prevention have included endometrial cancer as a secondary end point. Although these studies have suggested either no difference in endometrial cancer incidence with raloxifene compared with placebo[6] or a reduced incidence for raloxifene compared with tamoxifen,[10] the risk estimates are limited to the specific patient populations studied and may not reflect the true relative incidence of endometrial cancer in women who do or do not use these agents in the general population for a variety of indications.

To address the need for more generalizable risk estimates for endometrial cancer in the general population of SERM users, we used a large, population-based, case-control study of endometrial cancer in Philadelphia, PA, and surrounding areas to examine the odds of endometrial cancer associated with use of raloxifene or tamoxifen compared with nonusers of a SERM and compared with each other, the odds of endometrial cancer associated with duration of SERM use, and the characteristics of endometrial tumors occurring in raloxifene users compared with those occurring in tamoxifen or non-SERM users in the general population.

METHODS

The current report represents a subanalysis of the Women's Insights and Shared Experiences Study, a pair of case-control studies examining associations between exogenous hormone use, parity, estrogen-related genes, and endometrial or breast cancer. Detailed methods have been published previously.[10] Briefly, eligible cases were women age 50 to 79 years diagnosed with endometrial cancer between July 1999 and June 2002 while residing in a nine-county area surrounding and including Philadelphia. Cases were identified through all 68 hospitals and multiple physicians' offices in these counties and through quarterly reviews of the Pennsylvania Cancer Registry. The interval between diagnosis and case identification was limited to 6 months and between ascertainment and contact for the screening interview was limited to 12 months. Only primary, invasive, adenocarcinoma (endometrioid, type I), clear-cell, or papillary serous carcinoma subtypes were included; sarcomas and mixed müllerian histology were excluded as it was anticipated that these would be rare, and evidence supporting hormone-related etiology was less well established. Cancer diagnoses were verified by review of all pathology reports by one of the coauthors (S.C.R.) who had no knowledge of patients' hormone use and confirmed when possible through state cancer registries. Control patients from within the same geographic region as the cases were identified by a survey research firm through random-digit dialing.

The study sample size was determined based on the primary objectives of the parent study; although the current analyses were specified a priori, the study was not specifically powered to test the hypotheses related to SERM exposure.[10] The study was originally designed with a 1:1 control:case ratio and with frequency-matching of controls to cases on age (in 5-year age groups) and race (black or white). Approximately halfway through study accrual, however, the case accrual was lower than anticipated for endometrial cancer overall and for black patients specifically. To compensate, we increased the control:case ratio within specific strata, targeting a 2:1 ratio for white patients and taking all black women within the age group of our study; the details of this change in accrual strategy have been published.[10] This resulted in a final control:case ratio of 2.3:1 for white patients and 7.1:1 for black patients.

Odds ratios (OR) and 95% CIs[11] were calculated for three targeted comparisons: (1) tamoxifen use versus never use of a SERM, (2) raloxifene use versus never use of a SERM, and (3) raloxifene versus tamoxifen use, as well as for duration of SERM use (defined as < 3 years $v \geq 3$ years). Potential confounders were accepted for inclusion in subsequent conditional logistic regression models if they changed one or more of the target SERM ORs by $\geq 10\%$ when added to the unadjusted model of case-control status and SERM.[12,13] All analyses were performed in STATA (version 8.0; STATA Corp, College Station, TX).

This study was approved by the University of Pennsylvania institutional review board as well as the institutional review boards of all participating hospitals. The study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Figure 1 shows the ascertainment and enrollment for cases and controls. Overall, 547 cases and 1,410 controls were analyzed. Among the

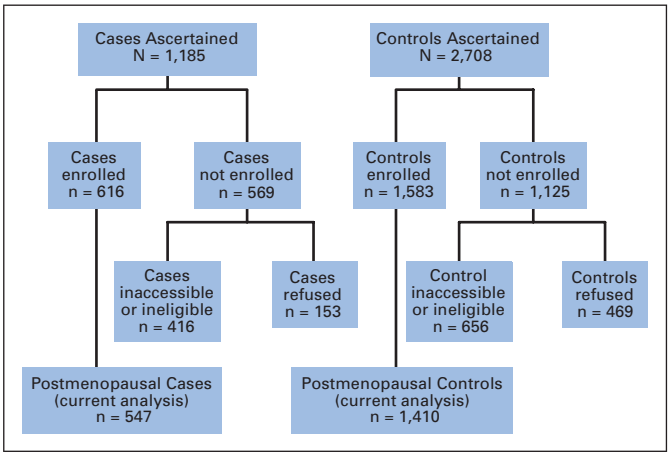

Fig 1. Patient ascertainment, enrollment, and eligibility for the current analysis.

1,185 cases with incident endometrial cancer meeting eligibility criteria, 386 (32.6%) were inaccessible for enrollment (seven patients were nursing home residents, 29 patients were non-English speakers, 17 patients were mentally or physically unable to participate, 194 patients were without physician consent, 70 patients were without correct address and/or phone number, and 69 patients died before contact). Of the 799 remaining, 153 patients refused participation, and 30 patients could not be reached for interview before the study ended. Thus 616 cases (52% ascertained, 77% eligible and accessible) were interviewed and available for analysis. Finally, we excluded cases self-identified as premenopausal at the time of the main interview (n = 69) because raloxifene is indicated only in postmenopausal women.

The survey research firm provided contact information for 2,708 potential random-digit dialing controls. Of these, 405 were ineligible because of age, sex, county, race, or history of hysterectomy or endometrial cancer. Additionally, 25 controls could not participate because of physical or mental impairments, 12 controls did not speak English, seven controls were deceased, 207 controls could not be recontacted because they moved or changed their phone number, and 469 controls refused. The remaining 1,583 controls completed the interview (58% referred, 77% eligible and could be contacted) and were available for analysis. Again, we excluded controls self-identified as premenopausal at the time of the main interview (n = 161). We also excluded two controls who had used both tamoxifen and raloxifene.

Demographic and clinical characteristics of both the overall study population and the population of SERM users are listed in Table 1. Overall, cases differed significantly from controls with regard to age, race, body mass index (BMI), smoking history, breast cancer history, family history of endometrial cancer, duration of active menses, and parity. Cases were also more likely to have used oral contraceptives and less likely to have taken combination estrogen/progestin replacement, though there was no difference in estrogen-only use. Among the SERM users in the study, only race, BMI, and breast cancer history differed significantly between cases and controls.

Table 2 lists endometrial cancer risk factors among tamoxifen and raloxifene users in the analysis cohort. Use of either tamoxifen or raloxifene was not associated with age, race, or BMI. Tamoxifen users were significantly more likely to have had a history of breast cancer. Notably, raloxifene users were more likely to have received either

Table 1. Potential Risk Factors for Endometrial Cancer by Case-Control Status Among Postmenopausal Women in This Study* and for SERM Users Only

	Overall Study					SERM Users Only				
	Cases (n = 547)		Controls (n = 1,410)			Cases (n = 52)		Controls (n = 127)		
Risk Factor	No.	%	No.	%	P†	No.	%	No.	%	P†
Age at index date, years					< .001					.823
50-59	169	30.9	605	42.9		20	38.5	43	42.9	
60-79	233	42.6	502	35.6		19	36.5	48	37.8	
70-79	145	26.5	303	21.5		13	25.0	36	28.4	
Race					< .001					.027
White	489	89.4	1,065	75.5		51	98.1	111	87.5	
Black	58	10.6	345	24.5		1	1.9	16	12.6	
BMI					< .001					.001
Mean	26.2		24.1			24.5		22.8		
SD	5.81		4.28			5.77		3.10		
BMI in NIH categories										
< 18.5, underweight	8	1.5	53	3.8	< .001	2	3.9	5	4.7	.034
18.5-24.9, average	273	49.9	922	65.4		34	65.4	94	74.0	
25.0-29.9, overweight	154	28.2	301	21.4		10	19.2	25	19.7	
≥ 30, obese	106	19.4	133	9.4		6	11.5	2	1.6	
Unknown	6	1.1	1	0.1		—		—		
Cancer history										
Ovarian tumors, benign	24	4.4	52	3.7	.472	2	3.9	4	3.2	.814
Breast cancer	71	13.0	84	6.0	< .001	37	71.2	36	28.4	< .001
Any other cancer‡	60	11.0	100	7.1	.005	8	15.4	10	7.9	.129
Age at menarche, years					< .001					.491
Mean	12.4		12.7			12.6		12.7		
SD	1.59		1.66			1.42		1.33		
Age at menopause, years					.017					.517
Mean	50.1		49.5			50.0		49.4		
SD	4.62		4.86			4.82		5.08		
Duration of menses, years					< .001					.397
Mean	37.6		36.8			37.4		36.7		
SD	4.80		5.10			5.01		5.26		
No. of full-term pregnancies					< .001					.495
Mean	2.4		2.8			2.5		2.7		
SD	1.67		1.86			1.64		1.86		
Age at first full-term pregnancy, years					.331					.248
Mean	24.1		23.9			24.6		25.4		
SD	4.56		4.97			4.42		4.42		
Duration or oral contraceptive use, years					< .001					.517
Never	342	62.5	669	47.4		24	46.2	68	53.5	
< 3	113	20.7	333	23.6		12	23.1	30	23.6	
≥ 3	92	16.8	404	28.6		16	30.8	29	22.8	
Smoker					< .001					.445
Never	285	52.1	575	40.8		23	44.2	56	44.1	
Former	220	40.2	562	39.9		26	50.0	56	44.1	
Current	42	7.7	271	19.2		3	5.8	15	11.8	
Unknown	0	0.0	2	0.1		—		—		
Unopposed ERT					.130					.381
Never any HRT	322	58.9	771	54.7		32	61.5	64	50.4	
Ever any ERT	74	13.5	184	13.0		5	9.6	18	14.2	
Other HRT exclusively	151	27.6	455	32.3		15	28.9	45	35.4	
Duration of ERT, years					.008					.483
Never any HRT	322	58.9	771	54.7		32	61.5	64	50.4	
< 3	43	7.9	139	9.9		3	5.8	14	11.0	
≥ 3	31	5.7	45	3.2		2	3.9	4	3.2	
Other HRT exclusively	151	27.6	455	32.3		15	28.9	45	35.4	
CHRT					.003					.374
Never any HRT	322	58.9	771	54.7		32	61.5	64	50.4	
Ever any CHRT	132	24.1	446	31.6		13	25.0	38	29.9	
Other HRT exclusively	93	17.0	193	13.7		7	13.5	25	19.7	

(continued on following page)

Table 1. Potential Risk Factors for Endometrial Cancer by Case-Control Status Among Postmenopausal Women in This Study* and for SERM Users Only (continued)

	Overall Study					SERM Users Only				
	Cases (n = 547)		Controls (n = 1,410)			Cases (n = 52)		Controls (n = 127)		
Risk Factor	No.	%	No.	%	P†	No.	%	No.	%	P†
Duration of CHRT, years					.008					.162
Never any HRT	322	58.9	771	54.7		32	61.5	64	50.4	
< 3	51	9.3	183	13.0		4	7.7	23	18.1	
≥ 3	81	14.8	263	18.6		9	17.3	15	11.8	
Other HRT exclusively	93	17.0	193	13.7		7	13.5	25	19.7	
Used other hormones§	45	8.2	109	7.7	.714	10	19.2	13	10.2	.103
Known first-degree family history of cancer										
Endometrial	42	7.7	72	5.1	.029	4	7.7	4	3.2	.182
Breast or ovarian	93	17.0	261	18.5	.436	11	21.2	34	26.8	.432
SERM					< .001					
Never any SERM	495	90.5	1,283	91.0		—		—		
Tamoxifen only	34	6.2	34	2.4		—		—		
Raloxifene only	18	3.3	93	6.6		—		—		

Abbreviations: SERM, selective estrogen receptor modulator; SD, standard deviation; BMI, body mass index; NIH, National Institutes of Health; ERT, estrogen replacement therapy; HRT, hormone replacement therapy; CHRT, combination hormone replacement therapy (estrogen plus progestin).
*Sixty-nine premenopausal cases and 171 premenopausal controls are excluded. Two menopausal women who took both tamoxifen and raloxifene are also excluded.
†χ^2 test used for categorical variables and F test used for continuous variables. Those with unknown value are not included in the test.
‡Except ovarian, cervical, and breast cancers. History of ovarian and history of cervical cancer are collinear with yes/no endometrial cancer.
§To get pregnant, to prevent pregnancy, or to prevent miscarriage.

unopposed estrogen replacement or combined hormone replacement and had longer duration of use.

Table 3 lists the adjusted ORs for endometrial cancer among tamoxifen users and raloxifene users relative to non-SERM users and the relationships with duration of use. Overall, raloxifene users had a 50% reduction in the odds of developing endometrial cancer compared with those who had not used a SERM in an adjusted model (OR = 0.50; 95% CI, 0.29 to 0.85). In contrast, tamoxifen users had an increased adjusted odds of endometrial cancer compared with nonusers of a SERM, though this did not reach statistical significance (OR = 1.5; 95% CI, 0.77 to 2.92). Compared with raloxifene users, the OR for endometrial cancer for tamoxifen users was 3.0 (95% CI, 1.3 to 6.9).

The only other confounding factors independently associated with endometrial cancer were a history of breast cancer and increasing BMI. Increasing BMI was significantly associated with odds of having endometrial cancer (OR = 1.12; 95% CI, 1.10 to 1.15) and changed the OR for the SERM-endometrial cancer relationship by more than 10% when included in the models for both raloxifene (unadjusted OR = 0.43 *v* 0.50 adjusted) and tamoxifen (unadjusted OR = 2.35 *v* 2.73 adjusted). A history of breast cancer was also significantly associated with endometrial cancer (OR = 1.87; 95% CI, 1.16 to 3.0), and modified the SERM-endometrial cancer relationship, but just for tamoxifen users (unadjusted OR = 2.35 *v* 1.29 adjusted), with no effect on raloxifene users (unadjusted OR = 0.43 *v* 0.43 adjusted). Factors that did not change the estimate of the SERM-endometrial cancer relationship for either drug included marital status; Jewish ethnicity; education; household income; health insurance; height; birth weight; diabetes; hypercholesterolemia; hypertension; myocardial infarction; stroke; venous thromboembolic disease; gallbladder disease; migraine headaches; liver disease; Stein-Leventhal Syndrome; ovarian cancer history; history of nonovarian, nonbreast cancer; oophorectomy; age at menarche; age at menopause; duration of menses; menopause type; age at first full-term pregnancy; number of full-term pregnancies; duration of breast feeding; use/duration of oral contraceptives; bilateral tubal ligation; previous dilation and curettage; tobacco use; alcohol use; hormone replacement therapies; use of natural or herbal remedies; and family history of endometrial cancer.

Regarding duration of SERM use (Table 3), raloxifene users had a 59% reduction in the odds of endometrial cancer with less than 3 years of use (OR = 0.41; 95% CI, 0.21 to 0.80), which decreased to a 22% reduction among users of raloxifene for 3 or more years (OR = 0.78; 95% CI, 0.31 to 1.95). Duration of tamoxifen use ≥ 3 years was associated with a higher odds of endometrial cancer than a shorter duration of use, but these estimates were not statistically significantly different (OR = 1.32; 95% CI, 0.54 to 3.23 for < 3 years *v* OR = 1.69, 95%, 0.77 to 3.69 for ≥ 3 years).

Table 4 shows the histopathologic characteristics of endometrial cancers identified among cases by SERM use. Twenty-four percent of tamoxifen users and 6% of non-SERM users had papillary-serous and clear-cell histologic subtypes not seen in raloxifene users. The stage and grade at presentation of any histologic type in tamoxifen or raloxifene users were not significantly different from those occurring in non-SERM users, with a predominance of early-stage cancers primarily of low histologic grade.

DISCUSSION

This population-based study demonstrates a 50% reduction in odds of endometrial cancer associated with use of raloxifene compared with those women not taking a SERM, and shows that tamoxifen users were three times more likely to develop endometrial cancer compared with raloxifene users. These data confirm

Table 2. Potential Risk Factors for Endometrial Cancer Among Postmenopausal Users of Tamoxifen or Raloxifene in This Study*

Risk Factor	Tamoxifen Only (n = 68)		Raloxifene Only (n = 111)		P†
	No.	%	No.	%	
Age at index date, years					.190
50-59	19	27.9	44	39.6	
60-79	26	38.2	41	36.9	
70-79	23	33.2	26	23.4	
Race					.063
White	58	85.3	104	93.7	
Black	10	14.7	7	6.3	
BMI					.258
Mean	23.7		3.0		
SD	3.75		4.32		
BMI in NIH categories					.266
< 18.5, underweight	1	1.5	7	6.3	
18.5-24.9, average	47	69.1	81	73.0	
25.0-29.9, overweight	17	25.0	18	16.2	
≥ 30, obese	3	4.4	5	4.5	
History of cancer					
Ovarian tumors, benign	3	4.4	3	2.7	.538
Breast cancer	67	98.5	6	5.4	< .001
Any other cancer‡	10	14.7	8	7.2	.105
Age at menarche, years					.269
Mean	12.5		12.8		
SD	1.33		1.36		
Age at menopause, years					.298
Mean	50.1		49.3		
SD	4.25		5.40		
Duration of menses, years					.179
Mean	37.6		36.5		
SD	4.31		5.63		
No. of full-term pregnancies					.060
Mean	2.9		2.5		
SD	1.83		1.49		
Age at first full-term pregnancy, years					.027
Mean	24.2		25.8		
SD	4.50		4.29		
Duration of oral contraceptive use, years					.176
Never	41	60.3	51	46.0	
< 3	13	19.1	29	26.1	
≥ 3	14	20.6	31	27.9	
Smoker					.314
Never	30	44.1	49	44.1	
Former	34	50.0	48	43.2	
Current	4	5.9	14	12.6	
Unopposed ERT					< .001
Never any HRT	49	72.1	47	42.3	
Ever any ERT	3	4.4	20	18.0	
Other HRT exclusively	16	23.5	44	39.6	
Duration of ERT, years					.001
Never any HRT	49	72.1	47	42.3	
< 3	1	1.5	16	14.4	
≥ 3	2	2.9	4	3.6	
Other HRT exclusively	16	23.5	44	39.6	
CHRT					< .001
Never any HRT	49	72.1	47	42.3	
Ever any CHRT	13	19.1	38	34.2	
Other HRT exclusively	6	8.8	26	23.4	
Duration of CHRT, years					.001
Never any HRT	49	72.1	47	42.3	
< 3	5	7.4	22	19.8	
≥ 3	8	11.8	16	14.4	
Other HRT exclusively	6	8.8	26	23.4	

(continued on following page)

Table 2. Potential Risk Factors for Endometrial Cancer Among Postmenopausal Users of Tamoxifen or Raloxifene in This Study* (continued)

Risk Factor	Tamoxifen Only (n = 68)		Raloxifene Only (n = 111)		
	No.	%	No.	%	P†
Used other hormones§	10	14.7	13	11.7	.561
Known first-degree family history of cancer					
Endometrial	5	7.4	3	2.7	.144
Breast or ovarian	15	22.1	30	27.0	.457

Abbreviations: SERM, selective estrogen receptor modulator; SD, standard deviation; BMI, body mass index; NIH, National Institutes of Health; ERT, estrogen replacement therapy; HRT, hormone replacement therapy; CHRT, combination hormone replacement therapy (estrogen plus progestin).
*Sixty-nine premenopausal cases and 171 premenopausal controls are excluded. Two menopausal women who took both tamoxifen and raloxifene are also excluded.
†χ^2 test used for categorical variables and F test used for continuous variables. Those with unknown value are not included in the test.
‡Except ovarian, cervical, and breast cancers. History of ovarian and history of cervical cancer are collinear with yes/no endometrial cancer.
§To get pregnant, to prevent pregnancy, or to prevent miscarriage.

and extend the findings of two randomized controlled trials reporting endometrial cancer with raloxifene use as a secondary end point. The Multiple Outcomes of Raloxifene Evaluation Trial[5] was a study of 7,705 postmenopausal women randomly assigned to either raloxifene or placebo for prevention of osteoporosis.[14] At 8 years of follow-up, there was a nonsignificant decrease in the rate of endometrial cancer among raloxifene users (0.32% *v* 0.39% in raloxifene and placebo groups, respectively; $P = .75$). The National Surgical Adjuvant Breast and Bowel Project P2 Study of Tamoxifen and Raloxifene randomly assigned 19,747 postmenopausal women at increased risk of breast cancer to either tamoxifen or raloxifene.[15] In this study, there were 36 cases of endometrial cancer in tamoxifen users compared with only 23 in raloxifene users. At 7 year cumulative follow-up, this translated to 14.7 cases/1,000 women treated with tamoxifen compared with 8.1 cases/1,000 women treated with raloxifene ($P = .07$). However, more than 50% of women in the Study of Tamoxifen and Raloxifene had had hysterectomies before enrollment, and an additional 355 patients underwent hysterectomy for noncancer indications while participating in the study, with the majority of these occurring in the tamoxifen group. Although endometrial cancer relative risk estimates were only considered among those at risk by virtue of having an intact uterus, the high proportion of patients who underwent hysterectomy may have underestimated the true magnitude of endometrial cancer attributable to these agents and the true difference between the groups. Numerous randomized, controlled trials and case-control studies in breast cancer have demonstrated elevations in the relative risk of endometrial cancer from tamoxifen, varying from 1.3 to 15.[2,16-20] Our finding that tamoxifen use was associated with an odds of endometrial cancer that was 50% higher than that of

Table 3. Adjusted* Odds of Endometrial Cancer by Type of SERM Use and Duration of Use

Factor	Cases (n = 547†)		Controls (n = 1,410†)		Adjusted OR	95% CI
	No.	%	No.	%		
Nonusers compared with both raloxifene and tamoxifen users						
Nonusers	495	90	1,283	91	1.0	Reference
Raloxifene	18	3.3	93	6.6	0.50	0.29 to 0.85
Tamoxifen	34	6.3	34	2.4	1.5	0.77 to 2.92
Tamoxifen compared with raloxifene users						
Raloxifene	18	3.3	93	6.6	1.0	Reference
Tamoxifen	34	6.3	34	2.4	3.0	1.3 to 6.9
Raloxifene compared with nonusers by duration of use, years						
< 3	11	2.2	74	5.3	0.41	0.21 to 0.80
≥ 3	7	1.4	19	1.3	0.78	0.31 to 1.95
Tamoxifen compared with nonusers by duration of use, years						
< 3	12	2.2	16	1.1	1.32	0.54 to 3.23
≥ 3	22	4	18	1.3	1.69	0.77 to 3.69
Tamoxifen use compared with raloxifene use, < 3 years of use						
Raloxifene	11	2.2	74	5.3	1.0	Reference
Tamoxifen	12	2.2	16	1.1	3.19	1.06 to 9.65
Tamoxifen use compared with raloxifene use, ≥ 3 years of use						
Raloxifene	7	1.4	19	1.3	1.0	Reference
Tamoxifen	22	4	18	1.3	2.15	0.67 to 6.95

Abbreviation: SERM, selective estrogen receptor modulator.
*Adjusted for age, race, body mass index (BMI), and history of breast cancer.
†Six cases missing data on BMI, one control missing data on BMI, and one control missing data on history of breast cancer were excluded from the multivariate model.

Table 4. Histopathologic Characteristics of Endometrial Cancer Cases by SERM Use

Category	Nonusers		Raloxifene		Tamoxifen		P
	No.	%	No.	%	No.	%	
Histologic type							
Adenocarcinoma	467	94	18	100	26	76	< .001
Papillary-serous or clear cell	28	6	0	0	8	24	
Total	495		18		34		
FIGO stage*†							
I	363	83	16	94	22	76	.53‡
II	35	8	0	0	4	14	
III	27	6	1	6	3	10	
IV	13	3	0	0	0	0	
Total	438		17		29		
Histologic grade*§							
1	214	46	12	67	16	52	.21‖
2	155	33	4	22	6	19	
3	97	21	2	11	9	29	
Total	466		18		31		

Abbreviations: SERM, selective estrogen receptor modulator; FIGO, International Federation of Gynecology and Obstetrics.
*Among all histologic types.
†Sixty-three cases are missing FIGO stage.
‡$P = .28$ for association of FIGO stages I/II+ with SERM use.
§Thirty-two cases are missing histologic grade.
‖$P = .19$ for association of grades 1/2+ with SERM use.

nonusers, although not statistically significant (OR = 1.5; 95% CI, 0.77 to 2.92) is in line with those reported by earlier studies.

The reduction in the odds of endometrial cancer with raloxifene use in this study was most pronounced among those with short-term (< 3 years) use. Although benefit was seen beyond 3 years of use, this did not reach statistical significance. The British Tamoxifen Second Cancer Study Group showed that the odds of endometrial cancer associated with tamoxifen use increased significantly with increasing duration of use up to 10 years ($P_{trend} < .001$)[21]; however, the impact of duration was most pronounced for müllerian and mesodermal mixed tumors and sarcomas, histologies not included in the current study. Although our findings are intriguing, the small sample size per group limit the precision of our estimates, and the clinical significance is unclear. Further study is clearly needed both in vitro and in vivo to better understand the biologic effects of raloxifene on endometrial growth and proliferation over time. Mechanistically, raloxifene could have an initial beneficial effect on endometrial estrogen receptors that is attenuated over time as these receptors lose sensitivity to the beneficial effects of raloxifene, in a similar fashion to changes in estrogen receptor function that have been reported during prolonged exposure to tamoxifen.[22]

All endometrial cancers identified in the current study among raloxifene users were adenocarcinomas (endometrioid or type I); no clear-cell or papillary-serous cancers were identified (in contrast with tamoxifen users, in whom 24% of tumors were clear-cell or papillary-serous). The majority of endometrial cancers diagnosed in this study were International Federation of Gynecology and Obstetrics stage I, and tumor grade did not differ by group. None of the previous studies of raloxifene that included endometrial outcomes have reported histologic information on endometrial cancers in this group. Thus these data provide new information on the profile of endometrial cancers seen in raloxifene users, suggesting that among raloxifene users who do develop endometrial cancers, the vast majority of tumors are potentially curable. Endometrial cancers among tamoxifen users in the National Surgical Adjuvant Breast and Bowel Project P-1 Trial were observed early in the follow-up period, and all were International Federation of Gynecology and Obstetrics stage I.[20] Of the 57 tumors diagnosed, 53 were adenocarcinomas and four were uterine sarcomas, predominantly of the carcinosarcoma type. Our study excluded sarcomas, thus precluding our ability to compare the frequency of this subtype between tamoxifen and raloxifene users in this study or with that reported in other studies. Although sarcomas may be important outcomes in patients taking these drugs, the exclusion of this subtype of endometrial cancer in no way diminishes the findings presented here for endometrial carcinoma.

Several limitations should be noted. First, although the case-control approach we used is particularly suited to the study of this relatively rare event, endometrial cancer, the current analysis was a secondary aim of a study that was not designed to primarily answer the question posed. Thus, despite the relatively large number of patients in this case-control study, the number of tamoxifen or raloxifene users in this population was relatively small, which may have limited the precision of our risk estimates. Nevertheless, our case-control design with a large case sample size allowed us to evaluate this relatively rare outcome of SERM use in a way that existing randomized controlled trials could not. By excluding controls with a history of hysterectomy (thereby precluding their ability to get endometrial cancer), we have potentially underestimated the frequency of SERM use in the general population. However, our focus is on endometrial cancer risk, which is only relevant in women who have not undergone hysterectomy. Many potentially eligible patients were not enrolled, potentially introducing bias. However, reasons for nonparticipation were not significantly different between cases and controls, providing no compelling reason that nonparticipation would be systematically related to use

of SERMs. In addition, the changes in accrual strategy that occurred during the study to augment the numbers of patients with endometrial cancer, African Americans, and controls for reasons of sample size resulted in a small imbalance in the age and race distributions between cases and controls, which has the potential to confound our results. We addressed this imbalance by performing conditional logistic regression to examine age and race strata specifically and performed formal tests of interaction to determine whether age or race modified the relationship between SERM use and outcome. Because those interaction tests were nonsignificant, we were able to drop those factors from further consideration in the models. Because use of conditional logistic regression is superior to direct adjustment in the setting of partial matching, and because even partial matching achieves most of the benefits of full matching,[23,24] we feel confident that potential confounding and bias have been minimized. Finally, there is the potential for our study to be confounded by indication. That is, if patients in this study were taking raloxifene for osteoporosis, and osteoporosis is associated with endometrial cancer, one must consider the possibility that the risk reduction attributed to raloxifene was a reflection of a lower risk in the population taking raloxifene. Lower estrogen levels might lead to such a connection between osteoporosis and reduced endometrial cancer risk. We did not collect information on estrogen levels or bone density, which would clearly be necessary to explore this hypothesis.

Nonetheless, this population-based, case-control study provides evidence that raloxifene use may be associated with a significantly lower odds of endometrial cancer compared with both SERM nonusers and users of tamoxifen. As of April 2006, more than 500,000 women were taking raloxifene in the United States, the majority of whom were not taking it for breast cancer prevention.[9] Because small differences in risk of endometrial cancer between these agents would have a relatively large impact on the absolute numbers of cases of endometrial cancer that develop, these findings warrant further investigation. If confirmed, this information provides important additional information to aid physicians and patients in individualizing SERM therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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