Tamoxifen Therapy for Breast Cancer and Endometrial Cancer Risk

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Background: **Tamoxifen is effective in treating breast cancer, reduces breast cancer incidence among high-risk women, and is associated with increased endometrial cancer risk. This study was designed to examine the possible modifying effects of endometrial cancer risk factors on the tamoxifen–endometrial cancer association.** ***Methods:*** **We conducted a case–control study of endometrial cancer (324 case patients and 671 individually matched control subjects) nested within a population-based cohort of patients with breast cancer diagnosed from 1978 through 1992 within four regions of the United States. We obtained information on breast cancer treatment and endometrial cancer risk factors through interviews and reviews of medical records. All *P* values reported are two-sided.** ***Results:*** **Endometrial cancer risk was associated with tamoxifen therapy for breast cancer (odds ratio = 1.52; 95% confidence interval [CI] = 1.07–2.17). Risk increased with duration of tamoxifen use (*P* for trend = .0002). Women with more than 5 years of exposure to tamoxifen had 4.06-fold greater odds of developing endometrial cancer than nonusers (95% CI = 1.74–9.47). Prior use of estrogen replacement therapy (ERT) increased risk associated with tamoxifen use (*P* for homogeneity of trends <.0001). Risk associated with tamoxifen use was stronger among heavier women than among thinner women, although trends did not differ statistically (*P* = .10). Tamoxifen dose–response effects were more pronounced among women with both previous ERT exposure and higher body mass index than among women in other risk groups.** ***Conclusions:*** **ERT use and obesity, both established endometrial cancer risk factors and markers of estrogen exposure, substantially modify the association between tamoxifen use and endometrial cancer risk among patients with breast cancer. Women with positive ERT histories and those who are obese, when prescribed tamoxifen, may warrant closer surveillance for endometrial cancer than women without such histories. [J Natl Cancer Inst 1999;91:1654–62]**

Tamoxifen, a nonsteroidal hormone that acts as an antiestrogen in breast tissue, was approved by the U.S. Food and Drug Administration for the treatment of advanced breast cancer among postmenopausal women in 1978. Currently, tamoxifen is used among women of all ages for the treatment of all stages of breast cancer *(1)*. Tamoxifen reduces the risk of subsequent contralateral breast cancer as well as breast cancer recurrences and mortality *(2–4)*. Because of its efficacy in breast cancer therapy, clinical trials were initiated in the United States, the U.K., and Italy among disease-free women to evaluate the efficacy of tamoxifen in the primary prevention of breast cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT), which is the largest of these trials, randomly assigned women whose breast-cancer risk was at least as great as that of a 60-year-old woman to receive either tamoxifen (20 mg/day for 5 years) or placebo and accrued more than 13 000 women *(5)*. This study was unblinded in April 1998 because of the substantial 49% reduced risk of invasive breast cancer among women receiving tamoxifen relative to those on the placebo arm. The two European prevention trials had different eligibility requirements, including women with different breast cancer risk profiles and permitting women to take hormone replacement therapy (HRT) while on trial. Neither of these trials has shown a benefit for women receiving tamoxifen *(6,7)*.

Tamoxifen has estrogen-like effects in the uterus *(8)*. Reports of endometrial cancers diagnosed among women receiving tamoxifen therapy for breast cancer began to appear in the literature as early as 1985 *(9)*. Elevated endometrial cancer risk has been confirmed in clinical trials of tamoxifen used for adjuvant therapy *(10)* and population-based studies of breast cancer patients *(11–14)*, although the numbers of patients diagnosed with endometrial cancer in most of the studies are relatively small. After reviewing the available animal and human evidence on the relationship of tamoxifen to the development of endometrial cancer, the International Agency for Research on Cancer *(15)* has classified tamoxifen as a human carcinogen. In the BCPT, women on the tamoxifen arm had a 2.5-fold greater incidence of endometrial cancer than women on the placebo arm (36 invasive cancers among women receiving tamoxifen versus 15 invasive cancers among women receiving the placebo) *(5)*. All of the endometrial cancers diagnosed among women on the tamoxifen arm of this trial were stage I, and the majority (75%) were diagnosed among women who were 50 years of age or older.

Several factors are known to affect endometrial cancer risk, including reproductive characteristics, obesity, use of steroid hormone preparations, certain medical conditions, and smoking *(16)*. Exposure to estrogen unopposed by progesterone, whether endogenous or exogenous, substantially increases women's risk of this disease. Use of combination oral contraceptive preparations substantially lowers risk. Obesity, a source of endogenous

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See "Notes" following "References."

(unopposed) estrogen among postmenopausal women, increases endometrial cancer risk. None of the prior studies of tamoxifen therapy and endometrial cancer risk has adequately considered whether these risk factors modify the tamoxifen–endometrial cancer relationship.

We designed a population-based, case–control study, nested within the cohort of breast cancer patients diagnosed within four geographically defined regions served by four Surveillance, Epidemiology, and End Results (SEER)[1] registries, to examine the relationship between tamoxifen use (including duration of use, recentness of use, and cumulative dose) and subsequent development of endometrial cancer. This study was also designed to address whether estrogen replacement therapy (ERT), oral contraceptive use, and obesity modify any observed relationship.

Subjects and Methods

Subject Identification and Eligibility

All women diagnosed with breast cancer who had had no prior or concurrent cancers (other than bilateral breast cancer) at the time of initial breast cancer diagnosis were identified at the four SEER registries. Patients first diagnosed from 1978 through 1992 were eligible for the study in Los Angeles County, whereas for the other SEER registries, the years of initial breast cancer diagnosis were 1983 through 1988 for Atlanta (GA), 1983 through 1990 for Iowa, and 1983 through 1989 for Seattle–Puget Sound (WA). Each of these SEER registries is a population-based cancer registry serving a designated geographic region as part of the National Cancer Institute's Cancer Statistics Program. Case patients were women diagnosed with endometrial cancer at least 6 months after an initial breast cancer diagnosis within the defined period. Case patients had no prior cancer diagnoses and no cancer diagnosed between their breast cancer diagnosis and their endometrial cancer diagnosis other than a second primary breast cancer (or basal or squamous cell skin cancer). The years of endometrial cancer diagnosis for subjects considered to be eligible for this study were 1978 through June 1993 in Los Angeles County and 1983 through 1991 in Atlanta, Iowa, and Seattle–Puget Sound. Within the latter three registries, no eligible case patient had an endometrial cancer diagnosis in 1983.

Control subjects were breast cancer patients who did not develop endometrial cancer and who were selected individually for each case patient to be comparable to the case patient with respect to specific characteristics. We individually matched two control subjects to each case patient on the year of first breast cancer diagnosis, year of birth, race/ethnicity (non-Hispanic white, Hispanic white, black, or Asian), SEER registry, and summary stage of disease (localized, regional extension, or metastatic disease). The duration of time that a case patient was at risk for endometrial cancer was calculated as the number of months between her initial breast cancer diagnosis and her endometrial cancer diagnosis; each control subject was required to have survived at least the same length of time as her matched case patient without any subsequent cancer diagnosis other than a second primary breast cancer (or basal or squamous cell skin cancer) and to have had an intact uterus on the last day of that follow-up period. Control subjects were required to have maintained their residence within the geographic area covered by the registry so that, had they become case patients, the registry would have ascertained their subsequent cancer.

From a roster of all patients with breast cancer eligible as potential matches for each case patient, we randomly selected control subjects and confirmed their eligibility by use of hospital and physician medical records and interview information so that at least two control subjects satisfying all eligibility criteria were selected. Where we lacked sufficient control subjects who were exact matches for a particular case, we first relaxed the matching criteria of year of birth to year of birth within 1 or 2 years; if necessary, we also relaxed the year of diagnosis matching criteria to year of diagnosis within 1 year. The hysterectomy status and residential history of each potential control subject were established through medical record reviews and telephone interviews.

In Los Angeles County, we identified more than two control subjects for some case patients as, initially, we randomly selected five to 10 potential control subjects for each case patient and initiated data collection for the first five. We expected frequent losses because of ineligibility by virtue of a control subject having had a prior hysterectomy. At other study sites, we only attempted to identify two control subjects per case patient. Across the four study sites, we identified 330 eligible case patients and 708 eligible control subjects. A total of 397 control subjects (56%) matched case patients exactly on all matching criteria.

Collection of Treatment Histories and Risk Factor Information

Detailed information on all treatments (surgery, radiation therapy, chemotherapy, and hormonal therapy) that a woman received for her breast cancer was abstracted from hospital medical records and the records of all physicians providing such treatment. Special efforts were made to ensure that any treatment given for progression of disease, recurrence of disease, or second primary breast cancer diagnosis was abstracted. In addition, information on age at menopause, parity, family history of breast cancer, and other medical conditions, such as diabetes, hypertension, stroke, and coronary heart disease, was obtained from the patient's medical records. Height and weight were obtained from medical records at the woman's admission physical at the time of her initial breast cancer diagnosis.

Patients alive at the time of the study were interviewed by telephone to obtain further information on relevant endometrial cancer risk factors and breast cancer therapy. Women were asked about their reproductive histories, medical history, smoking history, and use of oral contraceptives, ERT, or combined HRT (regimens of estrogen and a progestin). All women were asked to provide a roster of physicians who had provided their health care during their adult years, including general or family practitioners, internists, cardiologists, gynecologists, oncologists, and surgeons. In Los Angeles County, next of kin were also interviewed if the patient was deceased or unable to respond to the interview. We conducted 227 next-of-kin interviews (case patients—86 or 37% of the 232 eligible patients; control subjects—141 or 27% of the 521 eligible patients). At all sites, medical records were sought from all physicians mentioned in the interview, whether done with patients or next of kin as well as any physician mentioned in the hospital or other physician record. At sites other than Los Angeles County, when we were unable to conduct a patient interview, we relied completely on patient medical records for data collection.

At the beginning of the telephone interview, each participating subject provided informed consent. Study procedures were approved by institutional review boards at the University of Southern California (Los Angeles), University of Iowa (Iowa City), Fred Hutchinson Cancer Research Center (Seattle, WA), and Emory University (Atlanta, GA), in accord with assurances approved by the U.S. Department of Health and Human Services.

On the basis of all sources of information, we reconstructed a detailed medical history for each patient. In compiling all sources of information, we sought medical record confirmation for all drug exposures and breast cancer treatments. Although we were able to confirm most exposure histories of women with next-of-kin interviews through review of medical records, we were unable to confirm positive histories of tamoxifen use for eight of these patients, negative histories of tamoxifen use for 39 of these patients, positive histories of hormone use for 18 of these patients, and negative histories of such use for 61 of these patients. The compiled medical history included dosages of all chemotherapy regimens and the dates that they were administered; dates, duration, and dosages of tamoxifen therapy; details of radiation therapy; and dates and duration of ERT and HRT. For oral contraceptive use, we were able to determine whether women had used this method of contraception but were unable to obtain details on the duration of use for most women. We collected information on breast cancer therapies as well as the use of exogenous hormones throughout the defined follow-up period based on the number of days between the case patients' breast cancer and endometrial cancer diagnoses. We included use of estrogens by pill, patch, or injection in the category of ERT; some of this use occurred during the women's premenopausal and perimenopausal years. To determine whether a woman had used ERT, we required that there be no more than a 2-month lapse in continuous medical records. Otherwise, we considered that the history of ERT use was unknown. It is likely that most women so designated had never used ERT.

Statistical Analyses

The 330 eligible case patients included 232 from Los Angeles County, 50 from Iowa, 34 from Seattle–Puget Sound, and 14 from Atlanta. The majority of these women were non-Hispanic whites (n = 305); 14 were Hispanic whites, six were African-Americans, and five were Asian-Americans. A total of 708 control subjects were determined to be eligible matches for these 330 case patients. We

retained all eligible control subjects in the statistical analyses. Over all study sites, we were unable to identify a suitable control subject for one case patient and could not determine whether five case patients had taken tamoxifen. These six case patients and their 10 individually matched control subjects were excluded from all analyses. In addition, we excluded 27 eligible control subjects who had missing information on tamoxifen exposure. Exclusion of these control subjects did not result in the exclusion of any case patients because each had at least one remaining eligible matched control subject. Thus, the statistical analyses are based on 324 case patients (98% of total eligible patients) and 671 control subjects (96% of total eligible matches for the 324 case patients) with a matching ratio ranging from one to four. The distribution of patient characteristics is shown in Table 1.

Quetelet's index (weight in kilograms divided by height in meters squared) was used as a measure of body mass index. Exposure to tamoxifen was expressed as the total duration of exposure in months and as cumulative dose in milligrams. Exposure to ERT or HRT was expressed as the total duration of exposure in months. When creating analytic variables for ERT and HRT, we restricted the referent group to women who had not used either type of regimen. We classified women according to their smoking status at the time of breast cancer diagnosis as current smokers or current nonsmokers.

Univariate and multivariate conditional logistic regression methods with a variable number of control subjects matched to each case patient were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the OR *(17)*. In all categorical variable analyses, women with missing information for a particular variable were included in a separate category in the analysis. All multivariate analyses included duration of tamoxifen therapy, duration of ERT, any use of oral contraceptives, body mass index, smoking status at breast cancer diagnosis, and history of high blood pressure at breast cancer diagnosis except where a different form of one of these variables was being evaluated. Tests for trend were computed by fitting a conditional logistic regression model to continuous values of the variables. All reported trend test significance levels (*P* values) are two-sided. To assess whether other endometrial cancer risk factors statistically significantly modified the effects of tamoxifen on endometrial cancer risk, we constructed a likelihood ratio test to determine homogeneity of trends in risk with increasing levels of tamoxifen exposure.

Analyses of the effects of tamoxifen on endometrial cancer risk that were conducted within strata of exposure variables modeled all levels of the stratification variable simultaneously and excluded women who were missing information on the stratification variable or the duration of tamoxifen use unless otherwise indicated. For these analyses, we used unconditional logistic regression analyses and adjusted for all factors on which we matched in the study design. We also conducted analyses restricted to women who were postmenopausal at the time of their breast cancer diagnoses by use of the same statistical approach.

Table 1. Characteristics of study population

Characteristic	Case patients (n = 324)	Control subjects (n = 671)
SEER* Registry		
Atlanta	14	28
Iowa	50	95
Los Angeles County	228	486
Seattle–Puget Sound	32	62
Age at breast cancer diagnosis, y		
<50	18	43
50–59	64	129
60–69	127	267
70–79	92	186
⩾80	23	46
Year of breast cancer diagnosis		
1978	19	38
1979	14	29
1980	15	41
1981	18	44
1982	21	38
1983	38	78
1984	30	65
1985	34	70
1986	33	61
1987	33	68
1988	29	61
1989	18	36
1990	19	36
1991	2	4
1992	1	2
Months between initial breast cancer and endometrial cancer diagnosis (at-risk period for control subjects)		
<24	70	142
24–59	154	324
⩾60	100	205
Matching ratios: cases with		
1 matched control	27	
2 matched controls	253	
3 matched controls	38	
4 matched controls	6	

*SEER = Surveillance, Epidemiology, and End Results.

RESULTS

The majority of the case patients were diagnosed with localized (61.1%) or regional (37.3%) breast cancer. Eighteen case patients (5.6%) and 13 control subjects (1.9%) were diagnosed with a second primary breast cancer prior to their endometrial cancer diagnosis (case patients) or the end of their at-risk period (control subjects). A total of 70 case patients (21.6%) and 149 control subjects (22.2%) had recurrent or metastatic disease. The average age at breast cancer diagnosis was 65.9 years (range, 38.4–92.3 years) for case patients and 65.6 years (range, 38.8–93.6 years) for control subjects. The time interval between breast cancer diagnosis and endometrial cancer diagnosis for case patients averaged 3.9 years (range, 6 months to 13.5 years). One hundred case patients (and their 205 matched control subjects) had at least a 5-year at-risk interval (Table 1).

Women who used oral contraceptives were at modestly reduced risk of endometrial cancer relative to nonusers (OR = 0.59; 95% CI = 0.35–1.01) (Table 2). Any use of ERT was associated with a twofold increased risk (OR = 2.12; 95% CI = 1.52–2.96). Women with more than 8 years of ERT use had more than four times the risk of unexposed women. Of note, 14 case patients and nine control subjects used ERT following their breast cancer diagnoses. We determined how recently each ERT-exposed patient had used ERT. We observed an elevated risk for any ERT use within 5 years of endometrial cancer diagnosis or the end of the follow-up period (for control subjects) as well as for ERT use that ended more than 5 years before the endometrial cancer diagnosis or the end of the follow-up period (Table 2). The OR estimates for the two exposure groups did not differ statistically ($P = .22$).

Few women (23 case patients and 47 control subjects) were known to have used HRT; of these, 17 case patients (74%) and 23 control subjects (49%) had previously used ERT. We also documented that three case patients and nine control subjects used HRT following their breast cancer diagnoses. Overall, HRT use was associated with a modest elevation in endometrial cancer risk (OR = 1.69; 95% CI = 0.93–3.06). However, among those women with no prior ERT exposure, HRT use was not associated with increased endometrial cancer risk (OR = 0.78; 95% CI = 0.29–2.06) in a multivariate model.

Approximate quartile categories were created for body mass index on the basis of the distribution of this index among control subjects. Endometrial cancer risk increased with increasing category of body mass index. Women in the highest category had a twofold greater risk than women in the lowest category (OR = 2.06; 95% CI = 1.31–3.24) (Table 2).

Table 2. Odds ratios (ORs) and 95% confidence intervals (95% CIs) of endometrial cancer associated with selected exposures among patients previously diagnosed with breast cancer

Exposure	No. of case patients/ No. of control subjects	Univariate OR (95% CI)	Multivariate* OR (95% CI)	*P* for trend†
Oral contraceptives				
No	278/528	1.0 (referent)	1.0 (referent)	
Yes	30/92	0.54 (0.32–0.88)	0.59 (0.35–1.01)	
Unknown	16/51			
Use of exogenous hormones‡				
Estrogen replacement therapy				
No	150/365	1.0 (referent)	1.0 (referent)	
Yes	134/180	1.97 (1.44–2.70)	2.12 (1.52–2.96)	
Unknown if used	34/102			
1–12 mo	27/57	1.30 (0.78–2.17)	1.35 (0.79–2.30)	
13–48 mo	25/37	1.57 (0.87–2.84)	1.80 (0.96–3.36)	
49–96 mo	19/24	2.38 (1.24–4.58)	2.20 (1.08–4.47)	
⩾97 mo	51/48	3.51 (2.07–5.94)	4.17 (2.38–7.31)	<.0001
Unknown duration	12/14			
Use within past 60 mo	37/41	2.39 (1.45–3.93)	2.73 (1.62–4.63)	
Use >60 mo previously	81/119	1.83 (1.28–2.61)	1.92 (1.32–2.80)	
Combined hormone replacement therapy				
No	150/365	1.0 (referent)	1.0 (referent)	
Yes	23/47	1.37 (0.78–2.40)	1.69 (0.93–3.06)	
Unknown if used	34/102			
Body mass index, kg/m^2				
<22.1	59/171	1.0 (referent)	1.0 (referent)	
22.1–24.5	67/163	1.20 (0.80–1.80)	1.13 (0.73–1.74)	
24.6–28.0	82/157	1.47 (0.98–2.21)	1.46 (0.93–2.29)	
>28.0	108/167	1.88 (1.27–2.80)	2.06 (1.31–3.24)	<.0001
Unknown	8/13			
History of high blood pressure at breast cancer diagnosis				
No	145/375	1.0 (referent)	1.0 (referent)	
Yes	179/296	1.58 (1.20–2.08)	1.40 (1.04–1.90)	
History of diabetes at breast cancer diagnosis				
No	278/600	1.0 (referent)	1.0 (referent)	
Yes	46/71	1.36 (0.91–2.05)	1.33 (0.84–2.11)	
Smoking status at breast cancer diagnosis				
Nonsmoker	226/423	1.0 (referent)	1.0 (referent)	
Smoker	84/219	0.70 (0.51–0.96)	0.74 (0.52–1.05)	
Unknown	14/29			

*All multivariate models include categorical terms for months of tamoxifen therapy, months of estrogen replacement therapy, use of hormone replacement therapy only, oral contraceptive use, body mass index (body weight in kilograms divided by height in meters squared), smoking status at diagnosis, and history of high blood pressure at diagnosis, except where a different formulation of one of these variables was included in the model.

†Tests for trend were computed by fitting conditional logistic regression models to continuous values of the variables.

‡Referent group = women with no use of estrogen replacement therapy or combined hormone replacement therapy.

We restricted the history of other medical conditions to those diagnosed prior to the patient's diagnosis of breast cancer. Endometrial cancer risk was statistically significantly elevated among women with a history of high blood pressure (OR = 1.58; 95% CI = 1.20–2.08) and nonsignificantly elevated among those with a history of diabetes (OR = 1.36; 95% CI = 0.91–2.05) (Table 2). Adjustment for body mass index reduced the OR associated with diabetes to 1.23 (95% CI = 0.81–1.86), although it increased to 1.33 following adjustment for other factors in the multivariate model. After adjustment for body mass index, the OR for high blood pressure, although attenuated somewhat, remained statistically significant (OR = 1.43; 95% CI = 1.08–1.91). The OR for high blood pressure was reduced minimally after adjustment for other potential confounding factors. Endometrial cancer risk was not associated with a history of coronary heart disease or stroke (data not shown). Women who were current cigarette smokers had a nonsignficant, reduced risk of endometrial cancer relative to current nonsmokers (OR = 0.74; 95% CI = 0.52–1.05) (Table 2).

Neither chemotherapy nor radiation therapy for breast cancer was associated with an elevated risk of endometrial cancer (Table 3). Few women in this study received radiation therapy to the pelvic area.

Women treated with tamoxifen had a greater risk of endometrial cancer than those who did not take tamoxifen (OR = 1.52; 95% CI = 1.07–2.17) after multivariate adjustment (Table 3). Risk increased 18% per year of use and was statistically significantly elevated among women who were treated with tamoxifen for more than 2 years. We also show results for the total cumulative dose of tamoxifen a woman received. The majority of women received 20 mg/day throughout their treatment, although some had their doses altered during the course of their treatment and a few received other doses (10, 30, or 40 mg/day). Among women taking tamoxifen, cumulative dose and duration of use were highly correlated (Pearson $r = .99$ for case patients and $r = .97$ for control subjects). Therefore, the risk estimates for cumulative dose are similar to those for duration of therapy (Table 3).

Table 3. Odds ratios (ORs) and 95% confidence intervals (95% CIs) of endometrial cancer associated with treatment of breast cancer

Exposure	No. of case patients/ No. of control subjects	Univariate OR (95% CI)	Multivariate* OR (95% CI)	*P* for trend†
Chemotherapy				
No	243/502	1.0 (referent)	1.0 (referent)	
Yes	76/164	0.88 (0.58–1.32)	0.80 (0.50–1.26)	
Unknown	5/5			
Radiation therapy				
No	219/469	1.0 (referent)	1.0 (referent)	
Yes	102/190	1.16 (0.87–1.56)	1.19 (0.86–1.65)	
Unknown	3/12			
3000–5000 rads	20/47	0.92 (0.52–1.63)	1.09 (0.58–2.05)	
5001–6000 rads	22/35	1.39 (0.80–2.43)	1.38 (0.74–2.55)	
6001–7000 rads	41/63	1.35 (0.88–2.07)	1.24 (0.78–1.98)	
>7000 rads	12/31	0.82 (0.41–1.63)	0.86 (0.40–1.84)	.66
Unknown dose	7/14			
Tamoxifen therapy				
No	178/422	1.0 (referent)	1.0 (referent)	
Yes	146/249	1.55 (1.11–2.17)	1.52 (1.07–2.17)	
Unknown duration	1/4			
Duration, mo				
1–12	37/81	1.09 (0.66–1.79)	0.96 (0.55–1.65)	
13–24	29/60	1.27 (0.73–2.20)	1.35 (0.76–2.41)	
25–60	57/86	1.91 (1.18–3.10)	1.90 (1.15–3.16)	
>60	22/18	3.72 (1.69–8.18)	4.06 (1.74–9.47)	
OR per year of use			1.175 (1.079–1.280)	.0002
Cumulative dose, mg				
⩽7500	36/78	1.12 (0.68–1.85)	0.94 (0.54–1.64)	
7501–15 000	29/62	1.23 (0.71–2.10)	1.37 (0.77–2.42)	
15 001–30 000	50/72	1.95 (1.19–3.21)	1.86 (1.10–3.15)	
>30 000	30/33	2.97 (1.52–5.77)	3.30 (1.63–6.65)	
OR per 1000 mg			1.022 (1.010–1.034)	.0002
Unknown duration/dose	1/4			
Recentness of tamoxifen therapy				
Current use or use within past 12 mo	125/196	1.67 (1.18–2.37)	1.69 (1.16–2.44)	
No use within past 12 mo	20/49	1.03 (0.56–1.93)	0.87 (0.44–1.70)	
Recentness and duration of tamoxifen therapy				
Duration: 1–24 mo				
Current use or use within past 12 mo	52/98	1.33 (0.84–2.12)	1.33 (0.81–2.19)	
No use within past 12 mo	14/43	0.85 (0.43–1.69)	0.73 (0.35–1.53)	
Duration: >24 mo				
Current use or use within past 12 mo	73/98	2.15 (1.39–3.35)	2.15 (1.34–3.44)	
No use within past 12 mo	6/6	2.82 (0.86–9.24)	2.06 (0.59–7.16)	

*All multivariate models include categorical terms for months of tamoxifen therapy, months of estrogen replacement therapy, use of hormone replacement therapy only, oral contraceptive use, body mass index (body weight in kilograms divided by height in meters squared), smoking status at diagnosis, and history of high blood pressure at diagnosis, except where a different formulation of one of these variables was included in the model.

†Tests for trend were computed by fitting conditional logistic regression models to continuous values of the variables.

Most women with tamoxifen exposure were currently taking tamoxifen or had taken it within 12 months of the end of the at-risk period. We combined use within 12 months with current use into one category because case patients may have experienced symptoms such as bleeding prior to their endometrial cancer diagnoses, which might have resulted in their being advised to discontinue tamoxifen. Although having last used tamoxifen more than 12 months ago was not associated with endometrial cancer risk, this may be masking a duration effect since, among women with more than 2 years of tamoxifen use, the ORs for recent and past users were of similar magnitude (twofold increase in risk) (Table 3).

We examined the combined effects of tamoxifen therapy and ERT on the risk of endometrial cancer. Comparing women on the basis of whether they had ever used either drug, we observed no increased risk of endometrial cancer among those women who had ever used tamoxifen but had never used ERT relative to women unexposed to either drug (OR = 1.14; 95% CI = 0.73–1.81). Those using only ERT had a 60% increased risk of endometrial cancer (OR = 1.62; 95% CI = 1.05–2.50), whereas women who had used both drugs were at substantially increased risk of endometrial cancer (OR = 3.53; 95% CI = 2.15–5.78). We further examined the patterns of use among women exposed to both tamoxifen and ERT. Among those women who were treated with tamoxifen within 1 year of last use of ERT (19 case patients and 12 control subjects), the relative odds of endometrial cancer was 5.28 (95% CI = 2.35–11.9); the risk estimate was lower for women with more than 1 year between the use of both regimens (30 case patients, 31 control subjects; OR = 2.83; 95% CI = 1.51–5.31). On the basis of a test for homogeneity, these risk estimates do not differ statistically ($P = .18$).

The trend in risk associated with increasing duration of tamoxifen therapy was not statistically significant among women who had never used ERT ($P = .17$) (Table 4); women who used tamoxifen for more than 60 months had an elevated risk, but the CI for the OR includes 1.0. In contrast to these results, among women who had previously used ERT, tamoxifen therapy was strongly and statistically significantly associated

Table 4. Multivariate odds ratios (ORs) and 95% confidence intervals (95% CIs) of endometrial cancer associated with tamoxifen treatment of breast cancer in subgroups of women defined by other endometrial cancer risk factors*

Exposure	Duration of tamoxifen therapy, mo					*P* for trend†
	None	1–12	13–24	25–60	>60	
Any use of estrogen replacement therapy (ERT)						
No. of case patients/No. of control subjects						
No	97/249	12/46	9/33	27/46	10/12	
Yes	64/114	18/22	16/13	27/27	9/4	
Unknown	17/59	7/13	4/14	3/13	2/3	
OR (95% CI)						
No	1.0 (referent)	0.58 (0.29–1.14)	0.67 (0.30–1.46)	1.34 (0.78–2.31)	2.37 (0.96–5.85)	.17
Yes	1.0 (referent)	1.81 (0.89–3.71)	3.01 (1.36–6.66)	2.99 (1.62–5.54)	5.73 (1.64–20.0)	<.0001
Unknown	1.0 (referent)	1.51 (0.64–3.58)	0.84 (0.29–2.43)	0.39 (0.11–1.42)	5.57 (0.94–33.2)	.37
Body mass index (BMI)						
No. of case patients/No. of control subjects						
Low, ≤24.5	75/224	13/36	12/26	17/36	8/10	
High, >24.5	98/190	24/44	16/33	38/47	14/8	
OR (95% CI)						
Low, ≤24.5	1.0 (referent)	0.82 (0.41–1.62)	1.04 (0.49–2.22)	1.13 (0.59–2.15)	2.45 (0.89–6.78)	.065
High, >24.5	1.0 (referent)	1.30 (0.74–2.27)	1.23 (0.64–2.37)	1.84 (1.12–3.03)	4.98 (1.95–12.7)	.0001
ERT and BMI						
No. of case patients/No. of control subjects						
No ERT, low BMI	37/134	4/18	2/13	8/15	6/4	
No ERT, high BMI	58/114	8/27	7/19	19/29	6/6	
ERT, low BMI	35/68	8/11	9/8	9/16	3/2	
ERT, high BMI	28/46	10/11	7/5	18/11	6/2	
OR (95% CI)						
No ERT, low BMI	1.0 (referent)	0.57 (0.19–1.74)	0.44 (0.10–2.04)	1.46 (0.59–3.62)	1.91 (0.51–7.21)	.49
No ERT, high BMI	1.0 (referent)	0.62 (0.27–1.43)	0.86 (0.35–2.14)	1.39 (0.73–2.64)	2.88 (0.88–9.45)	.15
ERT, low BMI	1.0 (referent)	1.66 (0.64–4.27)	2.84 (1.05–7.71)	1.59 (0.66–3.80)	4.07 (0.65–25.5)	.0037
ERT, high BMI	1.0 (referent)	2.08 (0.84–5.17)	3.18 (0.97–10.4)	3.95 (1.77–8.84)	8.79 (1.69–45.5)	<.0001
Smoking status						
No. of case patients/No. of control subjects						
Nonsmoker	122/260	29/54	19/37	39/57	17/13	
Smoker	47/141	7/24	10/20	16/27	4/5	
OR (95% CI)						
Nonsmoker	1.0 (referent)	1.20 (0.72–2.00)	1.22 (0.66–2.27)	1.58 (0.97–2.58)	3.82 (1.70–8.61)	.0002
Smoker	1.0 (referent)	0.67 (0.27–1.67)	1.10 (0.48–2.53)	1.28 (0.65–2.55)	2.07 (0.52–8.31)	.28

*Excluding the exposure(s) of interest, the multivariate models include categorical terms for months of estrogen replacement therapy, use of hormone replacement therapy only, oral contraceptive use, body mass index (body weight in kilograms divided by height in meters squared), smoking status at diagnosis, and history of high blood pressure at diagnosis.

†Tests for trend were computed by fitting unconditional logistic regression models to continuous values of the variables.

with endometrial cancer risk (*P* for trend <.0001). Relative to women not treated with tamoxifen, those who used tamoxifen for 1–12 months had 1.8 times the risk of endometrial cancer. The ORs increased substantially with increasing duration of use and, among women who received tamoxifen for more than 60 months, the relative odds of endometrial cancer was 5.73 (95% CI = 1.64–20.0). On the basis of the test for homogeneity of trends, the dose–response effects of tamoxifen on endometrial cancer risk were statistically significantly different for users and never users of ERT (*P*<.0001). Among women with missing ERT information, the OR was elevated only among those with more than 60 months of tamoxifen use.

The trends in risk of endometrial cancer associated with tamoxifen therapy did not differ statistically between women with low versus high body mass index (test for homogeneity of trends, *P* = .10) (Table 4). For heavier women, those who had used tamoxifen for more than 60 months had nearly a fivefold greater risk of endometrial cancer than those who had not been treated with tamoxifen (OR = 4.98; 95% CI = 1.95–12.7). Among thinner women, this risk was 2.4-fold greater (OR = 2.45; 95% CI = 0.89–6.78).

We examined the risk of endometrial cancer in four groups of women: 1) those who had never used ERT and were thinner (i.e., below the median body mass index of control subjects), 2) those who had never used ERT and were heavier (i.e., above the median body mass index of control subjects), 3) those who had used ERT but were thinner, and 4) those who had used ERT and were heavier. Tamoxifen use was associated with a much greater increase in risk of endometrial cancer among heavier women who had previously used ERT than among women in the other categories of ERT use and obesity (test for homogeneity of trends, *P* = .0008) (Table 4). Among women with no ERT exposure, the OR estimates are quite similar for those with low and with high body mass. Fitting a single trend for these two subgroups provides an equivalent fit of the data with one fewer degree of freedom.

The trends in risk by smoking status did not differ statistically (test for homogeneity of trends, *P* = .23) (Table 4).

Women who had experienced their last menstrual period at least 1 year prior to their breast cancer diagnosis were considered to be postmenopausal. We were unable to determine directly the menopausal status of 112 women in the study; we classified 107 women with unknown status who were 56 years old or older at the time of their breast cancer diagnosis as post-

menopausal. Ninety-four women were known to be premenopausal at the time of their breast cancer diagnosis; the remaining five with unknown menopausal status were under age 50 years when diagnosed with breast cancer and were considered to be premenopausal. The 99 premenopausal women included 32 case patients and 67 control subjects. Among these 99 women, nine had used ERT (four case patients and five control subjects), six had used HRT (one case patient and five control subjects), and 29 had received tamoxifen (seven case patients and 22 control subjects). In an analysis restricted to postmenopausal women, risk estimates for exposure to ERT, HRT, and tamoxifen therapy did not differ substantially from those observed for all study subjects except for subjects in the longest duration of ERT- and tamoxifen-use categories. The OR for women who had used ERT for more than 96 months was lowered by 8% and that for women who had used tamoxifen for more than 60 months was lowered by 5%.

DISCUSSION

Tamoxifen therapy for breast cancer was associated with a fourfold increased risk of endometrial cancer among women with more than 5 years of exposure, a duration of treatment that is no longer recommended *(18)*. Tamoxifen was associated with a more modest increase in risk for women with 2–5 years of use and was unrelated to risk among women with a shorter duration of use.

That tamoxifen increases the risk of endometrial cancer is consistent with data on the known estrogen-like effects of tamoxifen in women. Tamoxifen appears to have selective affinity for endometrial tissue *(19)* and, among premenopausal women, acts directly on the ovaries to stimulate estrogen biosynthesis and increase plasma estrogen levels *(20,21)*. Among postmenopausal women, although tamoxifen may have a small suppressive effect on circulating estrogen levels *(22)*, this low estrogenic environment may permit the activation and increased synthesis of endometrial estrogen and progesterone receptors by tamoxifen *(23,24)*. Tamoxifen also has been shown to cause estrogen-like changes in the vaginal epithelium *(25)* and endometrium *(26)* of some women. Tamoxifen is also associated with endometrial thickening, endometrial hyperplasia, and endocervical and endometrial polyps *(27,28)* and thus may have a direct stimulatory effect on the uterine body and endometrium *(27)*. Women with pre-existing, asymptomatic endometrial lesions are more likely than women with no endometrial abnormalities to develop atypical lesions while on tamoxifen therapy *(29)*. Although estrogen-like effects of tamoxifen on the endometrium are the most likely explanation for increased endometrial cancer risk, other pathways, such as the regulation of insulin-like growth factor-I, may also play a role *(30)*.

Our results suggest that the relationship between tamoxifen use and subsequent endometrial cancer risk is substantially modified by ERT use and body mass index. In the absence of these exposures, tamoxifen may be associated with only a modest increase in risk. We find a relationship between tamoxifen therapy for breast cancer and endometrial cancer risk that is substantially greater among women with prior exposure to ERT and among those with high body mass index at breast cancer diagnosis than among those without such exposures. ORs increased dramatically among women with ERT exposure, and even short-term tamoxifen exposures ($\leq$24 months) were associated with increased risk. Among women without a history of ERT exposure, only those with more than 5 years of tamoxifen exposure appear to be at increased risk of endometrial cancer, although we cannot rule out a similar twofold increased risk with use of 2–5 years. Similarly, the trend in risk with increasing duration of tamoxifen therapy was greater among women with higher body mass index (>24.5 kg/m^2) than among women with lower body mass index, although we cannot rule out increased risk with long duration of use among thinner women. Additionally, the combined modifying effects of prior ERT exposure and body mass index suggest that women with prior ERT exposure and high body mass index are at the greatest risk of endometrial cancer in association with tamoxifen treatment of breast cancer. This analysis of all three factors (ERT exposure, body mass index, and tamoxifen exposure) also suggests that, among women with low body mass index, ERT and tamoxifen combine to increase endometrial cancer risk, whereas among women with no ERT exposure, the effects of tamoxifen are similar in both heavy and thinner women.

ERT is an acknowledged risk factor for endometrial cancer on the basis of results from cohort and case–control studies that show a strong, persistent duration response relationship (with risk estimates of 1.4 for up to 1 year of use, 2.8 for 1–5 years of use, 5.9 for 5–10 years of use, and 9.5 for more than 10 years of use that remain elevated more than 5 years after cessation of use) [reviewed in *(16)*]. Our risk estimates are somewhat lower than these; this may reflect the fact that a majority of our exposed women had not used ERT for many years prior to their endometrial cancer diagnoses (average: 10.2 years since last use for case patients and 12.2 years since last use for control subjects). However, we did examine whether recent use (within 5 years) or more remote use affected the magnitude of the association with ERT; both risk estimates were elevated and statistically consistent with each other.

Endometrial cancer risk is also related to obesity, although studies are inconsistent as to whether a dose–response relationship exists or whether only the most obese women are at increased risk *(16)*. In our study, endometrial cancer risk increased with increasing level of body mass index as measured by Quetelet's index. The relationship between obesity and endometrial cancer risk may also represent the effects of greater estrogen exposure on the uterus. Among obese postmenopausal women, the peripheral conversion of androstenedione to estrone is a major source of estrogen *(31)*. Since circulating levels of sex hormone-binding globulin are inversely related to obesity, this results in higher levels of unbound (and therefore, bioavailable) estrogen during ages when such levels are generally low *(31)*.

Our result showing about a 40% reduction in endometrial cancer risk associated with oral contraceptive use is consistent with the existing literature on this topic *(16)*. We were unable to collect detailed data on formulation or duration of use. Cigarette smoking and endometrial cancer risk are inversely related in many studies, possibly through an antiestrogenic mechanism *(16)*. We observe a small reduction in risk among women who were current smokers at the time of their breast cancer diagnoses. Other studies have reported an increased risk of endometrial cancer among women with diabetes and hypertension, although the majority did not consider potential confounding factors, such as obesity (for both conditions) and ERT (for hypertension) *(16)*. We, too, observed a modest elevated risk associated with these histories, with the association with hyper-

tension remaining statistically significantly elevated following adjustment for obesity and ERT.

Our results evaluating the main effect of tamoxifen on endometrial cancer risk are consistent with the majority of case–control studies in the literature showing that increasing duration of tamoxifen therapy for breast cancer results in a graded increasing risk of endometrial cancer *(12–14)*. One negative study *(32)* had limited duration of tamoxifen exposure among its participants. The cumulative total number of cases included in these previous case–control studies was only 311, with 97 cases in the Dutch study *(12)*, 36 cases in the negative U.S. study *(32)*, and 43 cases in the first and 135 cases in the second French study *(13,14)*. Only the U.S. case–control study *(32)* attempted to evaluate potential confounding factors. In the European studies *(12–14)*, substantially more women were exposed to doses of 30–40 mg/day than we observed in our study where nearly all women were treated with 20 mg/day. Our risk estimates are quite similar to those from the Dutch study *(12)* and from the study by Sasco et al. *(13)* (the first French study). Although Mignotte et al. *(14)* (the second French study) had higher risk estimates than ours, their CIs are wide and consistent with our risk estimates. Mignotte and colleagues compared their results with those from the Dutch study *(12)* and suggested that risk was higher among their patients because their patients had accumulated greater durations of exposure and larger cumulative doses of tamoxifen than the Dutch women. Our results suggest that other factors may explain these differences, particularly history of exposure to ERT and body mass index at the time of breast cancer diagnosis.

A study based on breast cancer patients' first course of treatment and subsequent primary cancer diagnoses collected by the SEER registries also showed a statistically significant twofold elevation in endometrial cancer risk associated with hormonal therapy *(11)*. These results are not definitive as to treatment because they do not include any therapy after the first course and breast cancer cases classified in the tamoxifen group may have received other hormonal therapies in addition to or other than tamoxifen.

Breast cancer clinical trials of tamoxifen have shown mixed results with regard to the tamoxifen–endometrial cancer relationship; some demonstrated an increased risk of endometrial cancer, whereas others showed no association *(33)*. The NSABP B-14 trial results on endometrial cancer risk showed a relative risk of 7.5 when tamoxifen-treated patients were compared with control subjects, who may have had a deficit of endometrial cancer, and 2.3 when tamoxifen-treated patients were compared with patients participating in another trial (B-06) *(10)*. Although this trial collected information on HRT use at the time of study entry, these data were not verified nor was information collected on type of drug (ERT versus HRT), duration of use, or recentness of use.

MacMahon *(33)* reviewed all studies of the relationship between tamoxifen use and endometrial cancer risk, covering reports published prior to 1997. He concluded that, although these studies taken together suggest an association, the studies do not adequately address potential confounding factors and the clinical trials do not address the issue of detection (unmasking) bias. He suggests that case–control studies can better address these issues than clinical trials. Our study was designed with sufficient sample size and detailed data collection procedures, including extensive medical record review and interviews, to evaluate the potential impact on this relationship of confounding and effect modification by acknowledged endometrial cancer risk factors, particularly ERT exposure and obesity.

The issue of possible detection bias noted by MacMahon *(33)* has been raised with regard to the relationship between ERT and endometrial cancer risk *(34,35)*. Since tamoxifen can cause gynecologic symptoms, women receiving tamoxifen are often investigated by transvaginal ultrasonography and hysteroscopy, resulting in the diagnosis of occult cancers. Although the first report of such a relationship between tamoxifen therapy and endometrial cancer risk was published in 1985 *(9)*, the major reports did not appear in the literature until 1994 *(12)* or later. Therefore, detection of occult endometrial cancers as a result of increased screening of asymptomatic women is not likely to have affected our study because case patients were diagnosed with endometrial cancer between 1980 and mid-1993.

In summary, this study confirms that tamoxifen therapy for breast cancer is associated with an increased risk for endometrial cancer. It further demonstrates that the strength of the relationship is substantially affected by the woman's history of exposure to unopposed exogenous estrogens and her body mass index at the time of breast cancer diagnosis. In the absence of prior ERT exposure or obesity, the effects of tamoxifen on risk are considerably lower than those observed among women with these exposures. These results are consistent with tamoxifen having an estrogenic effect on the endometrium, enhancing the effects of ERT and obesity. Because women with prior ERT use and those who are heavier appear to have a greater risk of endometrial cancer than women without these exposures, physicians should be particularly vigilant in monitoring tamoxifen-treated patients with these additional risk factors. Because tamoxifen has proven benefits in extending the disease-free and overall survival of breast cancer patients and in reducing the incidence of breast cancer among women at increased risk, it remains an important therapeutic option for women with all stages of breast cancer as well as for healthy women who are at increased risk of breast cancer.

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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis and the NCI makes the data available to the public for scientific research.

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