Tamoxifen Treatment for Breast Cancer and Risk of Endometrial Cancer: A Case–Control Study

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For the British Tamoxifen Second Cancer Study Group

Background: **Tamoxifen treatment of breast cancer is associated with an increased risk of endometrial cancer, but tamoxifen-related risks of endometrial cancer are unclear in premenopausal women, in long-term users of tamoxifen, and in women for whom several years have passed since ending treatment. We conducted a case–control study in Britain to investigate these risks.** ***Methods:*** **We compared treatment information on 813 case patients who had endometrial cancer after their diagnosis for breast cancer and 1067 control patients who had breast cancer but not subsequent endometrial cancer. We assessed risk by conditional logistic regression analysis. All statistical tests were two-sided.** ***Results:*** **Overall, tamoxifen treatment, compared with no treatment, was associated with an increased risk of endometrial cancer (odds ratio [OR] = 2.4; 95% confidence interval [CI] = 1.8 to 3.0). Risk increased statistically significantly (P_{trend}<.001) with duration of treatment (for ≥5 years of treatment compared with no treatment, OR = 3.6, 95% CI = 2.6 to 4.8). As an indication of background levels of treatment, 16% of control patients received 5 years or more of treatment. Risk of endometrial cancer adjusted for treatment duration did not diminish in follow-up to at least 5 years after the last treatment ended. Risk of endometrial cancer was not associated with the daily dose of tamoxifen and was comparable in pre- and postmenopausal women. Ever treatment with tamoxifen was associated with a much greater risk of Mullerian and mesodermal mixed endometrial tumors (OR = 13.5, 95% CI = 4.1 to 44.5) than of adenocarcinoma (OR = 2.1, 95% CI = 1.6 to 2.7) or clear cell and papillary serous tumors (OR = 3.1, 95% CI = 0.8 to 17.9).** ***Conclusions:*** **There is an increasing risk of endometrial cancer associated with longer tamoxifen treatment, extending well beyond 5 years. The increased risk of endometrial cancer associated with tamoxifen treatment should be considered clinically for both premenopausal and postmenopausal women during treatment and for at least 5 years after the last treatment. [J Natl Cancer Inst 2005;97:375–84]**

Tamoxifen is a nonsteroidal triphenylethylene derivative that has been widely used to treat breast cancer since the early 1970s and that also reduces the risk of a contralateral malignancy in patients with unilateral breast cancer *(1–6)*. Tamoxifen is being investigated in trials as a possible prophylactic agent in women at high risk of breast cancer *(4,5,7,8)*. Treatment with tamoxifen has also been associated with an increased risk of endometrial cancer *(1,2,8–20)*, in accord with the selective uptake of tamoxifen by endometrial tissue *(21)*, with its agonist effects on the endometrium *(4)*, and with laboratory results *(22)*. However, the magnitude of the increased risk varies substantially between studies. Moreover, considerable uncertainty exists about the risk of endometrial cancer associated with long-term use, the risk several years after cessation of use, and the risk associated with treatment with low dosages (e.g., those used in prophylactic trials) *(1–3,14,16–19,23)*. In addition, a greater risk of uterine sarcomas, compared with that of other histologic types of endometrial cancer, has been found in some *(18,20,24)* but not all *(24)* analyses, and the risks of specific histologic types of endometrial cancer associated with the duration of treatment have not been examined. Furthermore, tamoxifen has different hormonal effects before and after the menopause *(4,5,25)*, but most data on the risk of endometrial cancer in tamoxifen-treated women with breast cancer are for postmenopausal use, and analyses of premenopausal use have been based on small numbers of women. Consequently, risks of endometrial cancer associated with tamoxifen treatment need to be clarified, so that balanced consideration can be given to the advisability of prophylactic use of tamoxifen and of tamoxifen use beyond 5 years, for which no additional benefit has yet been identified *(26)*.

These uncertainties reflect the limited numbers of subjects in published studies, especially in analyses of long-term use and after long follow-up. So far, the largest published investigation had 324 case patients *(1)*. We therefore conducted a larger case–control study in Britain, with a design intended to increase the numbers of subjects who had the potential for long-term exposure to tamoxifen, to investigate the relationships between tamoxifen treatment and the risk of endometrial cancer in premenopausal women, in long-term users of tamoxifen, and in women for several years after ending treatment.

Patients and Methods

Design and Data Collection

We obtained the appropriate ethical approvals from the London School of Hygiene & Tropical Medicine Ethics Committee and numerous other ethics committees. We obtained anonymized listings of all women with breast cancer diagnosed from January 1, 1976, through December 31, 1996 (or to the most recent data year available from the cancer registry if earlier), from the population-based regional cancer registries of England, except for the Northern registry, and from the national cancer registries of

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Wales and Scotland. The listings included information on second cancers occurring in these women. The former Northern registry (now part of the Northern and Yorkshire registry), covering 5% of the population of Britain, was omitted because it was unable to identify the data necessary for the study. Women were eligible to be a case patient in the study 1) if they had a registered primary invasive (not in situ) breast cancer diagnosed from January 1, 1976, through December 31, 1996; 2) if they had no cancer (except non-melanoma skin cancer) previous to or concurrent with the breast cancer; and 3) if they had a registered primary endometrial cancer (invasive, not in situ) diagnosed from January 1, 1988, through December 31, 1996, at least 3 months after diagnosis of the breast cancer, with no other second malignancy except non-melanoma skin cancer or breast cancer occurring in the intervening period; and 4) if case notes could be located that covered the period from breast cancer diagnosis to endometrial cancer diagnosis. Although tamoxifen was introduced in the United Kingdom in September 1973, we restricted the study to patients treated from January 1, 1976, onward because we found in a pilot investigation that the prevalence of tamoxifen use was low before 1976, and so data collection for January 1, 1973, through December 31, 1975, would have been relatively inefficient. Similarly, we restricted the study to endometrial cancers occurring from 1988 onward to maximize the proportion of case notes that could be obtained and the proportion of subjects with long-term treatment and follow-up.

Control patients were women with breast cancer selected from the file of all patients diagnosed with incident breast cancers from January 1, 1976, through December 31, 1996. One control patient was randomly selected per case patient, with individual matching to case patients on 1) date of diagnosis of the primary breast cancer within 6 months; 2) age at diagnosis of the primary breast cancer within 6 months; 3) registry region of residence at the date of diagnosis of primary breast cancer; and 4) survival without second cancer, other than non-melanoma skin cancer or breast cancer, for at least as long after the diagnosis of breast cancer as the index duration (i.e., the time from breast cancer diagnosis to endometrial cancer diagnosis in the matched case patient). In addition, we required that 5) the control patient had not had a hysterectomy during the index period after breast cancer diagnosis and that 6) her case notes covered the period to the index date. Because criteria 5 and 6 could not be determined from the cancer registry file, we examined case notes for individuals who met control criteria 1 through 4. If criterion 5 or 6 was unfulfilled, a replacement control patient was chosen in the same way. This process was repeated if necessary.

In parallel with the endometrial cancer case–control study, we also conducted case–control studies of ovarian, colorectal, and liver cancers after breast cancer by use of the same data extraction forms and procedures. The control patients from these studies were selected by the same matching methods used for the endometrial cancer study, except that the matching ratio and the years of cancer incidence included varied by cancer site and that absence of hysterectomy was not a matching criterion. The control patients from these studies who had not had hysterectomies, therefore, met the general criteria to be control patients for the case patients in the endometrial cancer study, and we included all of the above-described control patients to maximize the data available for analysis.

For each patient, we attempted to locate the hospital case notes. When they were located, data were extracted on demographic details, identification of the general practitioner, tamoxifen treatment (start and stop dates and dosage for each period of treatment), other treatments (chemotherapy and radiotherapy) of the first primary cancer, abdominal and pelvic radiotherapy before the index date, occurrence of contralateral breast cancer, date of diagnosis of the first and second cancers, histologic type of the endometrial cancer, and potential confounding variables, including weight and height at diagnosis of the first cancer, parity, age at menopause, use of oral contraceptives and hormone replacement therapy, and, for control patients, hysterectomy. For case patients, the history was taken up to but not including the date of diagnosis of the second cancer; for matched control patients, the history was taken until the equivalent duration from diagnosis of the first primary (i.e., the index duration). For case and control patients for whom tamoxifen data from hospitals were incomplete, general practitioners were queried by mail for information that would validate and amplify hospital data. We could generally ascertain a definite date when tamoxifen treatment ended; however, when this date could not be determined with certainty, it was taken to be the date of last known treatment. The duration of tamoxifen use for patients who received the drug during two or more separate time periods was calculated by adding these periods together. The average daily dose of tamoxifen for those who changed dose over time was calculated as the average of the doses in the different periods weighted by the lengths of these periods. We also analyzed risks of endometrial cancer of different histologic subtypes, as categorized elsewhere *(18,27)*.

We identified 825 case patients with endometrial cancer for whom full case notes were found and who met the study criteria. We also identified 208 provisionally eligible case patients from cancer registry records whose case notes could not be located or had insufficient information for this study. Not all of these patients would have been eligible if their notes were located. The 208 case patients who were excluded were similar to the 825 case patients with full case notes with respect to age. However, breast cancer was more often diagnosed before 1985 in the 208 excluded patients (46% of patients) than in the 825 included patients (33% of patients), and so they also were more likely to have a longer (5 years or more) index duration (64% and 60% of patients, respectively). For 813 of the 825 case patients with full case notes available, at least one matched control patient was found, and these 813 subjects became the case patients in our analyses.

Full case notes were obtained for a total of 1152 control patients. We also identified about 678 potential control patients from cancer registry records whose notes were sought but not found. Many of these 678 subjects may have been ineligible if the notes had been located, because records of a hysterectomy were in case notes, not in cancer registry records. These 678 subjects were similar to the 1152 control patients with available notes with regard to age, but their breast cancer was diagnosed more often before 1985 (46% of the 678 subjects; 29% of the 1152 subjects), and they were more likely to have index durations of 5 years or more (60% and 48%, respectively). Of the 1152 control patients with full case notes, 1067 were matched to the case patients with full case notes and, therefore, became the control patients in our analyses.

Statistical Analysis

To assess the relationship of tamoxifen treatment and other factors to the risk of endometrial cancer, we calculated odds ratios (ORs), as estimates of relative risks. Matching strata were created with all of the important variables (age and date of diagnosis of breast cancer, index duration, and area of the country). Odds ratios and 95% confidence intervals (CIs) were calculated, and tests of trend were conducted, by use of conditional logistic

regression *(28)* with STATA version 8.2 *(29)*. The trend tests were calculated with continuous actual values for individual subjects. Where required because of small numbers, exact *P* values and confidence intervals were calculated with LogXact version 5.0 *(30)*. All statistical tests were two-sided.

Results

Most case and control patients lived in England, were aged 55 years or older at diagnosis of breast cancer, and had been diagnosed with breast cancer during the 1980s (Table 1). Endometrial cancer was diagnosed less than 5 years after the breast cancer diagnosis in 40% of case patients, after 5–9 years in 42%, and after 10 years or more in 18%. A greater percentage of case patients (82%) than of control patients (68%) had received tamoxifen treatment, whereas control patients more often than case patients had received other treatments (Table 1).

Tamoxifen treatment at least 3 months before the index date, compared with no such treatment, was associated with an increased risk of endometrial cancer (OR = 2.4, 95% CI = 1.8 to 3.0) (Table 2). (Unless otherwise stated, the same comparison group applies to tamoxifen analyses below.) The increased risk did not change with adjustment for weight and menopausal status (OR = 2.4, 95% CI = 1.9 to 3.1) or if only individually matched subjects were analyzed (OR = 2.4, 95% CI = 1.7 to 3.3). There was a highly statistically significant trend (P_{trend}<.001) of increasing risk with increasing duration of treatment (for 5

Table 1. Descriptive characteristics of study subjects

Characteristic	Case patients, No. (%)	Control patients, No. (%)
Country of residence		
England	695 (85.5)	894 (83.8)
Wales	13 (1.6)	17 (1.6)
Scotland	105 (12.9)	156 (14.6)
Age at diagnosis of breast cancer		
<45 y	33 (4.1)	109 (10.2)
45–54 y	173 (21.3)	302 (28.3)
55–64 y	260 (32.0)	267 (25.0)
65–74 y	235 (28.9)	252 (23.6)
≥75 y	112 (13.8)	137 (12.8)
Year of breast cancer diagnosis		
1976–1979	63 (7.8)	56 (5.3)
1980–1984	202 (24.9)	219 (20.5)
1985–1989	391 (48.1)	526 (49.3)
1990–1996	157 (19.3)	266 (24.9)
Interval between diagnosis of breast and endometrial cancers*		
<1 y	46 (5.7)	84 (7.9)
1–4 y	279 (34.3)	446 (41.8)
5–9 y	341 (41.9)	401 (37.6)
10–14 y	129 (15.9)	124 (11.6)
15–19 y	18 (2.2)	12 (1.1)
Breast cancer treatment†		
Radiation therapy	351 (43.2)	551 (51.6)
Nonhormonal chemotherapy	52 (6.4)	86 (8.1)
Tamoxifen	665 (81.8)	730 (68.4)
Other hormonal therapies	36 (4.4)	56 (5.3)
Total no. of subjects	813	1067

*Interval between diagnosis of breast cancer and of endometrial cancer (or among control patients, index date).

†At least 3 months before date of diagnosis of endometrial cancer (or among controls, at least 3 months before index date).

Table 2. Risk of endometrial cancer in relation to tamoxifen treatment, duration, daily dose, cumulative dose, and time since last use*

Tamoxifen treatment	Case patients No. (%)	Control patients No. (%)	OR (95% CI)	P†
Any tamoxifen treatment				
No	148 (18.2)	337 (31.6)	1.0 (referent)	
Yes	665 (81.8)	730 (68.4)	2.4 (1.8 to 3.0)	<.001
Duration of treatment				
Not used	148 (18.2)	337 (31.6)	1.0 (referent)	
<2 y	155 (19.1)	279 (26.2)	1.3 (1.0 to 1.9)	.086
2–4 y	196 (24.1)	237 (22.2)	1.9 (1.4 to 2.7)	<.001
5–7 y	160 (19.7)	130 (12.2)	2.8 (2.0 to 4.0)	<.001
8–9 y	62 (7.6)	29 (2.7)	4.7 (2.8 to 7.8)	<.001
10–17 y	47 (5.8)	13 (1.2)	7.2 (3.6 to 14.6)	<.001
Used, duration unknown	45 (5.5)	42 (3.9)	2.6 (1.6 to 4.2)	<.001
			$P_{heterogeneity}$<.001‡	
Trend: OR per y§			1.18 (1.14 to 1.23)	<.001
Average daily dose‖				
Not used	148 (18.2)	337 (31.6)	1.0 (referent)	
10 mg	15 (1.9)	15 (1.4)	2.4 (1.1 to 5.2)	.027
20 mg	425 (52.3)	483 (45.3)	2.4 (1.8 to 3.1)	<.001
30 mg	23 (2.8)	19 (1.8)	2.9 (1.5 to 5.7)	.002
40 mg	149 (18.3)	154 (14.4)	2.4 (1.8 to 3.3)	<.001
Used, dose unknown	53 (6.5)	59 (5.5)	2.1 (1.4 to 3.3)	.001
			$P_{heterogeneity}$<.001‡	
Trend: OR per 10 mg/day¶			1.03 (0.91 to 1.17)	.632
Cumulative dose				
Not used	148 (18.2)	337 (31.6)	1.0 (referent)	
<7500 mg	66 (8.1)	120 (11.3)	1.3 (0.9 to 2.0)	.222
7500–14 999 mg	73 (9.0)	119 (11.2)	1.7 (1.1 to 2.5)	.016
15 000–29 999 mg	108 (13.3)	156 (14.6)	1.8 (1.2 to 2.5)	.002
30 000–59 999 mg	194 (23.9)	177 (16.6)	2.7 (1.9 to 3.6)	<.001
≥60 000 mg	154 (18.9)	78 (7.3)	4.1 (2.9 to 5.9)	<.001
Used, dose unknown	70 (8.6)	80 (7.5)	2.1 (1.4 to 3.1)	<.001
			$P_{heterogeneity}$<.001‡	
Trend: OR per 10 000 mg§			1.16 (1.12 to 1.21)	<.001
Time since last known use				
Not used	148 (18.2)	337 (31.6)	1.0 (referent)	
Still on or <3 mo‡‡	493 (60.6)	559 (52.4)	2.4 (1.8 to 3.1)	<.001
3–11 mo	47 (5.8)	40 (3.8)	2.9 (1.8 to 4.7)	<.001
1–2 y	44 (5.4)	54 (5.1)	2.0 (1.2 to 3.2)	.004
3–4 y	21 (2.6)	26 (2.4)	1.9 (1.0 to 3.6)	.043
≥5 y	20 (2.5)	22 (2.1)	1.5 (0.8 to 2.9)	.209
Used, time unknown	40 (4.9)	29 (2.7)	3.7 (2.1 to 6.3)	<.001
			$P_{heterogeneity}$<.001‡	
Trend: OR per y¶			0.94 (0.86 to 1.01)	.864
Adjusted time since last known use**				
Still on or <3 mo‡‡	493 (60.6)	559 (52.4)	1.0 (referent)	
3–11 mo	47 (5.8)	40 (3.8)	1.3 (0.8 to 2.0)	.344
1–2 y	44 (5.4)	54 (5.1)	1.2 (0.8 to 2.0)	.374
3–4 y	21 (2.6)	26 (2.4)	1.6 (0.8 to 3.1)	.185
≥5 y	20 (2.5)	22 (2.1)	1.5 (0.7 to 3.3)	.272
Used, time unknown	40 (4.9)	29 (2.7)	—††	
			$P_{heterogeneity}$ = .49‡	
Trend: OR per y¶			1.09 (1.00 to 1.20)	.068

*Unless otherwise indicated, all tamoxifen-related exposures are those at least 3 months before the index date. OR = odds ratio; CI = confidence interval.

†*P* values were two-sided, from Wald test.

‡*P* values were two-sided, from likelihood ratio test.

§Trend includes zero group (i.e., tamoxifen non-users) but excludes missing value group.

‖Averaged over period known to be on tamoxifen: 10 = 1–14 mg/day but mostly 10 mg/day; 20 = 15–24 mg/day but mostly 20 mg/day; 30 = 25–34 mg/day but mostly 30 mg/day; 40 = 35 mg/day or more but mostly 40 mg/day.

¶Trend evaluated only among tamoxifen users and excludes missing value group.

‡‡Patient had also been on tamoxifen at least 3 months before index date.

**Adjusted for duration of use (tamoxifen users only).

††OR adjusted for duration cannot be calculated because duration of treatment is also unknown.

Table 3. Risk of endometrial cancer in relation to dose and duration of tamoxifen treatment

	Average daily dose of tamoxifen*					
	Not used (n = 151 cases)	<25 mg (n = 443 cases)		≥25 mg (n = 177 cases)		Used, dose unknown (n = 53 cases)	
Duration of tamoxifen treatment*	OR†	OR† (95% CI)	*P*‡	OR† (95% CI)	*P*‡	OR† (95% CI)	*P*‡
Not used	1.00 (referent)						
<2 y		1.4 (1.0 to 2.0)	.079	1.5 (0.9 to 2.4)	.111	0.8 (0.3 to 1.8)	.536
2–4 y		2.1 (1.5 to 2.9)	<.001	1.7 (1.1 to 2.6)	.031	2.1 (0.9 to 5.0)	.104
5–7 y		2.5 (1.7 to 3.7)	<.001	3.9 (2.3 to 6.6)	<.001	2.0 (0.5 to 8.3)	.335
8–9 y		4.8 (2.6 to 8.5)	<.001	5.1 (1.9 to 13.5)	.001	1.4 (0.1 to 15.6)	.789
10–17 y		7.9 (3.3 to 18.8)	<.001	5.6 (1.9 to 16.3)	.002	—	
Used, duration unknown		1.9 (0.8 to 4.6)	.138	2.0 (0.7 to 6.1)	.205	3.2 (1.7 to 6.0)	<.001
Trend among users§ (OR per y)		1.16 (1.09 to 1.24)	<.001	1.21 (1.11 to 1.33)	<.001		
		Interaction (trend): *P* = .362‖					

*All tamoxifen exposures are those at least 3 months before the index date.
†OR = odds ratio; CI = confidence interval.
‡*P* values were two-sided, from Wald test.
§Trend excludes missing value group.
‖*P* value was two-sided, from likelihood ratio test.

Table 4. Risk of endometrial cancer in relation to tamoxifen treatment, subdivided by age and menopausal status at diagnosis of breast cancer

	Case patients	Control patients	Tamoxifen use		Trend†	
Tamoxifen treatment*	No. (%)	No. (%)	OR‡ (95% CI)	*P*§	OR per y of use‡(95% CI)	*P*§
Age at diagnosis of breast cancer						
<45 y						
No tamoxifen	11 (33.3)	55 (50.5)	1.0 (referent)			
Tamoxifen	22 (66.7)	54 (49.5)	2.8 (1.1 to 7.1)	.035	1.25 (1.08 to 1.46)	.003
45–54 y						
No tamoxifen	49 (28.3)	116 (38.4)	1.0 (referent)			
Tamoxifen	124 (71.7)	186 (61.6)	2.1 (1.3 to 3.3)	.002	1.15 (1.07 to 1.24)	<.001
55–64 y						
No tamoxifen	48 (18.5)	81 (30.3)	1.0 (referent)			
Tamoxifen	212 (81.5)	186 (69.7)	2.2 (1.4 to 3.5)	<.001	1.17 (1.09 to 1.25)	<.001
65–74 y						
No tamoxifen	33 (14.0)	72 (28.6)	1.0 (referent)			
Tamoxifen	202 (86.0)	180 (71.4)	3.1 (1.9 to 5.0)	<.001	1.20 (1.12 to 1.28)	<.001
≥75 y						
No tamoxifen	7 (6.3)	13 (9.5)	1.0 (referent)			
Tamoxifen	105 (93.8)	124 (90.5)	1.7 (0.6 to 4.4)	.288	1.24 (1.07 to 1.44)	.004
			$P_{interaction}$ = .72‖		$P_{interaction}$ = .76‖	
Menopausal status¶ at diagnosis of breast cancer						
Premenopausal						
No tamoxifen	33 (32.4)	97 (43.9)	1.0 (referent)			
Tamoxifen	69 (67.7)	124 (56.1)	2.0 (1.2 to 3.5)	.013	1.16 (1.06 to 1.27)	.001
Postmenopausal						
No tamoxifen	109 (16.0)	216 (27.5)	1.0 (referent)			
Tamoxifen	571 (84.0)	569 (72.5)	2.5 (1.9 to 3.3)	<.001	1.19 (1.14 to 1.24)	<.001
Unknown menopausal status						
No tamoxifen	6 (19.4)	24 (39.3)	1.0 (referent)			
Tamoxifen	25 (80.7)	37 (60.7)	2.7 (0.9 to 7.9)	.075	1.24 (1.05 to 1.46)	.012
			$P_{interaction}$ =.79‖		$P_{interaction}$ = .78‖	

*At least 3 months before the index date.
†Among tamoxifen users only.
‡OR = odds ratio; CI = confidence interval.
§*P* values were two-sided, from Wald test.
‖*P* values were two-sided, from likelihood ratio test.
¶Menopausal status: as stated in case notes or, if missing, assumed to be premenopausal if younger than 45 years old at diagnosis and without oophorectomy before breast cancer (n = 30) and postmenopausal if 55 years old or more at diagnosis (n = 316).

years or more, OR = 3.6, 95% CI = 2.6 to 4.8). As an indication of background levels of treatment, 16% of control patients had received 5 years or more of treatment. The amount of the daily dose of tamoxifen, from 10 to 40 mg/day, was not associated with risk of endometrial cancer. This result was also obtained after adjustment for treatment duration or within strata of duration of treatment (e.g., for 10 years or more of treatment, OR for less than 25 mg/day = 7.9 [95% CI = 3.3 to 18.8] and OR for 25 mg/day or more = 5.6 [95% CI = 1.9 to16.3]; Table 3). Risk increased steadily with cumulative dose of tamoxifen received, but this increased risk was essentially a consequence of the effect of treatment duration. In analyses adjusted for treatment duration, cumulative dose was not statistically significantly associated with risk of endometrial cancer (OR per 10 000 mg = 1.02, 95% CI = 0.95 to 1.10).

Around 1994, the association between tamoxifen treatment and an increased risk of endometrial cancer became widely known *(1,6)*. When analyses were restricted to case patients diagnosed with breast cancer before 1994, the results were similar to those for all case patients (among those diagnosed before 1994, OR per year of tamoxifen treatment = 1.21 [95% CI = 1.15 to 1.27], and among all case patients, OR = 1.18 [95% CI = 1.14 to 1.23]). Analyses restricted to subjects for whom the end date of tamoxifen treatment was known (89% of treated subjects) and analyses that also included subjects whose end date of tamoxifen treatment was assumed from lack of evidence of further treatment gave virtually identical results (for patients with definite end dates of treatment, OR per year of tamoxifen treatment = 1.19 [95% CI = 1.14 to 1.24], and for all patients, OR = 1.18 [95% CI = 1.14 to 1.23]).

Although 423 of the 813 case patients developed endometrial cancer while they were still taking tamoxifen, the greatest relative risk was observed for patients who had ceased treatment within the last 2 months (OR = 7.7, 95% CI = 4.5 to 13.0). Because this increased risk is likely to be an artifact caused by symptoms associated with endometrial cancer that lead to discontinuing tamoxifen treatment, we reanalyzed the data by combining risk in patients still on treatment and risk in patients for the first 2 months after treatment ceased (Table 2). Increased risks of endometrial cancer were observed in all follow-up periods, although the risk increase was not statistically significant for the longest period (5 years or more) and risks tended to decrease statistically nonsignificantly with longer follow-up. After adjustment for duration of tamoxifen treatment, relative risk did not diminish in follow-up to 5 years or more.

Among each age group from that younger than 45 years to that 65–74 years old, an increased risk of endometrial cancer was statistically significantly associated with tamoxifen treatment (Table 4). However, among the age group of 75 years or older, risk was not statistically significantly greater among those who received tamoxifen than among those who did not receive tamoxifen, although there was a statistically significant trend for the association of risk with treatment duration, as indeed there was in each of the younger age groups. Data on menopausal status were usually but not always recorded in the case notes (a menopausal status was recorded for 81% of case plus control patients younger than 55 years old at diagnosis of breast cancer). A statistically significantly higher risk of endometrial cancer was observed for tamoxifen users than for non-users, both for patients reported to be premenopausal (OR = 2.0, 95% CI = 1.1 to 3.4) and for patients who were reported to be premenopausal or who were aged younger than 45 years old and had not had an oophorectomy (OR = 2.0, 95% CI = 1.2 to 3.5; Table 4). The increased risk in postmenopausal patients was comparable to the risk in premenopausal patients, regardless of whether postmenopausal status was limited to those reported

Table 5. Risk of endometrial cancer in relation to breast cancer treatment, subdivided by tamoxifen use

			Tamoxifen use					
	All patients		No		Yes		All patients	
Treatment*	Case, No.	Control, No.	OR† (95% CI)	P‡	OR* (95% CI)	P‡	OR† (95% CI)	P‡
Chemotherapy								
No	761	981	1.0 (referent)		1.0 (referent)		1.0 (referent)	
Yes	52	86	0.9 (0.4 to 2.1)	.749	1.1 (0.7 to 1.8)	.620	1.1 (0.7 to 1.6)	.767
				$P_{interaction}$ = .60				
Non-tamoxifen hormonal therapy								
No	777	1011	1.0 (referent)		1.0 (referent)		1.0 (referent)	
Yes	36	56	1.0 (0.1 to 11.4)	.982	0.8 (0.5 to 1.2)	.274	0.8 (0.5 to 1.2)	.281
				$P_{interaction}$ = .86§				
RT to breast area								
No	462	516	1.0 (referent)		1.0 (referent)		1.0 (referent)	
Yes	351	551	0.6 (0.4 to 0.9)	.023	0.8 (0.6 to 1.0)	.024	0.7 (0.6 to 0.9)	.002
				$P_{interaction}$ = 0.42§				
RT to abdomen/pelvis at least 5 years before index date‖								
No	804	1066	1.0 (referent)		1.0 (referent)		1.0 (referent)	
Yes	9	1	4.2 (0.2 to 283.6)	.544	∞ (1.00 to ∞)	.050	11.7 (1.5 to 548.2)	.012

*At least 3 months before the index date.

†OR = odds ratio; CI = confidence interval; RT = radiation therapy.

‡P values were two-sided, from Wald test.

§P values were two-sided, from likelihood ratio test.

‖CIs were from an exact method. These could not be adjusted for tamoxifen use nor could an interaction test could not be undertaken.

as such in the case notes (OR = 2.8, 95% CI = 2.0 to 3.9) or also included those determined to be postmenopausal by age (i.e., 55 years or older) (OR = 2.5, 95% CI = 1.9 to 3.3).

We next investigated risks of endometrial cancer associated with treatment variables other than tamoxifen, both overall and subdivided by whether or not tamoxifen was received (Table 5). Risk was not statistically significantly associated with chemotherapy or with non-tamoxifen hormonal treatment for breast cancer (mainly, megestrol and medroxyprogesterone). We found an increased risk associated with abdominal and/or pelvic radiation therapy, and this increase was statistically significant if the therapy was received 5 years or more before the index date (OR = 11.7, 95% CI = 1.5 to 548.2). All eight subjects in this analysis with a known reason for radiation therapy had received therapeutic ovarian ablation. We also found a statistically significantly decreased risk associated with radiation therapy to the breast. None of these variables showed a statistically significant interaction with tamoxifen treatment, although the interaction test could not be computed for abdominal radiotherapy.

A decreased risk of endometrial cancer was statistically significantly associated with current smoking compared with lifetime nonsmoking among all patients (OR = 0.7, 95% CI = 0.5 to 0.9), and risk of endometrial cancer increased statistically significantly with increasing weight among postmenopausal women (OR per 10 kg = 1.41, 95% CI = 1.23 to 1.62) (Table 6) but not among premenopausal women (data not shown). Among postmenopausal patients, increased risk was statistically significantly associated with use of hormone replacement therapy at

Table 6. Risk of endometrial cancer in relation to patient characteristics, subdivided by tamoxifen use

			Tamoxifen use					
	All patients		No		Yes		All patients	
Exposure	Case, No.	Control, No.	OR* (95% CI)	*P*†	OR* (95% CI)	*P*†	OR* (95% CI)	*P*†
Any pregnancy								
Yes	541	723	1.0 (referent)		1.0 (referent)		1.0 (referent)	
No	109	150	1.3 (0.7 to 2.4)	.361	0.8 (0.6 to 1.2)	.308	0.9 (0.8 to 1.4)	.636
Unknown	163	194	1.2 (0.7 to 2.0)	.517	1.0 (0.8 to 1.4)	.863	1.1 (0.8 to 1.6)	.643
			$P_{interaction}$ = .43‡					
HRT before breast cancer§								
No	668	775	1.0 (referent)		1.0 (referent)		1.0 (referent)	
Yes	12	10	3.0 (0.4 to 23.0)	.290	2.3 (0.8 to 7.1)	.133	2.5 (0.9 to 6.6)	.070
			$P_{interaction}$ = .83‡					
HRT≥3 months before index date§								
No	662	772	1.0 (referent)		1.0 (referent)		1.0 (referent)	
Yes	18	13	4.2 (1.0 to 18.7)	.056	2.3 (0.9 to 5.8)	.092	2.7 (1.2 to 6.1)	.015
			$P_{interaction}$ = .48‡					
Smoking status								
Lifelong nonsmoker	385	449	1.0 (referent)		1.0 (referent)		1.0 (referent)	
Ex-smoker	81	125	0.8 (0.4 to 1.8)	.623	0.8 (0.5 to 1.1)	.189	0.8 (0.6 to 1.1)	.168
Current smoker	116	224	0.7 (0.4 to 1.2)	.189	0.7 (0.5 to 0.9)	.014	0.7 (0.5 to 0.9)	.005
Unknown	231	269	1.1 (0.7 to 1.8)	.709	0.9 (0.7 to 1.2)	.584	1.0 (0.8 to 1.2)	.781
			$P_{interaction}$ = .95‡					
Weight: all patients								
<60 kg	85	171	1.0 (referent)		1.0 (referent)		1.0 (referent)	
60–69 kg	122	212	1.1 (0.5 to 2.5)	.755	1.1 (0.7 to 1.6)	.778	1.1 (0.8 to 1.6)	.650
70–79 kg	98	98	2.2 (0.9 to 5.3)	.072	1.7 (1.0 to 2.7)	.033	1.8 (1.2 to 2.7)	.005
80–89 kg	48	30	2.7 (0.9 to 8.1)	.087	2.8 (1.4 to 5.4)	.003	2.7 (1.5 to 4.7)	.001
≥90 kg	29	19	4.4 (1.2 to 16.3)	.026	2.6 (1.2 to 5.8)	.014	3.0 (1.5 to 5.9)	.001
Unknown	431	537	2.1 (1.1 to 4.0)	.028	1.3 (0.9 to 1.8)	.217	1.4 (1.0 to 2.0)	.028
			$P_{interaction}$ = .65‡					
Trend: per 10 kg‖			1.42 (1.10 to 1.83)	.007	1.32 (1.15 to 1.51)	<.001	1.34 (1.19 to 1.51)	<.001
			$P_{interaction}$ = .60‡					
Weight: patients with postmenopausal breast cancer								
<60 kg	66	119	1.0 (referent)		1.0 (referent)		1.0 (referent)	
60–69 kg	100	154	1.4 (0.5 to 3.8)	.535	1.1 (0.7 to 1.7)	.807	1.1 (0.7 to 1.7)	.578
70–79 kg	83	82	2.1 (0.7 to 6.1)	.158	1.6 (1.0 to 2.8)	.057	1.7 (1.1 to 2.7)	.019
80–89 kg	39	25	3.3 (0.8 to 13.3)	.100	2.8 (1.4 to 5.6)	.005	2.8 (1.5 to 5.3)	.001
≥90 kg	26	12	9.0 (1.8 to 44.6)	.007	3.8 (1.6 to 9.1)	.003	4.6 (2.1 to 10.0)	<.001
Unknown	366	393	2.7 (1.2 to 6.2)	.019	1.4 (0.9 to 2.0)	.145	1.6 (1.1 to 2.3)	.015
			$P_{interaction}$= .61‡					
Trend: per 10 kg‖			1.72 (1.23 to 2.41)	.002	1.35 (1.16 to 1.57)	<.001	1.41 (1.23 to 1.62)	<.001
			$P_{interaction}$= .19‡					

*OR = odds ratio; CI = confidence interval; HRT = hormone replacement therapy.

†*P* value was two-sided, from Wald test.

‡*P* value was two-sided, from likelihood ratio test.

§Among postmenopausal women.

‖Excludes those for whom weight was unknown.

least 3 months before the index date compared with its non-use during this period (OR = 2.7, 95% CI = 1.2 to 6.1), although this analysis was based on small numbers. No association was found between the risk of endometrial cancer and whether a woman was parous. Among postmenopausal patients, there was a statistically nonsignificant indication that the association between weight and the risk of endometrial cancer was greater among those not treated with tamoxifen than among those treated with tamoxifen (Table 6). We found no indication of any difference in the effect of tamoxifen on endometrial cancer risk between users and non-users of hormone replacement therapy or between different weight groups (<60 kg, 60–69 kg, and ≥70 kg; data not shown).

Among patients treated with tamoxifen, risk of Mullerian and mixed mesodermal tumors and sarcomas (OR = 13.5, 95% CI = 4.1 to 44.5) was greater than risk of adenocarcinoma (OR = 2.1, 95% CI = 1.6 to 2.7) or of clear cell and papillary serous carcinomas (OR = 3.1, 95% CI = 0.8 to 17.9) (Table 7). For mixed mesodermal tumors especially and also for adenocarcinoma, there was a statistically significant trend of greater risk with longer duration of tamoxifen treatment (both P_{trend}<.001). For clear cell and papillary serous tumors, however, no statistically significant trend was observed. Although analyses separating sarcoma (plus mesenchymoma) from mixed mesodermal tumors were hampered by small numbers in the former category (24 case patients), risks of both were increased (OR for sarcoma plus mesenchymoma = 6.5 [95% CI = 1.0 to 28.0], and OR for mixed mesodermal tumors = 17.2 [95% CI = 4.2 to 152]).

Discussion

In this case–control study, we found that the relative risk of endometrial cancer increased with duration of tamoxifen treatment up to at least 10 years. The relative risk, adjusted for duration of tamoxifen treatment, did not diminish in follow-up to 5 years or more after last treatment. The increased risk of endometrial cancer associated with tamoxifen treatment was similar for patients of pre- and postmenopausal ages and was greatest for Mullerian and mesodermal tumors.

A limitation of our study is that the proportion of patients omitted, because their case notes were unavailable, was greater than that in the data sets achieved in the previous largest studies *(1,18)*. Some of this problem was caused by our focus on women treated many years ago, whose case notes had often been destroyed for policy reasons (e.g., closure of hospitals) that were not connected with treatment. One concern in studies that use case notes is that treatment and its duration can be underestimated if case notes are incomplete. However, it seems unlikely that our results were appreciably distorted for this reason because our results were unchanged when we restricted the analyses to subjects with a known end date of treatment and because, for variables examined previously, our findings were similar to previous findings from major published studies *(1,18)*.

Another potential limitation is surveillance bias; that is, tamoxifen-treated women might be under greater surveillance for endometrial cancer than are other women with breast cancer, because endometrial cancer is a known side effect of tamoxifen treatment. Most of the cases of endometrial cancer in our study, however, occurred before 1994 when this side effect became widely accepted *(1,6)*, and analyses restricted to cases diagnosed before 1994 showed a statistically significant association, with no smaller risk per year of tamoxifen use than for cases diagnosed subsequently. The strong duration–response effect in our data would also be difficult to explain by surveillance bias because such a bias would be unlikely to increase substantially with time since first treatment. Furthermore, Bergman et al. *(18)* showed that endometrial tumors are diagnosed at a later stage and are associated with poorer survival in long-term tamoxifen users than in non-users—whereas the opposite would be expected if surveillance bias resulted in the observed increased risks. In addition, increased mortality from endometrial cancer has been associated with tamoxifen use *(17)*. Results of previous studies *(1,18)* indicate that confounding by known risk factors does not appear to account for our results. Adjustment for non-tamoxifen

Table 7. Risk of endometrial cancer, by histologic type, in relation to duration of tamoxifen treatment*

	Endometroid adenocarcinomas and mucinous carcinomas†			Clear cell and papillary serous carcinomas‡			Mullerian and mesodermal mixed tumors and sarcomas§		
Duration of tamoxifen treatment	No.	OR‖ (95% CI)	*P*¶	No.	OR‖ (95% CI)#	*P*#	No.	OR‖ (95% CI)	*P*¶
No mention of tamoxifen	136	1.0 (baseline)		3	1.0 (baseline)		4	1.0 (baseline)	
Tamoxifen treatment	538	2.1 (1.6 to 2.7)	<.001	22	3.1 (0.8 to 17.9)	.119	74	13.5 (4.1 to 44.5)	<.001
Duration**									
>0–<2 y	132	1.2 (0.9 to 1.7)	.258	7	2.5 (0.4 to 19.5)	.455	12	6.1 (1.6 to 23.6)	.009
2–4 y	164	1.8 (1.3 to 2.4)	.001	5	2.9 (0.4 to 23.3)	.375	15	7.1 (1.9 to 26.4)	.004
5–7 y	116	2.2 (1.5 to 3.2)	<.001	8	4.9 (1.0 to 34.2)	.055	27	20.2 (5.7 to 71.9)	<.001
8–9 y	54	4.6 (2.7 to 7.7)	<.001	1	1.9 (0.0 to 27.2)	.993	7	18.0 (4.0 to 82.4)	<.001
≥10 y	40	6.8 (3.3 to 13.9)	<.001	0	12.7 (0.0 to 495)	1.000	5	33.0 (5.7 to 192.5)	<.001
Used, duration unknown	32	2.2 (1.3 to 3.7)	.004	1	2.4 (0.0 to 32.7)	.854	8	18.4 (4.5 to 75.6)	<.001
Trend: OR per y††		1.17 (1.12 to 1.21)	<.001		1.13 (0.96 to 1.33)	.147		1.31 (1.19 to 1.44)	<.001

*Thirty-six cases excluded because histologic type missing (eight cases) or no histologic examination was undertaken (28 cases).
†Morphology *(22)*: 8070, 8071, 8140, 8211, 8260, 8380, 8480, 8481, 8560, 8570.
‡Morphology *(22)*: 8050, 8310, 8450, 8460.
§Morphology *(22)*: 8890, 8930, 8940, 8950, 8951, 8980, 8990.
‖OR = odds ratio; CI = confidence interval.
¶*P* value was two-sided, from Wald test.
#CI and two-sided *P* value were determined by an exact method.
**Number of completed years of treatment.
††Includes non-users.

risk factors also did not alter our risk estimates, but this is weak evidence, given our incomplete data on these factors.

Our data confirm that endometrial cancer risk is not associated with the dose of tamoxifen *(2,16–18,23)*, apparently even for the dose of 10 mg/day, a dose that has not been previously examined. Small numbers of subjects were taking this dose, however, and so the finding needs confirmation.

In contrast to dose, however, duration of treatment greatly affected risk in our study, as in most *(1,10,16–19,23)* but not all *(3)* previous studies. The longest duration of treatment previously examined has been 5 years or more. Our study had more than seven times as many participants with 5 years or more of treatment as any previous study, and we found that risk increased steadily with increasing duration of tamoxifen treatment to the category with 10 years or more of treatment (median = 11 years). However, randomized trials for breast cancer have shown treatment benefit with tamoxifen of only up to 5 years, and longer treatment apparently does not increase the benefit *(26,31)*. Two additional trials, however, are currently in progress *(26)*. Among all control patients, 16% had received tamoxifen for 5 years or more; among control patients with information on at least 5 years of follow-up (i.e., those matched to case patients who had developed cancer after at least 5 years), 32% had received tamoxifen for 5 years or more. Because the control patients were matched on length of follow-up and were required not to have had a hysterectomy, they cannot be used directly to determine the proportion of patients in Britain who have received more than 5 years of tamoxifen treatment. However, our data suggest that it may be an appreciable proportion of patients.

Results of an early study of endometrial cancer risks after tamoxifen treatment for breast cancer *(3)* and of one of the two largest studies to date *(18)* suggested that risk was not increased if tamoxifen treatment was less than approximately 2 years. Our results, however, indicated that risks increase continuously with longer duration and do not have a threshold.

We found that the increasing risk of endometrial cancer associated with cumulative dose of tamoxifen is a reflection of the treatment duration and not of daily dose. The overall relative risks of endometrial cancer associated with tamoxifen treatment have varied between 0.6 and 7.5 in different studies *(1,2,8–18,20)* but were often based on small numbers of subjects. Given the large association of treatment duration with risk, there is little validity in comparing such risks without taking account of the distribution of treatment durations. The risk per year of treatment that we found (OR = 1.18, 95% CI = 1.14 to 1.23) was similar to that reported by the other largest studies [in Bernstein et al. *(1)*, OR = 1.18 (95% CI = 1.08 to 1.28), and in Bergman et al. *(18)*, we estimate that OR = 1.27].

Few studies have examined relative risks of endometrial cancer in tamoxifen-treated women as a function of age or menopausal status, and these have included only small numbers of premenopausal subjects, for whom conflicting results have been reported *(1,7,8,14,20)*. Our data suggest that the risk needs to be considered clinically for both pre- and postmenopausal patients. Tamoxifen has different effects on estrogen levels in pre- and postmenopausal women, suggesting that it might also have different effects on endometrial cancer risks. In premenopausal women, tamoxifen stimulates the ovaries to synthesize estrogens and thus greatly increases the level of plasma estrogen *(32)*. In postmenopausal women, however, tamoxifen slightly reduces the level of plasma estrogen and often increases the level of serum hormone binding globulin, and so free estradiol levels may be reduced in postmenopausal women *(32,33)*. In premenopausal women, tamoxifen has antiestrogenic effects on the uterus, whereas in postmenopausal women, tamoxifen has estrogenic effects *(32)*. Consequently, the finding that tamoxifen was associated with a comparable risk of endometrial cancer among pre- and postmenopausal patients in our study is surprising. A possible explanation is that in premenopausal women, the increased estrogen levels may override the antiestrogen effect of tamoxifen on the uterus, whereas in postmenopausal women, the antiestrogen effect of tamoxifen on the uterus may predominate, although such speculation is entirely post hoc.

Although one cannot calculate absolute excess risks from a case–control study, our relative risks indicate that the absolute excess risks must be much larger for older women than for younger women, because incidence rates of endometrial cancer in Britain increase steeply with age up to approximately 70 years *(34)*.

With few exceptions *(1,3,18)*, published analyses of the time course of endometrial cancer risks after tamoxifen have concerned patients who are currently receiving treatment or patients who are within 12 months of last treatment. The only analysis of risks 2 years or more after last treatment *(18)* found a statistically nonsignificantly increased relative risk for this period (RR = 1.2, 95% CI = 0.6 to 2.2). An analysis of risks by time since breast cancer diagnosis, without information on length of treatment or end of treatment, found no diminution of risks after 10 years or more after diagnosis *(20)*. We found that risks remained statistically significantly increased for 4 years and were statistically nonsignificantly increased beyond this period, suggesting that potentially elevated risk should be considered clinically for at least 4 years after the completion of tamoxifen treatment. The continuing increased risks after cessation of treatment also support the evidence, discussed above, that surveillance bias is not the reason for the increased endometrial cancer risks associated with tamoxifen treatment.

Results of most previous studies *(16,18,20,24)* indicate that tamoxifen treatment is associated with a much greater risk for mixed mesodermal tumors and sarcomas of the endometrium than for adenocarcinomas, although results of one analysis *(24)* did not agree. The potential high risk of mixed mesodermal tumors and sarcomas is important because of the poor prognosis of these tumors *(18,20,35)*. In our analyses, the magnitude of risk was indeed different for different histologic tumor types (for mixed mesodermal tumors and sarcomas, OR = 13.5 [95% CI = 4.1 to 44.5], with a statistically significant trend for increased risk with greater treatment duration [P_{trend}<.001]; for adenocarcinomas, OR = 2.1 [95% CI = 1.6 to 2.7], again with a statistically significant trend for increased risk with greater treatment duration [P_{trend}<.001]). The relative risk for mixed mesodermal tumors was greater than that found in the previous study that calculated a relative risk *(20)*, but the latter investigated only initial hormonal treatment (believed mainly to be with tamoxifen) and lacked follow-up of women moving out of the Surveillance, Epidemiology and End Results Program (SEER)[1] catchment areas *(20)*. The risk for clear cell tumors in our study, from smaller numbers of case patients, was increased statistically nonsignificantly with tamoxifen treatment, and treatment duration was not statistically significantly associated with risk of this histologic type. The evidence for an increased risk of uterine sarcoma associated with tamoxifen has led the U.S. Food and Drug Administration to issue a warning for tamoxifen, with a statement that the warning is most relevant to women taking the drug for prophylaxis of

breast cancer *(35)*. We note, in addition, that the risk of uterine sarcoma increases greatly with longer period of use.

As in previous studies *(9,16,23)*, risk of endometrial cancer in women overall was greatly increased by prior pelvic radiotherapy. In the study by Sasco et al. *(23)*, risk was no greater after treatment with tamoxifen in addition to pelvic radiotherapy than after such radiotherapy alone *(23)*. However, in another, smaller study *(9)*, risk was greatest for the two exposures combined. Our data were insufficient to distinguish between these two alternatives.

We also found a decreased risk of endometrial cancer after breast radiotherapy in women overall; it does not seem plausible that this result could be etiological. In principle, confounding seems a possible explanation, but on examination of the data we found no plausible confounder.

The increased risks of endometrial cancer associated with hormone replacement therapy and with greater postmenopausal weight and the reduced risk associated with smoking among all patients that we found are as expected because these are established risk factors *(36)*. Our data on these factors were incomplete because they were mainly extracted from hospital case notes in which they may have had no essential clinical purpose. Nevertheless, because the information was recorded at the time of breast cancer diagnosis, it should not have been biased with respect to risk of subsequent endometrial cancer. It was insufficiently complete, however, to reach conclusions on interactions between the effects of hormone replacement therapy and of weight and that of tamoxifen.

In conclusion, the benefits of tamoxifen far outweigh the risks when used for 5 years or less for breast cancer treatment *(6)*. However, our data show that the risk of endometrial cancer after tamoxifen treatment increases for up to at least 10 years of treatment, whereas current evidence suggests that tamoxifen treatment beyond 5 years does not add to its treatment efficacy. Trials to obtain further information on the effectiveness of long-term tamoxifen treatment are several years from completion *(26)*; until the data are available, our results suggest that the associated risk of endometrial cancer makes treatment with tamoxifen beyond 5 years questionable.

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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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