

Distribution of Second Primary Malignancies Suggests a Bidirectional Effect Between Breast and Endometrial Cancer

A Population-Based Study

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Introduction: The aim of this study was to investigate the incidence of second primary tumors in patients with breast cancer (BC), with particular regard to bidirectional risk for endometrial cancer (EC).

Methods: A total of 7512 and 343 patients with first and second primary BC, respectively, were referenced to the expected number of cases calculated using the standardized incidence ratio (SIR) over the same period, to evaluate the observed and expected ratio between the groups. Data on tamoxifen use were also considered.

Results: A total of 499 women with primary BC developed a second tumor. The total SIR, that is, the ratio between observed second primary cancer among patients with BC and the expected primary cancers in the general population, was significantly higher (SIR = 1.23; 95% confidence interval, 1.12–1.34; $P = 0.007$), particularly for melanoma (2.25), EC (2.15), ovarian cancer (1.74), hematologic malignancies (1.36), and bilateral BC (1.25). A greater risk of BC after thyroid (2.22) and EC (1.62) was also observed. Furthermore, the risk of developing EC was higher in patients treated with tamoxifen (SIR = 2.50 vs 1.34).

Conclusions: Bidirectional risk of endometrial cancer was not exclusively related to tamoxifen use.

Key Words: Breast cancer, Endometrial cancer, Cancer registry, Tamoxifen, Second cancer

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Over the last decade, earlier detection of invasive and non-invasive breast cancer (BC) and more effective treatment options have significantly reduced BC mortality. However, an

improved prognosis for women with BC exposes long-term survivors to the risk of developing second primary malignancies.

Several studies have shown that women with BC are at a 3- to 4-fold increased risk of developing a new primary cancer in the contralateral breast. A significant increase of cancer of the endometrium, ovary, colon, skin, thyroid, and lymphoma^{1–3} relative to the general population was also observed. For some of these cancers, for example, bilateral BC, ovarian cancer (OC), and endometrial cancer (EC), the increased risk may be partly explained by a common etiology (eg, hormonal risk factors or genetic susceptibility). Other excessive risks may be treatment related or reflect the interaction of still unknown factors. The ECs that develop in association with tamoxifen exposure is due to the selective uptake of tamoxifen by endometrial tissue^{4,5} and have been related to long-term administration⁶ and high cumulative doses of the drug.

To assess the risk of developing a second primary malignancy after BC or BC after a primary malignancy, we performed

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TABLE 1. Description of all cases of primary ECs

Characteristics	n	%
Age		
≤49	125	9.7
≥50	1163	90.3
Histotype		
Endometrioid adenocarcinoma	1105	85.8
Serous papillary	33	2.6
Leiomyosarcoma	29	2.3
Carcinosarcoma	24	1.9
Carcinoma adenosquamous	10	0.8
Others	85	6.6
Total	1288	100
Stage (FIGO)		
I	420	32.6
II	201	15.6
III	88	6.8
IV	165	12.9
Unknown	414	32.1
Total	1288	100

a population-based study on cases registered in the Modena Cancer Registry (MCR) between January 1988 and December 2004. Specifically, the main aim of this study was to assess the incidence of second primary cancers among all patients with BC registered by MCR and compare this incidence to that expected in the general population. Similarly, the incidence of BC arising after any other primary cancer registered by MCR was evaluated. Lastly, we analyzed the relationship between EC and BC, with particular regard to tamoxifen use.

PATIENTS AND METHODS

Patients

Between January 1988 and December 2004, a total of 7812 patients with primary invasive BC were recorded by the MCR, which collects, in accordance with the *International Classification*

of Diseases for Oncology (3rd revision), data on histology, staging at presentation (based on the 2004 UICC-TNM classification), treatment, and vital status concerning incident cases of all malignant tumors in the province of Modena (Italy). Information on local or distant recurrence and causes of death were retrieved by experienced clinical documentation clerks with active research strategies.

Among the 7812 patients with BC, 97 concurrent malignancies that were those diagnosed in a period ranging from 3 months before to 3 months after a diagnosis of BC and 203 patients with follow-up time after diagnosis in fewer than 3 months were excluded. Thus, a total of 7512 patients diagnosed with a primary BC were evaluated for the analysis of second tumors. Patients aged 0 to 49 years were considered premenopausal, whereas patients aged 49 years and older were considered postmenopausal. For the development of BC after other tumors, all patients registered by MRC with primary cancer diagnosed within the same period (1988–2004) were considered. Overall, 22,932 cases were evaluated for the subsequent development of BC.

Tamoxifen Use and EC

To evaluate tamoxifen use, we recorded the start and end dates and the dosage during period of treatment. Among the 7512 patients with primary BC, information on tamoxifen treatment was available for 3335 patients (44.4%). The evaluation of patients was based on the following criteria: survival with an intact uterus between the diagnoses of BC and EC and the absence of any other cancer. To define an intact uterus, each patient was investigated by the health registry for any gynecologic hospitalization, and pathological records were evaluated for the kind of surgery. Data on duration and dosage of tamoxifen were available for all but 382 of these women. The duration of tamoxifen use was calculated as the number of days between the date of the first prescription and the date of diagnosis of EC or the date of discontinuation, and the total duration for all the courses was summed if there were distinct courses of the prescription and/or changes in the prescribed dose.

Information on the clinicopathologic characteristics of the EC were collected from clinical records, including the date of EC diagnosis and histology, according to the International Federation of Gynecology and Obstetrics (FIGO) stage (Table 1). The FIGO stage evaluation was unknown for 414 patients diagnosed with EC in the first period (1988–1995). For the histopathologic characteristics, a tissue section was reviewed by a reference pathologist who was blinded to the tamoxifen exposure of the patient.

TABLE 2. Description of all cases of primary BCs as the first cancer and of BC patients treated with tamoxifen

Characteristics		All BCs		BC With TAM Information		BC Without TAM Information		P
		n	%	n	%	n	%	
Age	0–49 y	1704	22.7	777	23.3	927	22	0.263
	≥50 y	5808	77.3	2558	76.7	3250	78	
	Total	7512	100	3335	100	4177	100	
Morphology	Ductal	5760	76.7	2650	79.5	3110	74.5	<0.0001
	Lobular	938	12.5	420	12.6	518	12.4	
	Other	558	7.4	235	7.0	323	7.7	
	Unspecified	256	3.4	30	0.9	226	5.4	
	Total	7512	100	3335	100	4177	100	
Period of diagnosis	1988–1996	3431	45.7	1316	39.5	2527	60.5	<0.0001
	1997–2004	4081	54.3	2019	60.5	1650	39.5	
	Total	7512	100	3335	100	4177	100	

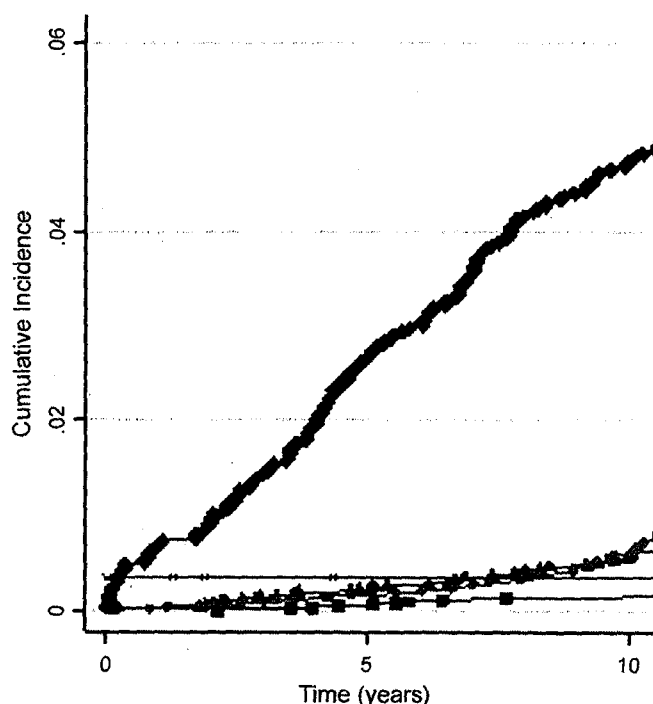


FIGURE 1. Cumulative risk in presence of death as competing event in patients with BC at 5 and 10 years. The overall 5- and 10-year cumulative probabilities of developing a second BC, EC, melanoma, and hematologic malignancies were 22% and 42%, 2.7% and 6%, 2.1% and 6%, 1.2% and 2%, and 4% and 4%, respectively (— = breast; — = endometrium; — = ovary; — = melanoma; — = hematologic malignancies).

Statistical Methods

We used person-years incidence analysis to study the risk of any second neoplasm. We compared the risk of developing a second primary tumor among patients with a primary cancer diagnosis (the observed incidence) with the risk of developing the same tumor in the general population (the expected incidence). Expected risk of cancer was calculated on the basis of age-specific incidences for the Modena province that were observed in the same calendar year. The total number of expected cases was calculated by multiplying the expected cancer incidence by the total person-years at risk. The standardized incidence ratios (SIRs) were determined by calculating the ratio of observed cancers to the expected number of cancers. The significance of SIR and the corresponding 95% confidence intervals (CIs) were based on the Poisson distribution.⁷ Overall survival was defined as the time from diagnosis of the primary cancer to death. Survival was estimated using the Kaplan-Meier method, and any differences in survival were evaluated with a stratified log-rank test. Statistical differences between characteristics of all patients with BC and patients with and without tamoxifen information were evaluated using the Fisher exact test. We estimated cumulative incidence in presence of death as competing event.⁸

RESULTS

Second Malignancies

Between 1988 and 2004, 7512 women were diagnosed with primary BC, yielding 42,812 person-years. At the time of the BC diagnosis, 1704 (22.7%) of 7512 women were premenopausal and 5808 (77.3%) of 7512 were postmenopausal according to the definition given earlier (Table 2). Information regarding tamoxifen treatment was obtained for 777 (23.3%) of 3335 women in the premenopausal-age group and 2558 (76.7%) of 3335 in the postmenopausal-age group. For the remaining patients without information on hormonal treatment, the distribution for age was

TABLE 3. Observed (Obs), Expected (Exp), and SIR with 95% CI by site of primary second cancer among 7512 BC patients in Modena province diagnosed between 1988 and 2004 overall and in strata of age

Site of Second Cancer	Obs	Exp	SIR (95% CI)	P	Obs	Exp	SIR (95% CI)	P	Obs	Exp	SIR (95% CI)	P
	All Ages				0–49 y				≥50 y			
All cancers	499	407.1	1.23 (1.12–1.34)	0.007	87	48.8	1.78 (1.43–2.20)	0.006	412	358.3	1.15 (1.04–1.27)	0.008
Endometrium	49	22.8	2.15 (1.59–2.84)	<0.001	6	3.0	2.00 (0.73–4.35)	NS	43	19.8	2.18 (1.57–2.93)	<0.001
Skin melanoma	14	6.2	2.25 (1.23–3.77)	0.003	3	1.3	2.38 (0.49–6.94)	NS	11	5.0	2.21 (1.10–3.96)	0.002
Ovary	28	16.1	1.74 (1.15–2.51)	0.004	4	2.1	1.87 (0.51–4.79)	NS	24	14.0	1.72 (1.10–2.56)	<0.001
Hematologic malignancy	47	34.5	1.36 (1.00–1.81)	0.04	2	3.1	0.66 (0.08–2.37)	NS	45	31.4	1.43 (1.05–1.92)	0.03
Kidney	17	11.0	1.55 (0.90–2.49)	NS	3	1.0	3.03 (0.62–8.85)	NS	14	10.0	1.41 (0.77–2.36)	NS
Contralateral BC	145	116.0	1.25 (1.05–1.47)	0.008	43	22.5	1.91 (1.38–2.58)	0.002	102	93.6	1.09 (0.89–1.32)	NS
Colon-rectum	55	57.9	0.95 (0.72–1.24)	NS	7	4.0	1.75 (0.70–3.60)	NS	48	53.9	0.89 (0.66–1.18)	NS
Brain	5	5.7	0.87 (0.28–2.03)	NS	0	0.8	0.00	0	5	4.9	1.01 (0.33–2.37)	NS
Pancreas	13	13.5	0.97 (0.51–1.65)	NS	1	0.6	1.73 (0.04–9.64)	NS	12	12.9	0.93 (0.48–1.63)	NS
Lung	28	23.3	1.20 (0.80–1.74)	NS	5	1.9	2.64 (0.85–6.17)	NS	23	21.5	1.07 (0.68–1.60)	NS
Stomach	29	25.1	1.15 (0.77–1.66)	NS	1	1.2	0.86 (0.02–4.79)	NS	28	24.0	1.17 (0.78–1.69)	NS
Head and neck	7	5.1	1.37 (0.55–2.83)	NS	1	0.7	1.51 (0.04–8.44)	NS	6	4.4	1.36 (0.50–2.95)	NS
Thyroid	12	9.1	1.32 (0.68–2.30)	NS	4	2.7	1.47 (0.40–3.77)	NS	8	6.4	1.25 (0.54–2.47)	NS
Bladder	16	13.0	1.23 (0.70–2.00)	NS	4	0.8	5.19 (1.41–13.28)	<0.001	12	12.3	0.98 (0.50–1.71)	NS
Other sites	34	47.9	0.71 (0.49–0.99)	NS	3	3.3	0.91 (0.19–2.66)	NS	31	44.6	0.70 (0.47–0.99)	NS

NS, not significant.

927 (22%) of 4177 before 50 years and 3250 (78%) of 4177 after 50 years. No differences in terms of age were seen between all the groups of patients. Totally, there were 3431 (45.7%) of 7512 women who were diagnosed between 1988 and 1996, and 4081 (54.3%) of 7512 who were diagnosed between 1997 and 2004. Most cases were ductal carcinomas (5760/7512 [76.7%]), followed by lobular carcinomas (938/7512 [12.5%]) and other (558/7512 [7.4%]). For the group with information on tamoxifen treatment 2650 (79.5%) of 3350 were ductal carcinomas, 420 (12.6%) of 3350 were lobular carcinomas, and 235 (7.0%) of 3350 were represented by other histotypes. In the group without information about tamoxifen treatment, a high number of unspecified cancer (226/4177 [5.4%]) was identified ($P < 0.0001$). Finally, differences for the period of diagnosis were seen between BC with and without information on tamoxifen treatment (1316/3335 [39.5%] vs 2527/4177 [60.5%] in the period 1988–1996, and 2019/3335 [60.5%] vs 1650/4177 [39.5%] in the period 1997–2004) ($P < 0.0001$).

Overall, 499 patients with BC developed a second primary cancer in contrast to the 407.1 expected cases in the general population (SIR = 1.23; 95% CI, 1.12–1.34; $P = 0.007$). Considering the death as competing event, the second primary BC had a cumulative incidence of 22% and 42%, respectively, at 5 and 10 years, whereas a little increased cumulative incidence was seen at 10 years for ovary and endometrium (Fig. 1). Patients with BC had a significantly increased risk of developing skin melanoma (SIR = 2.25; 95% CI, 1.23–3.77; $P = 0.003$), EC (SIR = 2.15; 95% CI, 1.59–2.84; $P < 0.001$), OC (SIR = 1.74; 95% CI, 1.15–2.51; $P = 0.004$), hematologic malignancies (SIR = 1.36; 95% CI, 1.00–1.81; $P = 0.04$), and contralateral BC (SIR = 1.25; 95% CI, 1.05–1.47; $P = 0.008$). The overall relative risk of second primary cancer was higher among women diagnosed before the age of 50 years (SIR = 1.78; 95% CI, 1.43–2.20; $P = 0.006$) compared with women diagnosed at 50 years and above (SIR = 1.15; 95% CI, 1.04–1.27; $P = 0.008$). Never-

theless, no statistically increased risk was observed in patients diagnosed before menopause for melanoma, EC, OC, or hematologic malignancies. An increased risk was observed only for bilateral BC (SIR = 1.91; 95% CI, 1.38–2.58; $P = 0.002$) and bladder cancer (SIR = 5.19; 95% CI, 1.41–13.28; $P < 0.001$). For EC, OC, skin melanomas, and hematologic malignancies, the SIR was significantly higher than expected in the postmenopausal-age group (Table 3).

When considering overall bidirectionality (ie, risk of BC after other primary tumors), 343 patients developed BC compared with 272.6 expected cases (SIR = 1.26; 95% CI, 1.13–1.40; $P = 0.007$). The risk of developing BC was significantly higher than expected among the 1288 patients with primary EC (SIR = 1.62; 95% CI, 1.13–2.26; $P = 0.004$), 7512 with previous BC (SIR = 1.25; 95% CI, 1.05–1.47; $P = 0.008$), and 785 with primary thyroid cancer (SIR = 2.22; 95% CI, 1.35–3.42; $P < 0.001$). Overall, the SIR was higher in the premenopausal-age group than at 50 years and older (1.56 vs 1.20). In the postmenopausal-age group, a primary EC and thyroid cancer lead to a significant increase of incidence of secondary BC compared with the expected incidence of primary BC in the general population (Table 4).

Risk of EC Associated With Tamoxifen Treatment

Forty-nine of 7512 patients developed EC after primary BC. EC was diagnosed less than 5 years after the BC diagnosis in 45% of cases. Among the 7512 women studied, only 3335 (44.4%) had available information about hormonal treatment. Totally, 1660 (49.8%) were treated with tamoxifen and 1675 (50.2%) were not. A total of 19 ECs were evaluated for an association with tamoxifen treatment. The most common daily dose of tamoxifen was 20 mg (range, 20–40 mg). Of the 19 EC patients evaluated, 13 were treated with tamoxifen and 6 were not. Tamoxifen treatment was associated with an increased risk of EC (SIR = 2.50; 95% CI, 1.36–4.20;

TABLE 4. Observed (Obs), expected (Exp), and SIR with 95% CI by site of primary second cancer among 22,932 cancer patients in Modena province diagnosed between 1988 and 2004 overall and in strata of age

Site (No. Observed Primary Cancers)	All Ages				0–49 y				≥50 y			
	Obs	Exp	SIR (95% CI)	P	Obs	Exp	SIR (95% CI)	P	Obs	Exp	SIR (95% CI)	P
All cancers (N = 22,932)	343	272.6	1.26 (1.13–1.40)	0.007	67	43.0	1.56 (1.21–1.98)	0.0066	276	229.7	1.20 (1.06–1.35)	0.009
Breast (7512)	145	116.0	1.25 (1.05–1.47)	0.008	43	22.5	1.91 (1.38–2.58)	<0.001	102	93.6	1.09 (0.89–1.32)	NS
Endometrium (1288)	35	21.6	1.62 (1.13–2.26)	0.004	2	2.1	0.95 (0.11–3.41)	NS	33	19.6	1.69 (1.16–2.37)	0.004
Skin melanoma (493)	11	6.6	1.67 (0.83–2.99)	NS	5	1.8	2.86 (0.92–6.68)	NS	6	4.8	1.24 (0.45–2.71)	NS
Ovary (836)	14	7.7	1.83 (0.99–3.07)	NS	3	1.5	2.04 (0.42–5.96)	NS	11	6.2	1.78 (0.89–3.19)	NS
Hematologic malignancy (2206)	24	24.3	0.99 (0.63–1.47)	NS	2	3.5	0.57 (0.07–2.07)	NS	22	20.9	1.05 (0.66–1.60)	NS
Kidney (571)	9	7.6	1.19 (0.54–2.25)	NS	1	1.1	0.93 (0.02–5.20)	NS	8	6.5	1.22 (0.53–2.41)	NS
Colon-rectum (2940)	37	33.5	1.11 (0.78–1.52)	NS	1	1.9	0.54 (0.01–2.99)	NS	36	31.6	1.14 (0.80–1.58)	NS
Brain (326)	0	1.0	0.00	0	0	0.3	0.00	0	0	0.7	0.00	0
Pancreas (503)	1	1.2	0.86 (0.02–4.74)	NS	0	0.1	0.00	0	1	1.1	0.91 (0.02–5.07)	NS
Lung (1039)	8	4.7	1.72 (0.74–3.38)	NS	0	0.5	0.00	0	8	4.2	1.90 (0.82–3.75)	NS
Stomach (1096)	7	9.0	0.77 (0.31–1.60)	NS	0	0.6	0.00	0	7	8.4	0.83 (0.33–1.72)	NS
Head and neck (303)	1	3.5	0.29 (0.01–1.61)	NS	0	0.4	0.00	0	1	3.4	0.33 (0.01–1.83)	NS
Thyroid (785)	20	9.0	2.22 (1.35–3.42)	<0.001	7	3.3	2.13 (0.85–4.39)	NS	13	5.7	2.26 (1.20–3.87)	<0.001
Bladder (702)	15	9.5	1.57 (0.88–2.59)	NS	0	0.5	0.00	NS	15	9.0	1.67 (0.93–2.75)	NS
Other sites (2332)	16	17.5	0.92 (0.52–1.49)	NS	3	3.2	0.95 (0.20–2.77)	NS	13	14.3	0.91 (0.48–1.56)	NS

NS, not significant.

TABLE 5. Standardized incidence ratio among 19 primary second EC patients and 3335 patients with primary BC according to tamoxifen treatment and duration of treatment

Tamoxifen Treatment	EC		Primary BC		SIR (95% CI)	P
	n	%	n	%		
Any tamoxifen treatment						
No	6	32	1675	50	1.34 (0.49–2.92)	0.75
Yes	13	68	1660	50	2.50 (1.36–4.20)	<0.0001
Duration of treatment						
<2 y	2	15	448	27	1.81 (0.22–6.54)	0.99
2–5 y	10	77	664	40	3.61 (1.73–6.64)	<0.0001
>5 y	1	8	166	10	1.17 (0.03–6.52)	0.82
Used, duration unknown	0	0	382	23	0.00	0
Total	19	100	3335	100	1.92 (1.16–3.00)	0.0016

$P < 0.0001$) compared with no tamoxifen treatment (SIR = 1.34; 95% CI, 0.49–2.92) (Table 5). Eighteen patients with EC were postmenopausal. The average duration of tamoxifen treatment was 37 months (range, 2–119 months), and 166 (10%) patients with BC had received tamoxifen for more than 5 years. The median interval between the diagnoses of BC and EC was 64 months (range, 3–153 months) in the treated group and 45 months (range, 13–161 months) in the nontreated group.

In both groups, the most frequent histological type was endometrioid adenocarcinoma. There were 4 sarcomas in the group who had taken tamoxifen and 1 sarcoma in the nontreated group ($P = 0.37$). Furthermore, there were no differences in the FIGO stage, tumor grade, or presence of myometrial invasion. Finally, the 5-year survival was superimposable between the 2 groups (80% in the treated group and 73% in the nontreated group; $P = 0.47$) (Fig. 2).

DISCUSSION

Our preliminary data confirm that women with a history of BC are at elevated risk of a second primary cancer. Higher risks of melanoma, EC, OC, hematologic malignancies, and bilateral BC

were observed in women with a previous diagnosis of BC, particularly for those diagnosed after the age of 50 years. Genetic factors may explain some of these findings. The *BRCA1* and *BRCA2* genes are known to be involved in an inherited susceptibility for BC and/or OC.^{9,10} Lynch and colleagues¹¹ showed that genetic factors are also involved in a familial tendency for EC and BC in the hereditary nonpolyposis colorectal cancer syndrome. Mutations in *CHEK2* were observed in an association between thyroid and BC.¹²

The increased risk of second primary BC could be also related to the radiotherapy delivered to patients with BC as part of their initial treatment.^{13–16} Radiotherapy has been shown to cause secondary cancers, especially in younger patients as might be demonstrated in our study.¹⁷ In fact, BC was the most common second primary cancer, and the risk increased in younger age groups. No differences in histology were seen between first and second primary BC being represented mainly by ductal, lobular, and other types of tumor.

Radiotherapy and chemotherapy for BC could also explain the increased risk of lymphomas and leukemia, whereas the incidence of lung cancer after BC was not significantly increased unlike in the study of Kaufman et al,¹⁸ in which radiotherapy plus cigarette smoking sharply increased the risk of second primary lung cancer but not in nonsmoking women. Our results were possibly due to the short follow-up time or to better treatment of the cohort group, which restricts the postmastectomy irradiation only to high-risk patients with 4 or more node-positive cancer¹⁹ or finally to the limited habit to smoking in Italian women.

An association between BC and EC has long been postulated, mainly because of their common estrogen-mediated effects and genetics. As previous studies have reported, an increased risk of EC could be associated with long-term tamoxifen treatment by SIR analysis.^{20–22} Our study showed overall a significant increased risk of developing EC after BC, especially for patients treated for 2 to 5 years. Otherwise, we found no clear association between tamoxifen and the development of more aggressive histological subtypes of EC. Although information on tamoxifen use was totally obtained in only 3335 women (44.4%), we do not think it could represent a selection bias, because the majority of missing data regarded the first analyzed period (1988–1996), whereas along the last 8 years (1997–2004), hormonal treatment outcome was increasingly collected, reaching the 100% of all cases in 2000, with an equal distribution into 2 similar groups (1675 not treated vs 1660 treated). On the other hand, a risk of BC after EC was also found. Geisler et al²³ concluded that women with uterine serous carcinoma have an increased risk of developing a subsequent BC compared with those with an endometrioid histology, but in our series, uterine

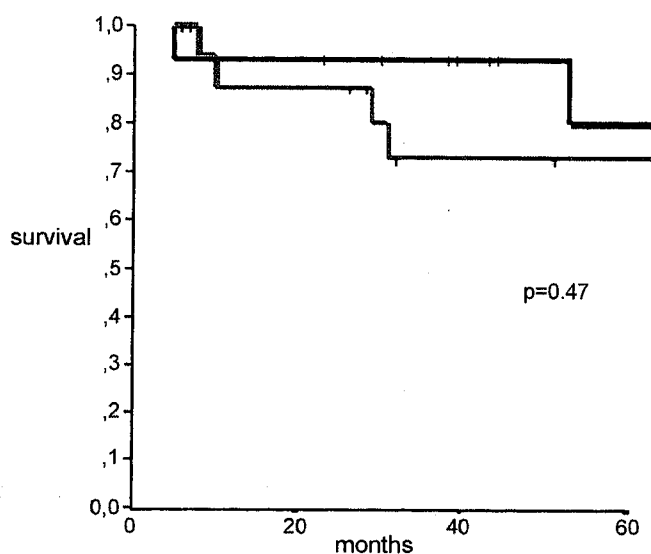


FIGURE 2. Five-year survival values between EC treated and nontreated by tamoxifen were equal to 73% and 80%, respectively ($P = 0.47$).---+--- = nontreated;---*--- = treated.

serous carcinomas represented only 1% of all cases, and none of these patients developed BC.

Regarding the higher risk of developing BC after thyroid cancer, possible explanations could be estrogen-related hormones, such as those in oral contraceptives, and older age at first pregnancy, both associated with an increased risk of thyroid cancer and BC. Finally, radiotherapy for BC could also be related to an increased risk of thyroid cancer.

In conclusion, our results emphasize the relationship between EC and BC as a bidirectional effect. More studies need to be carried out to identify other risk factors involved into the development of both cancers than the tamoxifen association.

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