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Evaluation of Metachronous Breast and Endometrial Cancers:

Preroutine and Postroutine Adjuvant Tamoxifen Use

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Abstract

Background—The time interval between diagnoses of breast cancer (BC) and endometrial cancer (EC) is not well established in women with metachronous primary tumors. We sought to examine this interval and identify associations with treatment-related and clinicopathologic factors.

Methods—We identified 141 patients who developed both cancers during 1966 to 2013. Patients were divided into 2 groups: group 1, BC first, and group 2, EC first. Subanalysis performed of group 1 (59 patients) stratified around adjuvant tamoxifen use: pre-1990 BC diagnosis and post.

Results—Fifty-nine and 82 patients were in groups 1 and 2, respectively. The mean time interval was comparable (76 vs 74 months, $P = 0.861$). Subanalysis divided group 1 into pre- ($n = 27$) and post- ($n = 32$) 1990 and resulted in different mean time intervals between diagnosis of metachronous cancers (106 vs 50 months, respectively [$P = 0.042$]). Median progression-free survival (PFS) and overall survival (OS) for EC were longer in the pre group (PFS, 51 vs 26 months [$P = 0.169$]; OS, 59 vs 27 months [$P = 0.190$]). Median PFS and OS for BC were also longer in this group (PFS, 147 vs 109 months [$P = 0.005$]; OS, 166 vs 114 months [$P < 0.001$]).

Conclusions—Our data indicate the mean time interval between the diagnosis of EC and BC was approximately 6 years. Disease-specific EC survival was worse for patients with a previous diagnosis of BC. Stratification around implementation of tamoxifen use shows comparable grade and stage but different time interval and survival, suggesting resulting effects from adjuvant therapy for BC. These results are useful in counseling women at risk.

Keywords

Metachronous endometrial and breast cancer; Tamoxifen

There are an estimated 13.4 million people living with cancer in the United States, of which 66.1% survive at least 5 years.¹ Compared with the general population, patients with cancer

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have 31% increased risk of developing subsequent cancer.² Because survival is improving with advancement of therapeutic options, the number of patients who live long enough to develop a second or greater cancer is also rising. Some women, especially those with hereditary cancer syndromes, can develop dual primary or metachronous cancers. Hereditary cancer syndromes account for 3% to 5%³ cases of endometrial cancer (EC) and 5% to 10% cases of breast cancer (BC).⁴ The most common genes associated with EC are *MLH1*, *MSH2*, *MSH6*, and *PMS2* and can result in Lynch syndrome.⁵ *BRCA1* and *BRCA2* gene mutations are associated with hereditary breast and ovarian cancer syndrome.^{6,7} Second cancers can be attributed to the late effects of treatment; lifestyle choices including tobacco, alcohol, and diet; host factors and genetics; environmental exposures; or any combination of those.⁸ The women at risk for a second primary comprise an important group that every effort should be made to identify early as medical, surgical, and lifestyle interventions are available.

In this study, we identified all individuals given a diagnosis of both EC and BC in our institutional cancer registry. The primary objective of our study was to define the mean interval between diagnoses of the 2 metachronous cancers as this timeline has not been well defined in the literature. In addition, we evaluated survival based on order of malignancy diagnosis primarily because these 2 cancers are the most common in women with more than 235 000 cases of BC and more than 52 000 cases of EC diagnosed annually.⁹

Tamoxifen, a nonsteroidal antiestrogen agent in a class of agents known as a selective estrogen receptor modulator, is widely used as adjunctive therapy for women with BC, and it has been approved by the US Food and Drug Administration for adjuvant treatment of BC and reduction in BC incidence in high-risk women as early as 1990. Many studies have found that the increased relative risk of developing EC for women taking tamoxifen is 2 to 3 times higher than that of an age-matched population,^{10,11} which is clearly covered in the American College of Obstetricians and Gynecologists Committee Opinion #601. Uniquely, this article also explores the potential impact of the introduction of tamoxifen in treatment and prevention of BC in the rare situation of metachronous BC followed by EC. Our results are important for counseling at-risk women who may deliberate strategies to modify risk.

MATERIALS AND METHODS

Study Population

The Roswell Park Cancer Institute Tumor Registry (Buffalo, NY) was searched for all cases diagnosed with both EC and BC between 1966 and 2013. After obtaining institutional review board approval, a retrospective review of the medical records was performed that included age, stage and grade of each cancer type at diagnosis, and outpatient and inpatient treatments, including surgery, radiation, and chemotherapy. Only epithelial (endometrioid, serous, clear cell, or mixed) tumors of the uterus were included. However, mesenchymal tumors and carcinosarcoma were excluded in this particular analysis. Endometrial hyperplasia was not included; however, superficial/minimal invasion of endometrial carcinomas were included. Ductal carcinoma in situ (DCIS) was included in the analysis because standard treatment of DCIS includes use of tamoxifen.^{12–14} To include those patients in the analysis for potential metachronous tumors in the subanalysis of pre-tamoxifen

versus posttamoxifen, the decision to include DCIS and not lobular carcinoma in situ was made secondary to tamoxifen use in the former.

Stage summary variables, in situ/localized/regional/distant, were assigned to using the SEER Program variables in attempt to standardize groups within disease sites secondary to changing staging guidelines during the years that were surveyed in this study. Study outcomes included overall survival (OS) and time to progression (progression-free survival [PFS]), measured from the time of diagnosis. Progression was defined as objective evidence of recurrence, either from examination or imaging studies. The duration of OS was the interval between diagnosis and date of last contact or death. Data were censored at the last follow-up for patients with no evidence of recurrence, progression, or death. Disease-specific PFS, denoted as EC PFS or BC PFS, is defined from diagnosis to recurrence of the specific cancer based on imaging, examination, or reinitiating treatment, despite the second cancer diagnosis. Disease-specific OS is defined from diagnosis to censoring at the last follow-up or death from the specific cancer. Combined OS is from the diagnosis of the first cancer to censoring based on the last encounter or death from either cancer.

The patients were divided into 2 groups. In group 1 patients, the diagnosis of BC predated the diagnosis of EC. In group 2 patients, the diagnosis of EC predated the diagnosis of BC. The time interval between diagnoses of the first and second malignancies was calculated for each group. Five patients were given a diagnosis of both malignancies on the same date and were excluded from this analysis.

Statistical Analysis

All statistical analyses were performed with SAS 9.3 software (SAS Institute, Cary, NC). Comparisons for categorical variables were obtained from Fischer exact test and for continuous variables via Wilcoxon rank sum test on medians. χ^2 Test was used to compare data set for trend evaluation. Estimated survival distributions were calculated by use of Kaplan and Meier. Tests of significance with respect to survival distributions were based on the log-rank test.

RESULTS

A total of 14 173 women were given a diagnosis of BC, and 3640 women were given a diagnosis of EC during the study period.¹⁵ One hundred forty-one women (0.8%) had metachronous diagnoses of BC and EC. Our study was focused on these 141 women. There were 59 women in group 1 (BC before EC) and 82 women in group 2 (EC before BC).

The characteristics of the study population are presented in Table 1. The median ages of the study population were 61 and 63 years for groups 1 and 2, respectively (range, 26–87 years; $P=0.15$). The median duration of follow-up for the entire group of 141 women was 13 months (range, 16–456 months). Most patients presented with localized early-stage EC (78.7%) with predominantly low-grade histology (51.1%). Similarly, most of the patients given a diagnosis of BC presented with either DCIS or local disease (52.5%) with moderately differentiated histology (44%). When evaluating each cancer individually, both EC grade ($P=0.004$) and EC stage ($P=0.002$) had significant differences between groups 1

and 2, with the greatest difference being a large cohort of grade 3 patients in group 1 and more grade 1 patients in group 2. Greater patients with regional stage EC comprised group 1 as well (Table 1). Conversely, BC grade and stage did not exhibit the same impact (P s = 0.618 and 0.313, respectively).

The mean time interval between diagnoses was comparable at 76 months in group 1 and 74 months in group 2 (P = 0.861; Table 2). Median PFS and OS for EC were longer in group 2 (PFS, 133 vs 36 months [P = 0.001]; OS, 134 vs 51 months [P = 0.001]; Figs. 1A, B). Median PFS and OS for BC were longer in group 1 (PFS, 61 vs 114 months [P = 0.002]; OS, 63 vs 140 months [P = 0.001]; Figs. 1C, D). Combined OS, defined as date of diagnosis of the first cancer to date of the last contact, was similar in both groups at 140 and 134 months, respectively (Fig. 2A).

With comparable mean follow-up, group 2 patients were more likely to be free of disease at the last follow-up, 72% versus 51% for EC and 70% versus 60% for BC (Table 2). Cause of death was attributed to cancer in 42% and 35% of patients in groups 1 and 2, respectively.

Table 3 is a subanalysis of group 1 patients divided by the year of Food and Drug Administration (FDA) approval of tamoxifen, for primary prevention of BC and treatment of advanced BC in 1990. In the 1990 or higher subgroup, there was higher incidence of grade 3 tumors (33.3% vs 40.6%), although stage of disease was comparable. The mean time interval between the pre-1990 subgroup versus the 1990-and-beyond subgroup was statistically different at 106 versus 50 months, respectively (P = 0.042). Combined OS was also worse in the 1990-and-beyond subgroup with median survival of 166 versus 114 months, respectively (P < 0.001).^{15,16}

DISCUSSION

Nearly 287 000 women were estimated to be given a diagnosis of either BC or EC in 2014 in the United States; metachronous cancer is much less common.⁹ One study used SEER data to evaluate more than 2000 women with history of both BC and EC, and they concluded that the cumulative mortality at 5 years after the second cancer diagnosis was almost 4-fold likely to be due to BC rather than EC.¹⁷ The association of EC after treatment with adjuvant tamoxifen treatment in patients with previous BC is well established.¹⁸ Higher-grade EC was also found to be more common in this population.^{16,19} However, currently available data are limited on the time interval between diagnoses in women who develop metachronous primary cancers of breast and endometrium.

This study was an observational study of 141 women identified from the Roswell Park Cancer Institute Tumor Registry. It specifically aimed at identifying the time interval between metachronous, not synchronous, BC and EC and recognizing differences in the 2 groups, BC before EC (group 1) and EC before BC (group 2), if they exist. The results of this study may aid clinicians in counseling, treatment, and surveillance of women who are given a diagnosis of both types of cancer.

All grades and stages of EC were included. There were 59 women (41.8%) who were given a diagnosis of BC first versus 82 (58.2%) with EC first; this was in contrast to 63.9% who

were given a diagnosis of BC first in the larger observational study using the SEER database.¹⁷ That study also showed a 45-month median between cancer diagnoses but however did not specifically divide patients into the 2 groups that we have done in this study. Here, the time interval between the 2 diagnoses was found to be similar among women in groups 1 and 2. The mean time interval was 76 and 74 months, respectively, with the median being 58 and 53 months.

Although the time interval was comparable, if one evaluates EC and BC independently by group, there are some striking differences. In group 1, there were more grade 3 ECs, 37.3% versus 13.4% in group 2, that would suggest a role in the adjuvant treatment for their BC in predisposing the women to subsequent higher-grade EC. This is consistent with findings from other single institution studies confirming the hypothesis that those with history of BC are more likely to have a high-risk uterine histologic subtype,¹⁶ although the specific association with tamoxifen use and higher incidence of adverse histology is controversial.²⁰ Likewise, the higher-grade EC in our group 1 women also had a higher incidence of advanced stage disease at 35.6% than 11% in the group 2 women, as is expected. Survival from EC was much lower with PFS of 36 months and OS of 51 months versus 133 and 134 months, respectively, in group 2 patients (Table 2). Group 2 patients did not have an increased incidence of more aggressive histology of BC, and as can be seen in Table 1, stage distribution of BC was comparable in groups 1 and 2, but survival from BC was shorter both in PFS and OS in group 2, indicating that the second cancer has shorter associated survival. There is limited literature evidence describing survival after diagnosis of a second cancer, most commonly reported in Hodgkin lymphoma with 42.1% 5-year survival rate and lung cancer with median survival of only 1 year. Survival for BC was more favorable, as was seen in our study, with 76.1% reaching 5-year survival.^{21–23} Studies, including epidemiological and molecular foundations, clearly need to be performed to clarify survival in a metachronous second primary cancer versus single primary cancers in the general population and describe factors that account for differences including genetic features.²⁴

Because routine tamoxifen use for primary prevention did not receive FDA approval until 1998, adjuvant treatment of node-negative BC was approved in 1990, and 47 of our 141 patients were given a diagnosis of BC before 1990, coupled with older medical record keeping, we were unable to report with confidence whether any cases of EC in the present patients were due to tamoxifen therapy. However, by dividing the group 1 patients into pre-1990 and 1990-and-beyond groups, one could infer that a portion of the latter group received tamoxifen therapy as it became established as a standard of care. The women in the subgroup from 1990 and beyond demonstrated a greater incidence of grade 3 tumors, as noted in previous studies of tamoxifen and EC.¹⁶

More interesting was the significant difference in time interval between diagnoses of the 2 subgroups. Before 1990, the mean time to develop EC was 106 months. However, from 1990 onward, the time was reduced to a mean of 50 months ($P = 0.042$). It is important to note that the factors leading up to the diagnosis of EC in group 1 patients are not known. Presenting symptoms including evaluation of abnormal uterine bleeding and increased screening after implantation of tamoxifen or perhaps the increased doctor surveillance after having 1 cancer may have contributed to the shorter time in the subanalysis as well. In

addition, the median combined OS was shorter, 166 versus 114 months ($P < 0.001$). However, 8 patients in this group were still alive at the time of data accrual, perhaps skewing this particular conclusion.

In the current study, the risk of mortality due to other causes was comparable with the risk of mortality from either BC or EC (Table 2). Regardless of which cancer was diagnosed first, cancer-associated mortality was more likely to be from progressive or recurrent BC (group 1, 48%; group 2, 55%) rather than EC (group 1, 40%; group 2, 41%). These findings are compatible with the SEER database study, where it was demonstrated that the risk of death from EC was markedly lower if the original malignancy was EC.¹⁷ Those authors hypothesized that the women in the SEER database with BC first would likely have received tamoxifen and thus would have been at risk for developing higher-grade ECs.²⁵ Despite the potential higher grade, however, in a study of 163 women who had BC followed by EC, EC survival was comparable in both tamoxifen and nontamoxifen users. This is attributed to the fact that ECs were mostly amenable to surgery.²⁶ Our findings further support that conclusion as mortality was comparable in both groups. Although it is possible that the presence of double primary cancers could be a potential problem in the evaluation of PFS because a recurrence could come from either of the primaries, in this study, knowledge of the site of recurrence and histology of the recurring tumor made it possible to associate a recurrence with one of the primaries in most of the cases based on the chart reviews.

It is possible that other alterations in estrogen levels, not only from tamoxifen use, such as bilateral oophorectomy that is often performed at the same time as hysterectomy for surgical management of EC, could have led to a reduction in the levels of endogenous estrogen in these women, especially in the premenopausal women at the time of diagnosis of EC. Many studies have commented on the continued estradiol production of the ovaries, even in the postmenopausal state.²⁷ Rebbeck et al²⁸ demonstrated the protective effect of bilateral oophorectomy on BC carriers of *BRCA1* or *BRCA2* mutations. With this information, one can properly counsel an at-risk patient for salpingo-oophorectomy.

Several reports indicate that 5% to 10% of all BCs and 3% to 5% of all uterine cancers are thought to be genetic in origin.^{3,4} In general, patients who develop sporadic BC or EC could survive long enough to develop a secondary cancer, although it is uncommon to have metachronous cancers of this type. The potential for genetic predisposition in any dual primary cancers must be entertained. Current 5-year survival estimates for BC and EC is 89.2% and 81.5%, respectively.^{29,30} The median survival data of the 141 women who had metachronous primary diagnosis of both cancers were 140 and 134 months, for groups 1 and 2, respectively. A limitation of this study is the lack of documentation of genetic evaluation on the study patients in our database because many patients were given a diagnosis before the 1994 discovery of BRCA testing. Perhaps, the increased use of personalized medicine and genetic testing may enhance screening and alter the data reported here.

The results of our study could have direct use in the management of women at high risk of EC and/or BCs as a result of inherited predisposition. It is clear that genetic testing and subsequent institution of appropriate surveillance/preventive measures are important; however, implementing and carrying out these plans may not be straightforward. For

illustration, in 1 large comprehensive cancer program, only 54% of patients who were counseled and tested received their DNA result.³¹ The Society of Gynecologic Oncology released a statement that quoted only 24% of newly diagnosed women with ovarian cancer underwent BRCA testing in the United States when all women with ovarian cancer should be tested.³² The main reasons patients declined genetic counseling and receipt of results are insurance discrimination (44%) and fear of a positive result (27%).³¹ Our results may be helpful in guiding clinicians in counseling these high-risk women especially after they have developed one of the cancers, and the findings should be included in discussions about prognosis with women of a parallel standing. Current guidelines state that a person with BC aged 40 or younger or aged 50 or younger with a close relative, any women with ovarian cancer, and a patient with EC younger than 50 years should have a genetic risk assessment.³² If preventive surgical intervention is medically appropriate and acceptable to the patient, the findings of our study may function as a guide to the timing of intervention. It is important to encourage genetic counseling and testing when appropriate, and it is imperative to continue appropriate surveillance of the first cancer even when a new primary has been discovered.

In summary, our most important objective was to identify information that could benefit women at risk for hereditary cancer syndromes. Our study included 141 women with both BC and EC diagnosis, a relatively large number from a single institution. To this extent, our study suggests that, in such women, the time interval between diagnoses of the 2 primary cancers is not influenced by the cancer that develops first. However, the secondary cancer tends to be more aggressive, although combined survival is comparable. Undoubtedly, a much larger multicenter study is required to confirm these findings as well as determine the optimal intervention strategies to prevent 1 or both cancers in women at high risk.

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FIGURE 1.

Kaplan-Meier analysis of (A) PFS and (B) OS for EC. Group 2 patients (EC first) had a longer PFS and OS than group 1 ($P = 0.1703$ and $P < 0.001$, respectively). Kaplan-Meier analysis of (C) PFS and (D) OS for BC. Group 2 patients (EC first) had a longer PFS and shorter OS than group 1 ($P = 0.2170$ and $P = 0.0956$, respectively).

FIGURE 2.

Kaplan-Meier analysis of (A) OS for BC and EC combined. Group 2 patients (EC first) had a longer PFS than group 1 but comparable OS ($P=0.0367$ and $P=0.0651$, respectively).

TABLE 1

Patient characteristics

Overall, n (%)		59 (41.8)	82 (58.2)	
	Mean	61 (range, 26–78)	63 (range, 32–87) (P = 0.15)	
Age at diagnosis of the first cancer, y	Median	60	65	
		No. patients (%)	No. patients (%)	Total
EC grade (<i>P</i> = 0.004)	1	23 (39.0)	49 (59.8)	72
	2	14 (23.7)	22 (26.8)	36
	3	22 (37.3)	11 (13.4)	33
BC grade (<i>P</i> = 0.618)	1	14 (23.7)	17 (20.7)	31
	2	23 (39.0)	39 (47.6)	62
	3	22 (37.3)	26 (31.7)	48
EC stage (<i>P</i> = 0.002)	Local	38 (64.4)	73 (89.0)	111
	Regional	20 (33.9)	9 (11.0)	29
	Distant	1 (1.7)	0 (0)	1
BC stage (<i>P</i> = 0.313)	In situ	2 (3.4)	8 (9.8)	10
	Local	27 (45.8)	37 (45.1)	64
	Regional	29 (49.1)	33 (40.2)	62
	Distant	1 (1.7)	4 (4.9)	5

TABLE 2

Time interval and survival

	Group 1: BC First	Group 2: EC First
Time interval between diagnosis		(<i>P</i> = 0.861)
Mean	2269 d or 76 mo	2208 d or 74 mo
Median	1742 d or 58 mo	1585 d or 53 mo
Range	7–11 852 d	1–8477 d
Survival time in months		
EC PFS	36	133 (<i>P</i> = 0.001)
EC OS	51	134 (<i>P</i> = 0.001)
BC PFS (median)	114	61 (<i>P</i> = 0.001)
BC OS	140	63 (<i>P</i> = 0.001)
Combined OS	140	134 (<i>P</i> = 0.001)
Status of disease at last contact, no. patients (%)	No. patients (%)	
EC		
Unknown	6 (10.2)	13 (15.9)
NED	30 (50.8)	59 (72.0)
AD	23 (39.0)	10 (12.2)
BC		
Unknown	4 (6.8)	13 (15.9)
NED	35 (59.3)	57 (69.5)
AD	20 (33.9)	12 (14.6)
Cause of death		
From cancer		
Other cause	25* (42.4)	29 [†] (35.4)
Alive	11 (18.6)	19 (23.2)

* Twelve BC, 10 EC, and 3 not differentiated.

[†] Sixteen BC, 12 EC, and 1 not differentiated.

AD, with evidence of this disease; NED, no evidence of this disease.

TABLE 3

Subanalysis of group 1, BC first, based on the date of FDA approval of tamoxifen for primary prevention of BC and treatment of advanced BC in 1990

Patient Characteristics	BC Before 1990	BC After 1990
Overall, n (%)	27 (45.8)	32 (54.2)
Age at diagnosis of the first cancer, y		
Mean (range)	60 (47–78)	61 (26–77)
Median	59	64
No. Patients (%)		
EC grade ($P = 0.796$)	12 (44.4)	11 (34.4)
1	12 (44.4)	11 (34.4)
2	6 (22.2)	8 (25.0)
3	9 (33.3)	13 (40.6)
EC stage ($P = 0.931$)		
Local	18 (66.7)	20 (62.5)
Regional	4 (14.8)	5 (15.6)
Distant	5 (18.5)	7 (21.9)
Time interval between diagnosis		($P = 0.042$)
Mean	3185 d or 106 mo	1497 d or 50 mo
Median	2222 d or 74 mo	1244 d or 41 mo
Range	46–11 852 d	7–4025 d
Survival time in months		
EC PFS	51	26 ($P = 0.169$)
EC OS	59	27 ($P = 0.190$)
BC PFS (median)	147	109 ($P = 0.005$)
BC OS	166	114 ($P < 0.001$)
Combined OS	166	114 ($P < 0.001$)
Cause of death	14 [*] (51.9)	10 [†] (26.1)
From cancer	14 [*] (51.9)	10 [†] (26.1)
Other cause	12 (44.4)	7 (30.4)
Alive	1 (3.7)	8 [‡] (43.5)

* Seven BC, 5 EC, and 2 not differentiated.

† Four BC, 5 EC, and 1 not differentiated.

‡ One of 8 with recurrent disease at data collection.