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Decreasing secondary primary uterine cancer after breast cancer: A population-based analysis

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HIGHLIGHTS

- Number of uterine cancer (UC) after breast cancer (BC) have increased until ~1990 and then decreased thereafter.
- Uterine tumors following breast cancer are associated with high-risk tumor characteristics.
- Women with UC after BC are less likely to die from UC but more likely to die from other malignancies.

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ABSTRACT

Objective. To report population-based statistics of women with uterine cancer and a history of prior breast cancer.

Methods. This is a retrospective study examining the Surveillance, Epidemiology, and End Results Program between 1973 and 2013. Temporal trends, clinico-pathological characteristics, and survival of women with uterine cancer who had prior breast cancer were assessed.

Results. Among 237,686 women with uterine cancer, 8235 (3.5%) women had antecedent breast cancer. The number of women with uterine cancer who had a history of breast cancer increased between 1975 and 1989 (21.1-fold relative risk-increase, $P < 0.001$) and then decreased between 1989 and 2013 (relative risk-reduction [RRR] 11.1%, $P = 0.008$). The number of uterine cancer among breast cancer survivors decreased between 1990 and 2008 (RRR, 86.0%, $P < 0.001$). Women with uterine cancer and antecedent breast cancer were more likely to be older and white compared to those without a history of breast cancer ($P < 0.05$). Uterine tumors after breast cancer were more likely to have serous (10.5% *versus* 5.7%), carcinosarcoma (8.9% *versus* 4.4%), or clear cell (2.1% *versus* 1.2%) histology and present with grade 3 (30.8% *versus* 21.5%) and stage I disease (64.6% *versus* 62.5%) compared to tumors in women without breast cancer (all, $P < 0.05$). After propensity score matching, women with uterine cancer after breast cancer were less likely to die from uterine cancer (adjusted-hazard ratio [HR] 0.675) but more likely to die from other malignancies (adjusted-HR 4.090), particularly breast cancer, and had poorer overall survival (adjusted-HR 1.154) compared to those without breast cancer.

Conclusion. The diagnosis of uterine cancer after breast cancer is decreasing. While uterine tumors following breast cancer are associated with high-risk tumor characteristics, women with uterine cancer after breast cancer are more likely to die from other malignancies.

1. Introduction

Uterine cancer is the most common gynecologic malignancy while breast cancer is the most common female malignancy overall in the United States. In 2019, it is estimated that ~62,000 women will be diagnosed with uterine cancer and ~269,000 women will be diagnosed with

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breast cancer [1]. Multiple epidemiologic studies have also shown that women diagnosed with breast cancer are at increased risk of developing secondary uterine cancer [2,3].

Various factors have been proposed to explain the association between the two malignancies. First, common risk factors such as age and obesity may predispose women to developing both diseases [4–6]. Second, estrogen plays a role in the pathogenesis of breast and uterine tumors, and estrogen receptors are targets for treatment [4,5]. Tamoxifen, a selective estrogen receptor modulator used in the treatment of estrogen-receptor positive breast cancer due to its anti-estrogen actions on breast tissue, also increases the risk of secondary uterine cancer such as uterine carcinosarcoma *via* agonist properties on the endometrium [7,8]. Postmenopausal hormone replacement therapy (HRT) use may be another linkage between the two cancers. Lastly, genetic mutations such as those in the hereditary breast-ovarian cancer syndromes can be implicated in both tumors. In particular, mutations of the BRCA1 gene, the most common gene alteration associated with breast cancer, has recently been suggested to be possibly associated with increased risk of uterine cancer with serous histology [9–11].

To date, population-based trends of secondary uterine cancer after breast cancer diagnosis are lacking. It has also been hypothesized that trends and characteristics of secondary uterine cancer after breast cancer have changed over time in the United States, potentially as a result of our aging population with increasing rates of obesity as well as paradigm shifts in the hormonal treatment of breast cancer such as the use of aromatase inhibitors (AI) in place of tamoxifen in postmenopausal women with breast cancer and decreasing HRT use [12–18]. The objective of the study was to report population-based statistics of women with uterine cancer who had a prior history of breast cancer.

2. Materials and methods

2.1. Data source

This is a retrospective study examining the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. This database is the largest population-based tumor registry in the United States, covering approximately 34.6% of the population in the most recent version [19]. Launched in 1973, this database has an over four-decade history as a powerful tool to examine trends and incidences of malignancy. Patient identification, data entry, and quality control for this database are managed by registered personnel trained by the program and the National Cancer Registrars Association [20]. This study was deemed exempt from review by the University of Southern California institutional review board because of the use of publicly available deidentified data.

2.2. Eligibility

For the uterine cancer cohort, primary uterine cancer cases, including both epithelial and non-epithelial, between 1973 and 2013 were eligible for analysis. Women with uterine cancer and synchronous breast cancer and those who developed a secondary primary breast cancer after the uterine cancer diagnosis were excluded from the study. Secondary entries to the database and metastatic tumors to the uterus were also excluded from the analysis. Cervical cancer and pre-invasive uterine cancer were not included in the study. For the breast cancer cohort, primary breast cancer cases between 1973 and 2013 were eligible for analysis.

2.3. Study approach

The cases were abstracted from the database by utilizing SEER*Stat 8.3.2 (IMS Inc., Calverton, MD, USA). Two independent cohorts were generated for uterine cancer and breast cancer cases, limited to malignancy and female sex. Cases with the same study identification number were identified, and the secondary entry cases were excluded to retain only the primary entries. Then, the two datasets were linked. Patients with the same study identification numbers included in both datasets were considered secondary primary cancer (SPC) cases as previously described [21–23].

2.4. Clinical information

The following variables were abstracted from the database: *(i)* patient demographics at diagnosis (age, year and month, race/ethnicity, marital status, and registration area), *(ii)* tumor characteristics (histologic subtype, tumor grade, cancer stage, tumor size, and regional lymph node status), *(iii)* treatment types (hysterectomy and radiotherapy), and *(iv)* survival outcomes (follow-up time, vital status, and cause of death).

2.5. Study definition

The chronologic sequence of the two cancers was examined, and when the time interval between the two diagnoses was ≤2 months, the case was considered a synchronous SPC as described previously [24]. If the SPC was diagnosed >2 months after the index cancer, the case was considered a postcedent SPC. If the SPC was diagnosed >2 months prior to the index cancer, the case was considered an antecedent SPC.

The American Joint Committee on Cancer surgical-pathological staging classification schema was used for disease staging [25]. The International Classification of Diseases for Oncology third edition site/histology validation and the World Health Organization histological classification codes were used to define histologic subtype as described before [21–23]. Definition and categorization of clinico-pathological factors in this study were based on recent studies [21–23].

For survival outcomes, cause-specific survival (CSS) and overall (OS) were examined. CSS was defined as the time interval between diagnosis of the uterine cancer and death from the uterine cancer. OS was defined as the time between diagnosis of the uterine cancer and death from any reason. Cases without survival events were censored at the available last follow-up. In this program, cause of death is also externally linked with state mortality records and the National Death Index for verification [26].

2.6. Study aim

The primary objective of the analysis was to examine temporal trends of women with uterine cancer who had antecedent breast cancer. The secondary objective was to examine clinico-pathological characteristics and survival of women with uterine cancer and antecedent breast cancer compared to those without subsequent breast cancer.

2.7. Statistical consideration

Continuous variables were assessed with the Student *t*-test or the Mann-Whitney *U* test as appropriate. Differences in ordinal/categorical variables were assessed by the chi-square test. A binary logistic regression model was used for multivariable analysis. Patient demographics, tumor characteristics, and treatment type were entered in the final model. For survival analysis, the Kaplan-Meier method was used to construct survival curves, and the differences were assessed with the log-rank test. For multivariable analyses, Cox proportional hazard regression models were used to estimate hazard ratio (HR) with a 95% confidence interval (CI). Patient demographics, tumor characteristics, and treatment type were entered in the final model.

Joinpoint Trend Software (version 4.4.0.0, National Cancer Institute, Bethesda, MD, USA) was used to examine temporal trends. Single calendar years were used as time increments, and percent frequencies with CI or mean values with standard error were reported. Linear segmented

regression was used for temporal trends, and log-transformation was performed to determine annual percentage rate change (APC) of the slope with 95%CI [27].

Propensity score matching was used to adjust for background differences between the two groups (uterine cancer with antecedent breast cancer *versus* uterine cancer without secondary breast cancer) [28]. Cases were matched according to patient demographics, tumor characteristics, and treatment type. The propensity score was computed by multivariable logistic regression analysis, and all the aforementioned covariates were entered in the propensity score model. An automated algorithm was used for 1-to-1 propensity score matching between the two groups with a greedy matching method and a propensity score radius difference of 0.01 [29]. Standardized difference was examined to determine frequency distributions between the two groups in the post-matching model, and a value ≤0.10 was considered to indicate a good balance [29].

Various sensitivity analyses were performed. First, postcedent uterine cancer was examined among women with breast cancer who did not die of breast cancer and had a follow-up of ≥5 (and ≥10) years, termed cancer survivors. This is based on the rationale that diagnosis of postcedent SPC depends on duration of follow-up, and short follow-up periods may result in lead-time bias for SPC [30]. Second, trends in standardized incidence ratios (SIR) for uterine cancer and breast cancer were examined based on observed and expected population incidence [31]. Last, histology-specific and stage-specific associations were examined, as certain types of uterine cancer are more likely to be associated with breast cancer and sequelae of breast cancer treatment [10,32,33].

A $P < 0.05$ was considered statistically significant (two-tailed hypotheses). Statistical Package for Social Sciences (SPSS, version 24.0, IBM Corp, Armonk, NY, USA) was used for the statistical analysis. The STROBE guidelines were utilized to outline the observational study [34].

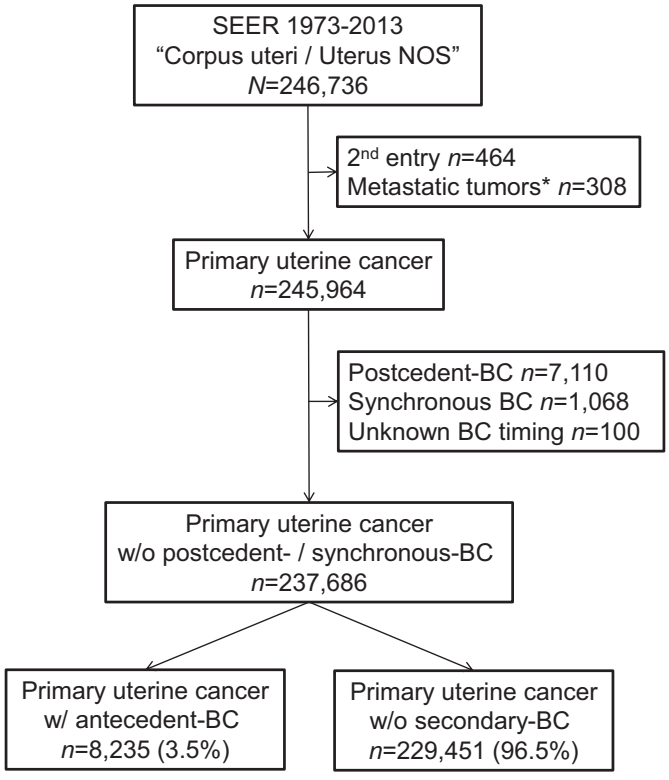

Fig. 1. Study schema. *metastatic tumors to the uterus. Abbreviation: NOS, not otherwise specified; BC, breast cancer, w/ with; and w/o, without.

3. Results

The study schema is shown in Fig. 1. There were 246,736 women with uterine cancer identified during the study period. Among 245,964 women with primary uterine cancer, those with postcedent breast cancer ($n = 7110$), synchronous breast cancer ($n = 1068$), and breast cancer of unknown chronology ($n = 100$) were excluded, and the remaining 237,686 uterine cancer women represented the study population. Among those, there were 8235 (3.46%, 95%CI 3.39–3.54) women who had antecedent breast cancer. The median time from antecedent breast cancer diagnosis to uterine cancer diagnosis was 6.0 years (interquartile range, 2.9–10.6).

Patient demographics related to antecedent breast cancer are shown in Table 1. Women with uterine cancer who had antecedent breast cancer were more likely to be older (mean, 69.5 *versus* 62.8), white (81.4% *versus* 76.8%), Central U.S. residents (25.7% *versus* 23.3%), and married (51.7% *versus* 47.9%) compared to those without breast cancer on multivariable analysis (all, $P < 0.05$). Uterine tumors in the antecedent breast cancer group were more likely to have serous (10.5% *versus* 5.7%), carcinosarcoma (8.9% *versus* 4.4%), clear cell (2.1% *versus* 1.2%), or mixed type (4.2% *versus* 3.0%) histology and less likely to have sarcoma histology (2.8% *versus* 4.4%) compared to uterine tumors in the non-breast cancer group (all, $P < 0.05$).

Uterine tumors after breast cancer were more likely to present with grade 3 (30.8% *versus* 21.5%) and either stage I (64.6% *versus* 62.5%) or stage III disease (9.9% *versus* 8.6%) compared to tumors unrelated to breast cancer (all, $P < 0.05$). Uterine tumors after breast cancer were also slightly more likely to have pelvic nodal metastasis (9.2% *versus* 8.0%) with a higher ratio of positive lymph nodes (median, 25.0% *versus* 20.0%) (both, $P < 0.05$). Women with uterine cancer who had antecedent breast cancer were more likely to undergo hysterectomy (85.6% *versus* 78.0%) but less likely to undergo external beam radiotherapy (18.4% *versus* 20.6%) compared to those with uterine cancer but without breast cancer (both, $P < 0.05$).

Trends in uterine cancer and antecedent breast cancer were examined. Women with uterine cancer who had antecedent breast cancer were older than those without a history of breast cancer, and this age difference widened during the study period (mean age differences: 4.9 in 1974, $P = 0.233$, and 6.6 in 2013, $P < 0.001$; Fig. 2A). The number of women with uterine cancer who had antecedent breast cancer increased between 1975 and 1989 from 0.2% to a peak of 4.4% in 1989 (21.1-fold relative risk-increase for SIR, APC 3.6, $P < 0.001$; Fig. 2B). However, between 1989 and 2013, the number of women with uterine cancer and antecedent breast cancer decreased to 3.7% by 2013 (relative risk-reduction [RRR] for SIR 11.1%, APC -0.2, $P = 0.008$). At the peak year, 4.4% of uterine cancer women had antecedent breast cancer that increased from 0.2% in the beginning of the study and decreased to 3.7% in the most recent year (Supplemental Fig. S1).

There were 568,841 women with breast cancer who did not have antecedent or synchronous uterine cancer and who had ≥5 years of follow-up after breast cancer diagnosis (median 10.8 years, interquartile range 7.6–15.2). There were 6438 (1.1%, 95%CI 1.1–1.2) women who developed postcedent uterine cancer during follow-up. The number of women with breast cancer who developed postcedent uterine cancer decreased between 1990 and 2008 (RRR for SIR, 86.0%, APC –2.4 between 1990 and 2000, APC –8.7 between 2000 and 2008, $P < 0.001$; Figure 2B). During the time, the number of women with breast cancer who developed postcedent uterine cancer decreased from 1.7% to 0.4% (Supplemental Fig. S1).

Propensity score matching was performed (Table 2), and a total of 16,470 women were selected for further analysis. Clinico-pathological factors were well-balanced between the two groups after the matching (all, standardized difference ≤0.10; Supplemental Fig. S2). The median follow-up time was 5.6 years (interquartile range, 2.3–10.6). There were 8346 deaths recorded during follow-up, including 3137 deaths from uterine cancer, 1872 deaths from malignancies other than uterine

Table 1
Patient demographics.

Characteristic	No BC	Antecedent-BC	Adjusted-OR (95% CI)‡	*P*-value
Number	$n = 229{,}451$	$n = 8235$		
Age	62.8 (±12.7)	69.5 (±11.3)	1.041 (1.039–1.043)	<**0.001**
Year				<**0.001**
Before 1980	20,066 (8.7%)	117 (1.4%)	1	
1980–1989	26,180 (11.4%)	638 (7.7%)	3.089 (2.434–3.920)	<**0.001**
1990–1999	37,651 (16.4%)	1799 (21.8%)	4.463 (3.497–5.696)	<**0.001**
2000–2009	96,409 (42.0%)	3758 (45.6%)	3.830 (3.007–4.878)	<**0.001**
2010 or later	49,145 (21.4%)	1923 (23.4%)	3.803 (2.978–4.857)	<**0.001**
Race/ethnicity				<**0.001**
White	176,199 (76.8%)	6700 (81.4%)	1.340 (1.225–1.465)	<**0.001**
Black	18,096 (7.9%)	583 (7.1%)	1	
Hispanic	18,489 (8.1%)	413 (5.0%)	0.925 (0.811–1.056)	0.248
Asian	12,138 (5.3%)	439 (5.3%)	1.508 (1.322–1.720)	<**0.001**
Others	4529 (2.0%)	100 (1.2%)	1.017 (0.817–1.266)	0.879
Registry area				<**0.001**
West	118,199 (51.5%)	4090 (49.7%)	1	
Central	53,528 (23.3%)	2119 (25.7%)	1.221 (1.154–1.291)	<**0.001**
East	57,724 (25.2%)	2026 (24.6%)	0.999 (0.944–1.058)	0.974
Marital status				<**0.001**
Single	33,940 (14.8%)	924 (11.2%)	1	
Married	118,605 (51.7%)	3946 (47.9%)	1.121 (1.041–1.207)	**0.002**
Others	66,992 (29.2%)	2967 (36.0%)	1.017 (0.940–1.110)	0.683
Unknown	9914 (4.3%)	398 (4.8%)	1.159 (1.026–1.310)	**0.018**
Histology				<**0.001**
Endometrioid	166,125 (72.4%)	5237 (63.6%)	1	
Serous	13,178 (5.7%)	865 (10.5%)	1.645 (1.516–1.786)	<**0.001**
Clear cell	2800 (1.2%)	177 (2.1%)	1.437 (1.225–1.685)	<**0.001**
Carcinosarcoma	10,026 (4.4%)	735 (8.9%)	1.749 (1.598–1.914)	<**0.001**
Sarcoma	10,101 (4.4%)	231 (2.8%)	0.867 (0.753–0.999)	**0.048**
Mixed	6985 (3.0%)	348 (4.2%)	1.299 (1.158–1.458)	<**0.001**
Others	20,236 (8.8%)	642 (7.8%)	1.038 (0.950–1.134)	0.409
Grade				<**0.001**
1	79,821 (34.8%)	2349 (28.5%)	1	
2	59,831 (26.1%)	1775 (21.6%)	0.920 (0.862–0.981)	**0.011**
3	49,424 (21.5%)	2535 (30.8%)	1.330 (1.241–1.425)	<**0.001**
Unknown	40,375 (17.6%)	1576 (19.1%)	1.214 (1.127–1.308)	<**0.001**
Stage				<**0.001**
I	143,440 (62.5%)	5319 (64.6%)	1.332 (1.218–1.457)	<**0.001**
II	9697 (4.2%)	367 (4.5%)	1.102 (0.964–1.260)	0.154
III	19,705 (8.6%)	818 (9.9%)	1.173 (1.053–1.306)	**0.004**
IV	17,518 (7.6%)	688 (8.4%)	1	
Unknown	39,091 (17.0%)	1043 (12.7%)	1.301 (1.169–1.448)	<**0.001**
Tumor size				0.122
≤2 cm	20,801 (9.1%)	835 (10.1%)	1.084 (1.001–1.175)	**0.049**
>2 cm	77,902 (34.0%)	3187 (38.7%)	1	
Unknown	130,748 (57.0%)	4213 (51.2%)	1.005 (0.953–1.059)	0.856
Pelvic lymph node*				
No metastasis	169,964 (92.0%)	6311 (90.8%)		
Metastasis	14,839 (8.0%)	641 (9.2%)		
Pelvic LNR**	20.0 (9.1–50.0)	25.0 (9.5–60.0)		
Hysterectomy				<**0.001**
No	19,002 (8.3%)	838 (10.2%)	1	
Yes	178,867 (78.0%)	7049 (85.6%)	1.194 (1.091–1.306)	<**0.001**
Unknown	31,582 (13.8%)	348 (4.2%)	0.794 (0.665–0.948)	**0.011**
Lymphadenectomy†				**0.002**
No	91,514 (39.9%)	3707 (45.0%)	1	
Yes	102,786 (44.8%)	3899 (47.3%)	0.996 (0.945–1.050)	0.890
Unknown	35,151 (15.3%)	629 (7.6%)	0.778 (0.676–0.895)	<**0.001**
Radiotherapy				<**0.001**
None	158,263 (69.0%)	5906 (71.7%)	1	
External beam	47,264 (20.6%)	1512 (18.4%)	0.842 (0.792–0.896)	<**0.001**
Brachytherapy	12,428 (5.4%)	589 (7.2%)	1.073 (0.980–1.175)	0.129
Both	6645 (2.9%)	89 (1.1%)	0.922 (0.737–1.153)	0.476
Unknown	4851 (2.1%)	139 (1.7%)	0.719 (0.602–0.859)	<**0.001**

Mean (±standard deviation), median (interquartile range), or number (percent per column) is shown. All the listed variables showed statistical significance on univariable analysis ($P < 0.05$), a binary logistic regression model was used for multivariable analysis. Pelvic lymph node status and lymph node ratio were not entered in the model. Significant *P*-values are emboldened. *among staged cases with known results. **among node positive cases. † pelvic lymph nodes. ‡ Lymph node status was not entered in the model due to multicollinearity for stage. Abbreviations: BC, breast cancer; OR, odds ratio; CI, confidence interval; and LNR, lymph node ratio.

cancer such as breast cancer ($n = 825$), lung ($n = 163$), colorectal ($n = 135$), and ovarian ($n = 117$) cancers, and 1688 deaths from cardiovascular disease.

On multivariable analysis (Table 3), women with uterine cancer who had antecedent breast cancer had superior CSS (adjusted-HR 0.675, $P < 0.001$; Fig. 2C) but had poorer OS (adjusted-HR 1.154, $P < 0.001$; Fig. 2D) compared to those without breast cancer. Among 15,408 women with endometrial cancer, women who had antecedent breast cancer were 30% less likely to die from uterine cancer (adjusted-HR 0.700, $P < 0.001$) but 18% more likely to die from any cause (adjusted-HR 1.184, $P < 0.001$) compared to those without secondary breast cancer (Table 3).

Similar trends were observed for endometrioid-type endometrial cancer (adjusted-HR for CSS 0.65, $P < 0.001$; and for OS 1.271, $P < 0.001$; Table 3). Among serous, carcinosarcoma, and mixed types, women with antecedent-BC had superior CSS than those without breast cancer (all, $P < 0.05$; Table 3). When uterine tumors were stratified by stage, women with antecedent breast cancer had superior CSS but poorer OS compared to women without a history of breast cancer in stage I-III disease (all, $P < 0.05$; Table 4).

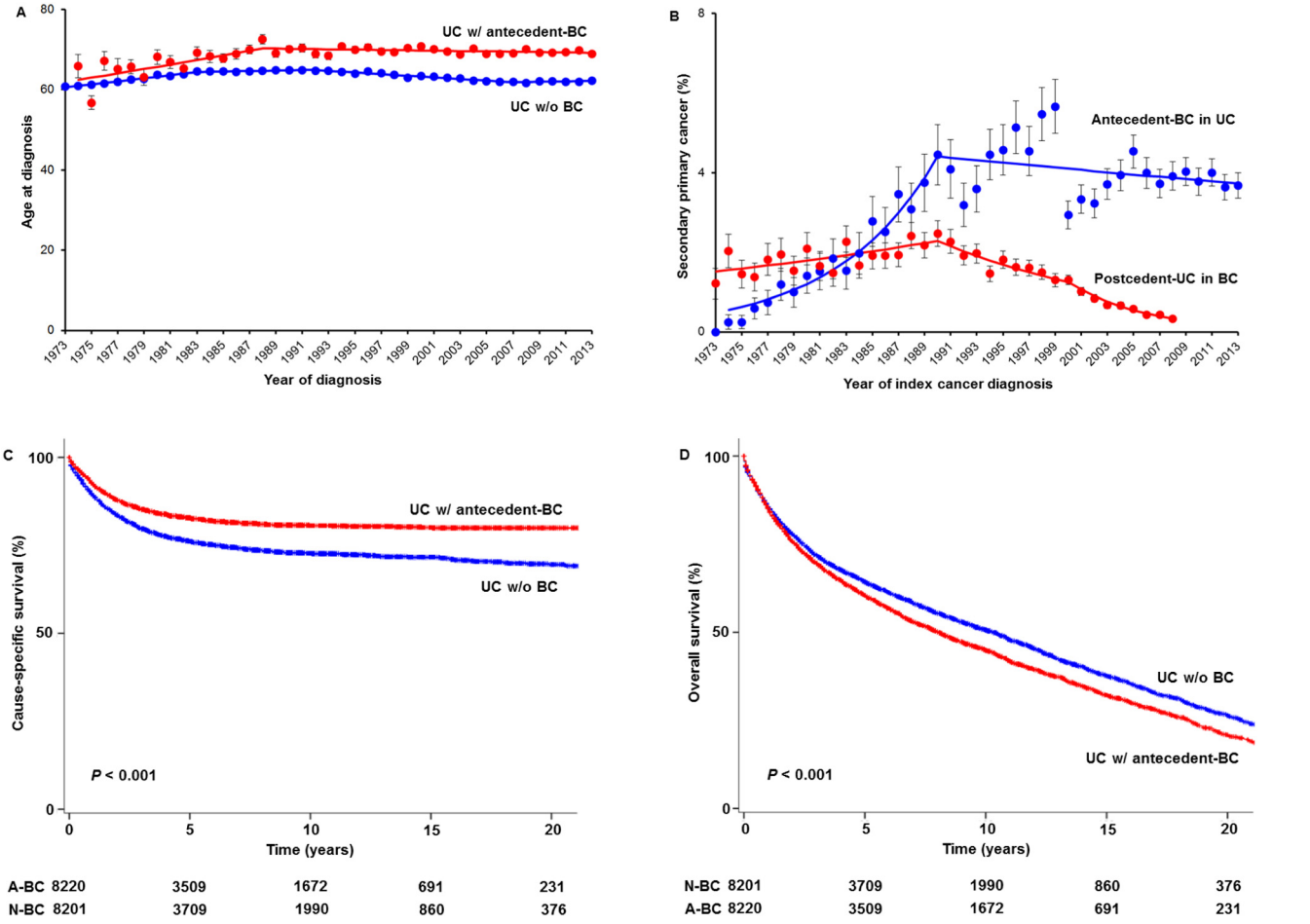

Fig. 2. Trends and outcomes of uterine cancer with antecedent breast cancer. **A**) Age at cancer diagnosis per year. Dots represent mean, and bars represent standard error. Solid lines represent model lines. **B**) SIR for antecedent-BC among uterine cancer and postcedent uterine cancer among BC survivors are shown per year. Dots represent percentages, and bars represent confidence intervals. Solid lines represent model lines. **C**) Cause-specific survival from uterine cancer and **D**) overall survival are shown for cases with antecedent breast cancer compared to cases without secondary breast cancer. Abbreviations: w/ with; w/o without; SIR, standardized incidence ratio; BC, breast cancer; and UC, uterine cancer.

Causes of death were further examined (Table 3). Women with uterine cancer and antecedent breast cancer were more likely to die from malignancies other than uterine cancer (adjusted-HR 4.091, $P < 0.001$). Even when stratified further by type, stage, and histology (Supplemental Table S1), women with uterine cancer and antecedent breast cancer were still more likely to die from breast cancer (adjusted-HR 40.442, $P < 0.001$) or from other malignancies (adjusted-HR 1.997, $P < 0.001$) compared to those without breast cancer.

4. Discussion

Our analysis of U.S. population-based tumor registry found that the diagnosis of uterine cancer in women with a history of breast cancer is decreasing in recent years. Moreover, while uterine tumors following breast cancer are associated with high-risk tumor characteristics, women with uterine cancer and antecedent breast cancer are less likely to die from uterine cancer but more likely to die from other malignancies.

The number of women with uterine cancer who had antecedent breast cancer started increasing in the early-1970s; concurrently, the Food and Drug Administration (FDA) approved tamoxifen for use in breast cancer treatment in 1977. Since that time, multiple studies have reported the association between tamoxifen use and uterine cancer, particularly for the high-grade histology types [7,8]. The temporal trends and tumor characteristics in women with uterine cancer who had antecedent breast cancer identified in this study also support a causal role of tamoxifen in this population.

Subsequently, in the early-1990s, the number of women with uterine cancer women and antecedent breast cancer reached a peak and then started to decrease. At that time, there was mounting evidence that adjuvant hormonal therapy with AIs was also effective in postmenopausal women with hormone receptor-positive breast cancer, and the FDA approved the use of AIs for this purpose in 2005 [14,35]. Generally, the risk of uterine cancer with AIs is lower compared to tamoxifen, and the American Society of Clinical Oncology (ASCO) has incorporated AI monotherapy into their practice guidelines as an acceptable option for adjuvant therapy in postmenopausal women with breast cancer [36]. Thus, we speculate that AIs largely replaced tamoxifen in this population, resulting in decreasing trends of postcedent uterine cancer after breast cancer in recent years.

Additionally, the increasing utilization of genetic testing for BRCA may have played a role in the decreasing risk of postcedent uterine cancer [37]. BRCA carriers are recommended to undergo risk-reducing salpingo-oophorectomy (RRSO) for ovarian cancer prevention or to reduce mortality from breast cancer. More than half of women who undergo RRSO also choose to undergo hysterectomy in addition (55.8%), ~40% of which are recommended by care providers [9,38,39]. In their study, RRSO with hysterectomy resulted in lower all-cause mortality than RRSO or hysterectomy alone among BRCA carriers; however, their study did not examine incidence of uterine cancer after uterine preservation or uterine cancer-specific mortality [38].

Currently, whether BRCA mutations increase the risk of uterine cancer remains controversial. A recent prospective cohort study showed

Table 2
Demographics after propensity score matching.

Characteristic	No BC	Antecedent-BC	*SD*
Number	$n = 8235$	$n = 8235$	
Age	69.5 (±11.8)	69.5 (±11.3)	0.003
Year			0.003
Before 1980	115 (1.4%)	117 (1.4%)	
1980–1989	645 (7.8%)	638 (7.7%)	
1990–1999	1823 (2.1%)	1799 (21.8%)	
2000–2009	3718 (45.1%)	3758 (45.6%)	
2010 or later	1934 (23.5%)	1923 (23.4%)	
Race/ethnicity			0.023
White	6746 (81.9%)	6700 (81.4%)	
Black	596 (7.2%)	583 (7.1%)	
Hispanic	398 (4.8%)	413 (5.0%)	
Asian	422 (5.1%)	439 (5.3%)	
Others	76 (0.6%)	100 (1.2%)	
Registry area			0.020
West	4023 (48.9%)	4090 (49.7%)	
Central	2118 (25.7%)	2119 (25.7%)	
East	2094 (25.4%)	2026 (24.6%)	
Marital status			0.001
Single	888 (10.8%)	924 (11.2%)	
Married	4002 (48.6%)	3946 (47.9%)	
Others	2971 (36.1%)	2967 (36.0%)	
Unknown	374 (4.5%)	398 (4.8%)	
Histology			0.007
Endometrioid	5297 (64.3%)	5237 (63.6%)	
Serous	860 (10.4%)	865 (10.5%)	
Clear cell	150 (1.8%)	177 (2.1%)	
Carcinosarcoma	703 (8.5%)	735 (8.9%)	
Sarcoma	227 (2.8%)	231 (2.8%)	
Mixed	337 (4.1%)	348 (4.2%)	
Others	661 (8.0%)	642 (7.8%)	
Grade			0.007
1	2369 (28.8%)	2349 (28.5%)	
2	1768 (21.5%)	1775 (21.6%)	
3	2548 (30.9%)	2535 (30.8%)	
Unknown	1550 (18.8%)	1576 (19.1%)	
Stage			−0.007
I	5302 (64.4%)	5319 (64.6%)	
II	356 (4.3%)	367 (4.5%)	
III	831 (10.1%)	818 (9.9%)	
IV	681 (8.3%)	688 (8.4%)	
Unknown	1065 (12.9%)	1043 (12.7%)	
Tumor size			0.005
≤2 cm	877 (10.6%)	835 (10.1%)	
>2 cm	3136 (29.1%)	3187 (38.7%)	
Unknown	4222 (51.3%)	4213 (51.2%)	
Hysterectomy			0.002
No	827 (10.0%)	838 (10.2%)	
Yes	7064 (85.8%)	7049 (85.6%)	
Unknown	344 (4.2%)	348 (4.2%)	
Lymphadenectomy			0.003
No	3751 (45.5%)	3707 (45.0%)	
Yes	3824 (46.4%)	3899 (47.3%)	
Unknown	660 (8.0%)	629 (7.6%)	
Radiotherapy			0.012
None	5836 (70.9%)	5906 (71.7%)	
External beam	1565 (19.0%)	1512 (18.4%)	
Brachytherapy	611 (7.4%)	589 (7.2%)	
Both	87 (1.1%)	89 (1.1%)	
Unknown	136 (1.7%)	139 (1.7%)	

Mean (±standard deviation) or number (percent per column) is shown. SD ≤0.10 indicates a good balance between the two groups. Abbreviations: BC, breast cancer; and SD, standardized difference.

that BRCA1 mutations were associated with a ~20-fold increased risk of serous-type uterine cancer, but the incidence remains low (<1%) [10,39]. Another study showed that the frequency of BRCA mutations in type II uterine cancer was higher than in type I (0.9% *versus* 0.1%) [11]. While the association between BRCA and uterine cancer is yet well-established, it is speculated that as more BRCA carriers with breast cancer chose to undergo prophylactic hysterectomy at the time of RRSO, the resultant reduced risk of secondary uterine cancer may have contributed to decreasing trends in postcedent uterine cancer after breast cancer [36]. Further study on whether BRCA mutations increase the risk of uterine cancer is warranted.

Moreover, decreasing postmenopausal HRT use occurred around the late-1990s and early-2000s reflecting the results of large trials clearly changed the landscape of the breast cancer epidemiology. [17,18,40,41] Since then, multiple population-based studies have demonstrated that decreasing HRT use has resulted in decreasing postmenopausal breast cancer incidence [17,18]. Parallel to this decrease in breast cancer incidence, the incidence of uterine cancer decreased until mid-2000s [42]. Thus, it is speculated that decreasing postmenopausal HRT use ultimately attributed to the decreasing incidence of both cancers.

Another possibility to explain decreasing secondary uterine cancer trends after breast cancer may be the use of the levonorgestrel-releasing intra-uterine system (LNG-IUS). A recent study concluded that the LNG-IUS may reduce the risk of benign or pre-cancerous uterine pathology in women with breast cancer on tamoxifen [43]. While would be intriguing to examine if LNG-IUS use further decreases the incidence of secondary uterine cancer, the LNG-IUS is currently considered contra-indicated in women with known breast cancer [44].

Uterine cancer-specific prognosis after breast cancer was superior compared to that for uterine cancer without secondary breast cancer. This association was also seen when stratified by histology or stage. We do not know the exact causality of this finding. With respect to tamoxifen use, prior analyses showed that among women with non-endometrioid uterine cancer, long-term tamoxifen users had higher uterine cancer-specific mortality compared to non-users, but more recent studies have shown no association [45–47]. As our study does not include information on tamoxifen use, we were not able to assess the impact of tamoxifen in particular on uterine cancer-specific mortality. It is speculated that tumor biology of or genetic alterations in uterine tumors related to tamoxifen may be different from uterine tumors unrelated to tamoxifen, and future study is warranted to prove this hypothesis.

On the contrary, OS in women with uterine cancer and antecedent breast cancer was poorer compared to those without secondary breast cancer. Detailed analyses suggested that women with uterine cancer and antecedent breast cancer were more likely to die from malignancies other than uterine cancer compared to those without secondary breast cancer, resulting in poorer OS. And, notably, more than half of these deaths were not from breast cancer. This finding adds new information to literature and indicates a relatively high percentage of women with breast cancer who had postcedent uterine cancer will develop yet a third malignancy. While SPC after breast cancer or uterine cancer has been well studied, third primary cancer in this population has not. Because the statistics for possible third primary cancer reported in this study were based on cause of death information in the uterine cancer dataset, further investigation by examining multiple cancer datasets would be useful to compile the actual incidence of third primary cancers.

The main strengths of our study include that this is a population-based study including large sample size and that we add new information in the literature for secondary uterine cancer following breast cancer. Propensity score matching and various sensitivity analyses enriched the robustness of analytic quality. There are various limitations in this study. First, selection bias is inherent to the retrospective nature of this population study. As this database does not cover the entire U.S. geographic area, relocation of women from a data-covered area to a non-covered area may have rendered us unable to detect some SPC events.

Moreover, while we proposed that both genetic and treatment factors contributed to the trends observed in this study, data to support these speculations is missing in this study. For instance, this database does not include genetic testing results or information on the use of tamoxifen or AIs, the LNG-IUS, postmenopausal HRT, or prophylactic hysterectomy. Thus, while these cause-and-effect relations sound plausible as discussed above, the lack of information limits interpretation of actual study results.

Table 3
Survival analysis for uterine cancer with antecedent breast cancer.

Characteristic	Cause-specific survival		Overall survival		Other malignancy†	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
All cases						
Non-BC	1		1		1	
Antecedent-BC	0.675 (0.628–0.725)	<**0.001**	1.154 (1.105–1.205)	<**0.001**	4.091 (3.657–4.576)	<**0.001**
Endometrial						
Non-BC	1		1		1	
Antecedent-BC	0.700 (0.648–0.755)	<**0.001**	1.184 (1.132–1.239)	<**0.001**	4.030 (3.590–4.526)	<**0.001**
Endometrioid						
Non-BC	1		1		1	
Antecedent-BC	0.659 (0.584–0.743)	<**0.001**	1.271 (1.199–1.347)	<**0.001**	4.074 (3.539–4.690)	<**0.001**
Serous						
Non-BC	1		1		1	
Antecedent-BC	0.724 (0.611–0.859)	<**0.001**	0.985 (0.871–1.113)	0.803	3.408 (2.447–4.746)	<**0.001**
Clear cell						
Non-BC	1		1		1	
Antecedent-BC	0.882 (0.597–1.303)	0.527*	1.105 (0.834–1.465)	0.487*	3.388 (1.469–7.815)	**0.004***
Carcinosarcoma						
Non-BC	1		1		1	
Antecedent-BC	0.768 (0.658–0.898)	**0.001**	1.085 (0.957–1.230)	0.203	4.172 (2.889–6.023)	<**0.001***
Mixed						
Non-BC	1		1		1	
Antecedent-BC	0.596 (0.413–0.862)	**0.006***	0.938 (0.723–1.219)	0.634*	5.620 (2.374–13.302)	<**0.001***
Sarcoma						
Non-BC	1		1		1	
Antecedent-BC	0.589 (0.437–0.793)	<**0.001***	1.002 (0.799–1.256)	0.989*	5.497 (2.886–10.468)	<**0.001***

Cox proportional hazard regression models for multivariable analysis are shown. Covariates adjusted for the association of uterine cancer with antecedent-BC and survival included: patient age (continuous), year at diagnosis (<1980, 1980–9, 1990–9, 2000–9, and ≥2010), registry area (West, Central, and East), race/ethnicity (White, Black, Hispanic, Asian, and others), marital status (single, married, and others), histology (endometrioid, serous, clear cell, carcinosarcoma, sarcoma, mixed, and others), cancer stage (I, II, III, IV, and unknown), tumor grade (1, 2, 3, and unknown), and tumor size (≤2, >2 cm, and unknown), hysterectomy (no, yes, and unknown), and lymphadenectomy (no, yes, and unknown), and radiotherapy (no, external beam with or without brachytherapy, brachytherapy alone, and unknown). Significant *P*-values are emboldened. *unadjusted due to insufficient event number for analysis. †malignancy other than uterine cancer. Abbreviations: BC, breast cancer; HR, hazard ratio; and CI, confidence interval.

This database also does not have information on cancer recurrence, and thus, complete risk assessments of oncologic outcomes were not possible in this study. For instance, 44% of those who had a cause of death other than uterine cancer died of breast cancer. While it is unknown if these were recurrent or primary breast cancers due to lack of recurrence information, these cases most likely represent recurrent breast cancer.

In summary, postcedent uterine cancer after breast cancer is not rare and approximately one in 30 women with uterine cancer has a history of prior breast cancer. However, diagnosis of uterine cancer following breast cancer seems to be decreasing over the past decades, which is encouraging for both patients and care providers. Further study is also warranted to validate these results in a different population.

Author contributions

Conceptualization: K.M.; Data curation: H.M.; Formal analysis: K.M.; Funding acquisition: K.M., L.D.R.; Investigation: all authors; Methodology: K.M.; Project administration: K.M.; Resources: H.M.; Software: H.M., K.M.; Supervision: K.M., J.D.W.; Validation: K.M.; Visualization: K.M.; Writing - original draft: K.M.; Writing - review & editing: all authors.

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Table 4
Survival analysis for uterine cancer with antecedent breast cancer (stage-specific).

Characteristic	Cause-specific survival		Overall survival		Other malignancy†	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Stage I						
Non-BC	1		1		1	
Antecedent-BC	0.590 (0.512–0.679)	<**0.001**	1.200 (1.129–1.275)	<**0.001**	3.785 (3.263–4.391)	<**0.001**
Stage II						
Non-BC	1		1		1	
Antecedent-BC	0.674 (0.488–0.932)	**0.017**	1.154 (1.016–1.312)	**0.028**	4.751 (2.911–7.756)	<**0.001***
Stage III						
Non-BC	1		1		1	
Antecedent-BC	0.845 (0.717–0.996)	**0.045**	1.154 (1.016–1.312)	**0.028**	2.978 (2.153–4.118)	<**0.001**
Stage IV						
Non-BC	1		1		1	
Antecedent-BC	0.741 (0.645–0.852)	<**0.001**	1.021 (0.908–1.148)	0.725	8.032 (5.176–12.463)	<**0.001**

Cox proportional hazard regression models for multivariable analysis are shown. Covariates adjusted for the association of uterine cancer with antecedent-BC and survival included: patient age (continuous), year at diagnosis (<1980, 1980–9, 1990–9, 2000–9, and ≥ 2010), registry area (West, Central, and East), race/ethnicity (White, Black, Hispanic, Asian, and others), marital status (single, married, and others), histology (endometrioid, serous, clear cell, carcinosarcoma, sarcoma, mixed, and others), cancer stage (I, II, III, IV, and unknown), tumor grade (1, 2, 3, and unknown), and tumor size (≤2, >2 cm, and unknown), hysterectomy (no, yes, and unknown), and lymphadenectomy (no, yes, and unknown), and radiotherapy (no, external beam with or without brachytherapy, brachytherapy alone, and unknown). Significant *P*-values are emboldened. *unadjusted due to insufficient event number for analysis. †malignancy other than uterine cancer. Abbreviations: BC, breast cancer; HR, hazard ratio; and CI, confidence interval.

Declaration of Competing Interest

Consultant, Tesaro and Clovis Oncology (J.W.); honorarium, Chugai, book editorial, Springer, meeting expense, VBL therapeutics (K.M.); and consultant, Tempus Lab (L.D.R.); none for others.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.05.014.

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