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Long-term, adverse genitourinary outcomes among endometrial cancer survivors in a large, population-based cohort study

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Abstract

Objective—With the increasing incidence of endometrial cancer, the high survival rate, and the large number of endometrial cancer survivors, investigations of long-term genitourinary outcomes are important for the management of these outcomes among endometrial cancer survivors.

Methods—Cohorts of 2,648 endometrial cancer survivors diagnosed in the state of Utah between 1997–2012 and 10,503 general population women were identified. All ICD-9 diagnosis codes

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were collected from the state's two largest healthcare systems and statewide databases. Multivariate Cox regression models were used to estimate hazard ratios at 1–5 years and >5–10 years after endometrial cancer diagnosis for genitourinary outcomes.

Results—Endometrial cancer survivors were at elevated risk for urinary system disorders between 1–5 years (HR: 1.64, 95% CI: 1.50–1.78) and >5–10 years (HR: 1.40, 95% CI: 1.26–1.56) and genital organ disorders between 1–5 years (HR: 1.71, 95% CI: 1.58–2.03) and >5–10 years (HR: 1.33, 95% CI: 1.19–1.49). Significantly elevated risk was observed among endometrial cancer survivors for renal failure, chronic kidney disease, urinary tract infections, and nonmalignant breast conditions, persisting between >5–10 years. Between 1–5 years after cancer diagnosis, those with higher stage, higher grade, older age and treated with radiation or chemotherapy were at higher risk for urinary disorders.

Conclusions—Endometrial cancer survivors were at higher risk for many genitourinary outcomes compared to women from the general population. This study presents evidence suggesting the necessity of increased monitoring and counseling for genitourinary disorders for endometrial cancer patients both immediately after treatment cessation and for years afterwards.

Introduction

In the United States, endometrial cancer is the second most common cancer among female cancer survivors, and the fourth most commonly diagnosed cancer among women[1]. Since 1988, Incidence rates for women under the age of 50 have increased by 1.3% per year and by 1.9% per year among women over the age of 50 since 2005 [2]. The mortality rate due to endometrial cancer has increased by 1.1% each year over the last 15 years. There are an estimated 757,000 endometrial cancer survivors in the United States today [3]. The current 5-year survival rate in the United States is 81.7% for endometrial cancer overall, 95.3% for women diagnosed with stage I disease, 68.2% in women diagnosed with stage II and III disease, and 16.9% for women diagnosed with IV [2].

A wide range of acute and long-term adverse genitourinary outcomes that are often directly related to treatment with surgery and/or radiotherapy have been observed among endometrial cancer survivors [4]. Following treatment with radiation therapy (RT), long-term damage to the genital organs has been well documented [5–7]. RT can induce damage to connective tissue of the vagina, chronic vaginal discharge, necrosis, ulceration, fistula formation, thinning and atrophy of the vaginal epithelium, fibrosis, and loss of elasticity of the vagina. Individuals treated with external beam radiation therapy (EBRT) can suffer chronic bony pain secondary to hip fracture that affects locomotion [6].

Many prior investigations of genitourinary outcomes among endometrial cancer survivors have often lacked disease diagnoses to capture outcomes, examined symptoms that are secondary to more clinically relevant genitourinary conditions, or were conducted using small sample sizes or restrictive populations from clinical trials [5–7]. Large cohort studies that are sufficiently powered to examine a large number of genitourinary outcomes from reliable sources such as electronic medical records that have a detrimental effect on quality of life and mortality are necessary to better understand the experience of endometrial cancer survivors years after diagnosis. Thus, the goal of the current study was to examine the risk

for long-term, adverse genitourinary diseases among endometrial cancer survivors compared to the general population.

Methods

Data Collection

Using the Utah Population database (UPDB), we identified women diagnosed with endometrial cancer in the state of Utah between 1997–2012. The eligibility criteria were that endometrial cancer survivors be aged 18+ at time of diagnosis, had a first invasive primary diagnosis of endometrial cancer (SEER ICD-O-3 codes: C54.0–C55.9), had at least one year of follow-up time after diagnosis, lived in the state of Utah for at least one year after diagnosis, and had stage and grade included in data from the statewide SEER Utah Cancer Registry. The inclusion of stage and grade was important for this population because of their potential role in risk for long-term, adverse genitourinary outcomes. We classified type I endometrial cancer as histological subtypes adenocarcinoma, endometrioid, mucinous adenocarcinoma, and adenocarcinoma with squamous differentiation (ICD-O-3 morphology codes: 8140, 8260, 8380, 8382, 8480, 8482, 8560, and 8570) and type II endometrial cancer as clear-cell carcinomas and papillary serous carcinomas (ICD-O-3 morphology codes: 8310, 8441, and 8460) [8]. Individuals in the endometrial cancer survivors cohort were matched on birth year and birth state with up to five individuals from the general population in Utah. Birth state was matched on since more information would be available on individuals born in Utah in the UPDB.

To capture long-term genitourinary outcomes, we used all ICD-9 diagnosis codes collected from the electronic data warehouses at the University of Utah Health Sciences Center and Intermountain Healthcare (the two largest healthcare providers in the state of Utah) as well as all statewide ambulatory inpatient and surgery records from the Utah Department of Health. Records from these sources as well as data from the Utah Cancer Registry, Utah Department of Health, vital records, and Utah Driver's License were linked using the Utah Population Database. We limited our final sample to those diagnosed after 1997 because widespread use of electronic medical records among the data sources used in this study did not start until 1996. This allowed at least one year prior to endometrial cancer diagnosis to capture prevalent diagnoses of the genitourinary outcomes of interest in this study.

Categorization of Outcomes

We used the Healthcare Cost and Utilization Project's Clinical Classification Software [9] to collapse ICD-9 codes into discrete diagnosis categories with four levels of specificity. Diseases of the genitourinary system (level one) according to this classification were used in this analysis. Level two outcomes included diseases of the urinary system and disease of the genital organs. Level three and four outcomes were more specific conditions within these categories. Examples of this hierarchy include diseases of the urinary system (level two), acute and unspecified renal failure (level three), acute renal failure (level four).

Long-term genitourinary outcomes were identified at 1–5 years and >5–10 years after endometrial cancer diagnosis. Follow-up time for incident cases of each outcome was

calculated separately from the endometrial cancer survivor's initial cancer diagnosis to the date of diagnosis for each outcome, last date of follow-up, or date of death. Individuals who did not have that outcome were censored at the date of last follow-up (last residence date in Utah or death) if that date fell within the analysis time period (1–5 years or >5–10 years) or at the end of each analysis time period if their date of last-follow-up exceeded the end of the analysis time period. Levels three or four outcomes diagnosed prior to the start of each analysis time period were considered prevalent cases of those outcomes and were excluded from the models. Level one and two outcomes were broader, thus we did not exclude prevalent diagnoses. There were a total of 38 outcomes investigated. Using a p-value<0.05 for significance, 1 in 20 associations observed would be expected to be due to chance alone; thus ~2 of our 38 outcomes may be due to chance.

Statistical Analysis

Chi-square tests were used to compare baseline characteristics between the endometrial cancer survivors and general population cohorts. Univariate and multivariate Cox proportional hazard models were used to calculate hazard ratios and 95% confidence intervals for long-term genitourinary outcomes at 1–5 years, >5–10 years and 1+ years (overall) after endometrial cancer diagnosis. Multivariate models were adjusted for matching factors, baseline body mass index (BMI), baseline Charlson Comorbidity Index (CCI)[10], and race (white vs. nonwhite). Cox proportional hazard models were also used to investigate risk factors such as treatment type, stage, grade, age at diagnosis, year of diagnosis, race, BMI, and rural/urban residence for genitourinary disease among endometrial cancer survivors. The proportional hazards assumption was checked for each model using a test for non-zero slope of the Schoenfeld residuals vs time. Models that were in violation of the proportional hazards assumption were then tested with flexible parametric survival models with restricted cubic splines. Hazard ratios from the Cox proportional hazard models were reported where there were no substantive differences.

Baseline BMI values at least one year prior to cancer survivors' endometrial cancer diagnosis were calculated from the self-reported height and weight from the driver's license records. For the cancer-free women, the most recent BMI value recorded at least one year prior to the endometrial cancer diagnosis date of the matched cancer patient was included. Approximately 35% of the endometrial cancer survivors cohort and 39% of the general population cohort were missing baseline BMI. For individuals missing BMI, BMI values were imputed using a linear regression model with 10 imputations that included cancer diagnosis, baseline CCI, and age at endometrial cancer diagnosis as covariates. Models were run with and without the imputed values to assure that the inferences did not change due to the imputation of BMI.

Results

Of the initial 3,624 endometrial cancer survivors, 153 were missing stage at diagnosis, 470 were missing grade, 285 did not have the required amount of follow-up time, and 65 did not live in the state of Utah for at least one year after diagnosis. There were a total of 2,648 endometrial cancer survivors and 10,503 individuals from the general population included in

the final sample. The endometrial cancer survivors cohort had a higher proportion of obese individuals (44.2% vs 19.2%) and was less diverse in ethnicity than the general population cohort ($p<0.001$ for both, Table 1). A higher proportion of individuals diagnosed with endometrial cancer (27.3%) were deceased compared to 15.2% in the general population cohort ($p<0.001$) as expected. Nearly 81.5% of the endometrial cancer survivors were diagnosed with grade I or II and 80.3% with stage I disease (Table 2). The mean follow-up time among survivors was 8.5 years.

We also compared the baseline demographics of endometrial cancer patients and the general population cohort with and without genitourinary outcomes (supplemental table 1). Among women with GU outcomes, there was a very high proportion of endometrial cancer patients who were obese compared to the general population cohort. For clinical characteristics among the endometrial cancer patients, women with GU outcomes were more likely to be diagnosed in previous years, and at older ages (supplemental table 2).

Between 1–5 years after cancer diagnosis, elevated risk for urinary system disorders was observed among cancer survivors for 20 out of 23 outcomes that were investigated (Table 3). For the overall estimates combining different follow up times, 19 of 23 outcomes were associated with higher risk among endometrial cancer patients. More than 37.4% of endometrial cancer survivors were diagnosed with a urinary system disorder compared to 24.5% of the general population during this time period. Elevated risk persisted between >5–10 years after diagnosis for 13 of those outcomes. Higher risk for diseases of the kidneys (including nephritis, nephrosis, renal sclerosis, and acute renal failure) and urinary tract infections (cystitis and urethritis and urinary tract infections of unspecified site) among endometrial cancer survivors were observed between both 1–5 and >5–10 years after diagnosis. Figure 1 shows that the endometrial cancer survivors have a higher cumulative incidence for genitourinary diseases, consistently in comparison to the general population cohort.

Between 1–5 years after diagnosis, 36.9% of endometrial cancer survivors were diagnosed with a genital organ disorder compared to 26.2% of individuals in the general population (Table 4). Endometrial cancer survivors were at elevated risk of genital organ disorders overall at both 1–5 years and at >5–10 years. Additionally, endometrial cancer survivors were at higher risk for non-malignant breast conditions, inflammatory diseases of the pelvic organs, other genital disorders, and genital pain and other symptoms between 1–5 years. Elevated risk continued at >5–10 years after diagnosis only for non-malignant breast conditions.

Individuals treated with surgery in combination with RT and/or chemotherapy were at higher risk for both urinary system and genital organ disorders compared to those treated with surgery alone at 1–5 years after diagnosis but not at >5–10 years, with the exception of those treated with surgery and RT for urinary system disorders. Individuals diagnosed with regionally advanced disease were at elevated risk for urinary system disorders compared to those with localized disease at both 1–5 and >5–10 years after diagnosis. Stage at diagnosis was not associated with risk for genital organ disorders at either 1–5 or >5–10 years after diagnosis. Higher grade endometrial cancers were associated with elevated risk for urinary

system disorders compared to grade I cancers at 1–5 years but not >5–10 years after diagnosis. Individuals diagnosed with stage IV disease were at higher risk of genital organ disorders compared to those diagnosed with grade I at 1–5 years after diagnosis. Among endometrial cancer survivors, higher BMI was not strongly associated with urinary system or genital organ disorders.

Discussion

These results present an important addition to previous studies concerning long-term, adverse genitourinary outcomes among endometrial cancer survivors. The majority of previous investigations focused on urinary and genital symptoms that affect health-related quality of life among survivors that were measured using self-report from patients. This is the first large cohort study to compare all available genitourinary outcomes from EMR data between endometrial cancer survivors and matched individuals from the general population. This analysis supports many of the findings of prior investigations with increased risks of genitourinary diseases that are associated with symptoms of urinary incontinence, daytime leakage, nocturia, voiding difficulty, and bladder, genital, and pelvic pain. In a randomized trial, genitourinary adverse events were identified in 30.0% of early stage endometrial cancer patients treated with radiation and surgery, and in 7.9% of patients with surgery only [11]. In another randomized trial, bladder problems were reported in 18% of endometrial cancer patients who had external beam radiation and vaginal brachytherapy, and 12.3% in patients with vaginal brachytherapy only [12]. In our study population, endometrial cancer survivors were at elevated risk for both urinary system and genital organ disorders between 1–5 and >5–10 years after diagnosis. Within 5 years of cancer diagnosis, 37.4% of endometrial cancer patients were diagnosed with urinary diseases and 36.9% with genital organ disorders. Our results also provide evidence that those treated with RT and/or chemotherapy compared to those treated with surgery alone are at higher risk for both urinary system and genital organ disorders within 5 years of diagnosis.

Previous studies on urinary system disorders due to cancer treatment among endometrial cancer survivors largely focused on urinary incontinence [13–18] which may be secondary to the diseases that were assessed in this study and risks of urinary diseases in comparison to a general population cohort were not available. In this study, endometrial cancer survivors were at elevated risk for nearly all of the urinary system disorders that were examined at 1–5 years, with risk persisting at >5–10 years for many that have not been previously investigated on this scale. Using data from EMRs may provide an additional measure of these conditions which may not have been captured by patient self-report or were not previously measured.

An additional important finding of our study is the elevated risk for a number of renal diseases among endometrial cancer patients, which has not been previously reported, to our knowledge. Renal toxicities due to radiation therapy are generally not expected during treatment or in the long-term for endometrial cancer patients [19, 20]. An onco-nephrology review reported that the prevalence of renal involvement in cancer patients has been difficult to quantify but that studies of cancer prevalence among patients with glomerulopathy suggest associations between glomerular diseases and cancer [21]. Our study shows that the

long term renal disease diagnoses are fairly rare among endometrial cancer patients (≤4%). Unfortunately due to small sample sizes, we were unable to assess risk factors specifically for renal diseases, but increased urinary disease risks were observed for radiation, chemotherapy, later stage, and older age at diagnosis in our study. Possible mechanisms for the renal disease risks among endometrial cancer patients include altered immune status in cancer patients [21], radiation damage to renal microvasculature [22] and renal failure associated with gemcitabine associated thrombotic microangiopathy [23]. Another possible explanation is that obesity and advanced age are shared risk factors for some of the renal diseases and for endometrial cancer. Although obesity was not a clear risk factor for urinary disease risk in our study, the risk estimate for obese women (HR=1.19, 95%CI=0.97–1.47) was suggestive of an association.

Although the risk of second primary breast cancer is thought to be fairly moderate among first primary endometrial cancer patients [24], the increased risks we observed for nonmalignant breast conditions in both follow up periods may be related to the subsequent increase in breast cancer risk. For the other genital organ disorders among endometrial cancer survivors, the risks for specific outcomes were largely confined to the 1–5 year range. Our results support previous findings from patient reported outcomes on pelvic pain and that it may be associated with radiation therapy among endometrial cancer survivors [25–27]. To our knowledge, risks for pain diagnosed by physicians among endometrial cancer patients have not been estimated in previous studies. Inflammatory diseases and the risk of endometrial cancer has been previously assessed [28–31], but to our knowledge, our study is the first to report an increased risk of inflammatory diseases among endometrial cancer patients 1–5 years after cancer diagnosis. The association may be due to shared risk factors such as chronic inflammation or obesity.

This study has a number of significant strengths. The large sample size (>2,600 endometrial cancer survivors and >10,500 cancer free women) and use of EMR data provides an additional measure of the experience of endometrial cancer survivors with respect to genitourinary outcomes. In addition, the EMR data used in this study comes from the state's two largest healthcare systems as well as statewide ambulatory surgery and inpatient data, providing a more complete record of the medical history of study patients. These data also contain a large amount of follow-up time for individuals in both cohorts. The mean follow-up time among survivors was 8.5 years. Approximately 27% had total follow-up time between one and five years, 39% between five and ten years, and 34% in excess of ten years. In contrast to cancer survivor studies that rely on self-reports of disease which are susceptible to survival bias, our study is less susceptible to survival bias because we used long term health records as the source of disease diagnoses.

This study also has a number of limitations. While the data used for this study is comprised of comprehensive EMR data from the two largest healthcare systems in the state, as well as statewide ambulatory surgery and inpatient data, there remains the possibility that study participants will have been diagnosed with outcomes of interest to these analyses in hospitals and clinics not covered by the data sources. However, approximately 99.6% of cancer patients and 98.6% of the general population cohort did have records in these data sources. Additionally, because 42.7% of individuals in the survivor cohort were diagnosed

after 2006, the potential to examine risk for these outcomes after ten years is limited due to lack of follow-up time for this proportion of the study population. However, with the UPDB as a data source, we are able to update our analysis on a regular basis. While data were available to investigate treatment related risk factors among endometrial cancer survivors, these data were limited to broad treatment categories and did not include potentially informative factors such as RT type and dosage, specific chemotherapy agents, and duration of treatment. However, the treatment data that were available did provide evidence that risk for several genitourinary outcomes vary by treatment type. Additionally, cancer patients are likely to be under increased medical surveillance, especially in the first 5 years after cancer diagnosis. Our results for 5–10 years after cancer diagnosis would be less likely to be subject to surveillance bias, and increased risks were observed in this time period.

Future research is necessary to more accurately assess causal relationships between treatment for endometrial cancer and the outcomes measured in this study. Further analysis that incorporates more specific treatment related factors are also needed. Additionally, because EMR data is derived from sources that are constantly updated, this study has the potential to examine these outcomes in an increasing number of survivors and over a longer period of time as new data are collected.

In conclusion, endometrial cancer survivors in this cohort were at higher risk for renal failure, chronic kidney disease, urinary tract infections, and nonmalignant breast conditions. These results present a wide range of outcomes encompassing urinary system disorders and genital organ disorders. Many of the conditions examined in this study have shared risk factors with endometrial cancer, making it difficult to disentangle the effects of the disease or its treatment; but the ability to adjust for many of these risk factors provides a clearer picture than has been previously available. Endometrial cancer survivors in this population-based cohort experienced a high burden of adverse genitourinary outcomes, especially urinary system disorders. These results suggest that increased monitoring and possibly counseling by physicians for genitourinary disease over long periods of time among endometrial cancer survivors is warranted. Further, these results highlight the need to place more emphasis on survivorship in addition to shorter-term outcomes that encompass the majority of the literature on treatment-related effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Endometrial cancer survivors had increased risks of genitourinary disease diagnoses
- 37.4% of patients were diagnosed with urinary system disorders
- 36.9% of patients were diagnosed with a genital organ disorder
- Specific diseases included renal failure, CKD, UTI, & nonmalignant breast conditions
- Chemotherapy or radiation increased risk for genitourinary disorders

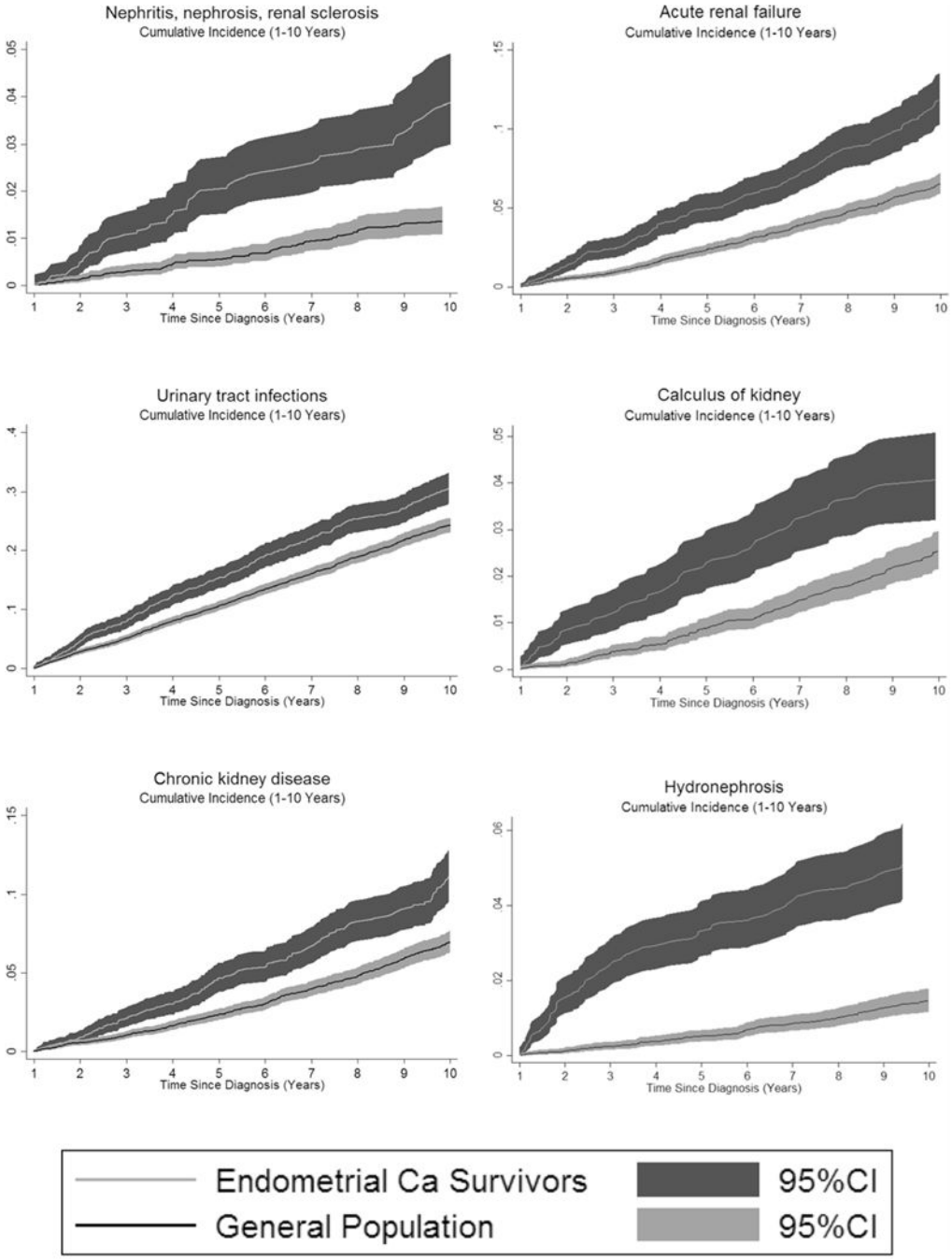

Figure 1.

Table 1

Demographic characteristics among endometrial cancer survivor and general population cohorts

	Endometrial Cancer n=2,648		General population n=10,503		
	n	**%**	**n**	**%**	***p***
Birth Year					
<1920	116	4.4	473	4.5	
1920–1929	310	11.7	1,192	11.4	
1930–1939	541	20.4	2,015	19.2	
1940–1949	787	29.7	3,085	29.4	
1950–1959	591	22.3	2,444	23.3	
>1960	303	11.4	1,294	12.3	0.54
Race					
White	2,525	95.4	9,617	91.6	
Black	10	0.4	29	0.3	
American Indian/Alaskan Native	111	1.1	32	1.2	
Asian	277	2.6	19	0.7	
Pacific Islander	60	0.6	48	1.8	
Unknown	14	0.5	409	3.9	*<0.001*
Vital Status					
Alive	1,924	72.7	8,906	84.8	
Dead	724	27.3	1,597	15.2	*<0.001*
Baseline BMI					
<18.5 kg/m^2	18	0.7	307	2.9	
18.5–24.9 kg/m^2	645	24.4	4,994	47.6	
25–29.0 kg/m^2	814	30.7	3,190	30.7	
>30 kg/m^2	1,171	44.2	2,012	19.2	*<0.001*
Age Attained at the End of Follow–up					
<50	161	6.1	697	6.6	
50–59	389	14.7	1,697	16.2	
60–69	826	31.2	3,142	29.9	

	Endometrial Cancer n=2,648		General population n=10,503		
	n	%	n	%	*p*
70–79	692	26.1	2,637	25.1	
80–89	442	16.7	1,787	17.0	
90+	138	5.2	543	5.2	0.303
Follow up Period					
1–5 years	726	27.4	2,742	26.1	
>5–10 years	1,028	38.8	4,062	38.7	
>10–15 years	595	22.5	2,576	24.5	
15+ years	299	11.3	1,123	10.7	0.122

Table 2

Clinical characteristics among endometrial cancer survivors

	Endometrial Cancer n=2,648	
	n	**%**
Diagnosis Year		
1997–2000	563	21.3
2001–2003	471	17.8
2004–2006	483	18.2
2007–2009	572	21.6
2010–2012	559	21.1
Age at Diagnosis		
<40	140	5.3
40–49	307	11.6
50–59	786	29.7
60–69	758	28.6
70–79	451	17.0
80+	206	7.8
Grade		
Grade I (Well differentiated)	1,314	49.6
Grade II (Moderately differentiated)	845	31.9
Grade III (Poorly differentiated)	421	15.9
Grade IV (Undifferentiated)	68	2.6
Stage		
Local	2,121	80.1
Regional	437	16.5
Advanced	90	3.4
Histology		
Endometrioid adenocarcinoma	1,853	70.0
Adenocarcinoma with squamous differentiation	56	2.1
Serous adenocarcinoma	87	3.3
Other	652	24.6
Endometrial Cancer Type		
Type I	2,300	86.9
Type II	87	3.3
Unknown	261	9.9
Treatment Type		
Surgery only	1,813	68.5
Surgery and radiation	579	21.9
Surgery and chemotherapy	84	3.2
Surgery, radiation, and chemotherapy	124	4.7
No available treatment information	48	1.8

Table 3

Urinary system disease risk at 1–5 and >5–10 years after cancer diagnosis among endometrial cancer survivors in comparison to a general population cohort of women.

	1–5 Years						5–10 Years						Overall 1+ years
	Survivors		General Population				Survivors		General Population				
Outcome	n	%	n	%	HR	(95% CI)	n	%	n	%	HR	(95% CI)	HR (95%CI)
Diseases of the urinary system	991	37.4	2,572	24.5	1.64	(1.50–1.78)	638	24.1	2,169	20.7	1.40	(1.26–1.56)	1.50 (1.40, 1.62)
Nephritis; nephrosis; renal sclerosis	46	1.7	52	0.5	3.53	(2.16–5.78)	26	1.0	48	0.5	2.84	(1.57–5.16)	3.32 (2.36, 4.68)
Acute and unspecified renal failure	139	5.3	249	2.4	2.21	(1.73–2.83)	95	3.6	254	2.4	1.61	(1.22–2.12)	1.83(1.56, 2.15)
Acute renal failure	112	4.2	219	2.1	2.04	(1.55–2.69)	96	3.6	234	2.2	1.82	(1.38–2.41)	1.80(1.52, 2.13)
Unspecified renal failure	50	1.9	81	0.8	2.52	(1.64–3.88)	27	1.0	72	0.7	1.52	(0.90–2.56)	2.04 (1.53, 2.73)
Chronic kidney disease	104	3.9	218	2.1	1.78	(1.36–2.33)	88	3.3	257	2.5	1.40	(1.05–1.86)	1.46(1.23, 1.73)
Urinary tract infections	268	10.1	831	7.9	1.52	(1.29–1.78)	177	6.7	678	6.5	1.45	(1.18–1.77)	1.42(1.26, 1.60)
Infections of kidney	41	1.6	135	1.3	1.79	(1.25–2.55)	33	1.3	107	1.0	1.25	(0.79–1.97)	1.19(0.91, 1.56)
Cystitis and urethritis	51	1.9	121	1.2	1.14	(0.77–1.68)	32	1.2	102	1.0	1.83	(1.16–2.89)	1.81(1.39, 2.35)
Urinary tract infection; site not specified	252	9.5	800	7.6	1.50	(1.27–1.77)	185	7.0	660	6.3	1.47	(1.21–1.79)	1.40(1.24, 1.57)
Calculus of urinary tract	76	2.9	140	1.3	1.95	(1.43–2.67)	45	1.7	129	1.2	1.35	(0.92–1.99)	1.65(1.32, 2.07)
Calculus of kidney	52	2.0	79	0.8	2.97	(1.97–4.47)	25	0.9	91	0.9	1.24	(0.76–2.04)	1.97(1.49, 2.61)
Calculus of ureter	38	1.4	62	0.6	1.97	(1.25–3.10)	18	0.7	60	0.6	1.36	(0.77–2.40)	1.63(1.19, 2.24)
Other and unspecified urinary calculus	24	0.9	62	0.6	1.39	(0.85–2.28)	21	0.8	53	0.5	1.61	(0.89–2.92)	1.43(1.02, 2.05)
Other diseases of kidney and ureters	211	8.0	376	3.6	2.25	(1.86–2.73)	107	4.0	327	3.1	1.56	(1.22–2.01)	1.88(1.64, 2.17)
Hydronephrosis	79	3.0	47	0.5	5.74	(3.85–8.55)	25	0.9	51	0.5	2.40	(1.44–4.02)	3.98(3.00, 5.28)
Other diseases of kidney and ureters	196	7.4	360	3.4	2.26	(1.85–2.76)	103	3.9	302	2.9	1.62	(1.25–2.11)	1.89(1.64, 2.19)
Other diseases of bladder and urethra	66	2.5	142	1.4	1.97	(1.41–2.75)	45	1.7	122	1.2	1.69	(1.13–2.53)	1.74(1.38, 2.19)
Genitourinary symptoms and ill-defined conditions	248	9.4	811	7.7	1.65	(1.40–1.96)	112	4.2	596	5.7	1.18	(0.93–1.51)	1.39(1.22, 1.58)
Hematuria	102	3.9	204	1.9	2.16	(1.65–2.82)	38	1.4	170	1.6	1.17	(0.78–1.75)	1.68(1.38, 2.05)
Retention of urine	27	1.0	73	0.7	1.16	(0.71–1.90)	15	0.6	76	0.7	0.71	(0.37–1.35)	1.00(0.71, 1.41)

Models adjusted for matching factors, baseline BMI, baseline Charlson Comorbidity Index, and race

Table 4

Genital organ disease risk at 1–5 and >5–10 years after cancer diagnosis among endometrial cancer survivors in comparison to a general population cohort of women.

	1–5 Years						5–10 Years						Overall 1+ years
	Survivors		General Population				Survivors		General Population				
Outcome	n	%	n	%	HR	(95% CI)	n	%	n	%	HR	(95% CI)	HR (95%CI)
Diseases of female genital organs	976	36.9	2,756	26.2	1.71	(1.58–1.86)	531	20.1	1,895	18.0	1.33	(1.19–1.49)	1.58(1.47, 1.71)
Nonmalignant breast conditions	240	9.1	682	6.5	1.70	(1.43–2.03)	146	5.5	445	4.2	1.47	(1.17–1.85)	1.56(1.37, 1.78)
Inflammatory diseases of female pelvic organs	78	3.0	210	2.0	1.88	(1.39–2.55)	24	0.9	115	1.1	1.20	(0.73–1.95)	1.51(1.18, 1.92)
Pelvic peritoneal adhesions	9	0.3	25	0.2	1.27	(0.53–3.04)	2	0.1	9	0.1	1.57	(0.23–10.93)	1.44(0.71, 2.90)
Other inflammatory diseases of pelvic organs	88	3.3	166	1.6	2.16	(1.62–2.89)	27	1.0	95	0.9	1.59	(0.98–2.57)	1.78(1.44, 2.20)
Endometriosis	15	0.6	47	0.5	2.05	(0.98–4.29)	2	0.1	14	0.1	0.84	(0.14–5.01)	1.87(0.99, 3.52)
Menstrual disorders	14	0.5	175	1.7	0.80	(0.43–1.48)	5	0.2	111	1.1	0.40	(0.16–1.03)	0.62(0.39, 1.00)
Ovarian cyst	12	0.5	92	0.9	0.58	(0.30–1.11)	1	0.0	46	0.4	0.09	(0.01–0.75)	0.43(0.24, 0.77)
Menopausal disorders	108	4.1	604	5.8	1.30	(1.02–1.65)	44	1.7	364	3.5	0.80	(0.56–1.15)	1.08(0.89, 1.30)
Other female genital disorders	107	4.0	487	4.6	1.97	(1.52–2.55)	25	0.9	245	2.3	1.07	(0.66–1.74)	1.70(1.37, 2.11)
Female genital pain and other symptoms	107	4.0	326	3.1	1.51	(1.18–1.93)	36	1.4	212	2.0	1.06	(0.71–1.57)	1.49(1.26, 1.76)
Other and unspecified female genital disorders	81	3.1	281	2.7	2.21	(1.63–2.99)	13	0.5	125	1.2	0.87	(0.46–1.66)	1.74(1.44, 2.10)

Models adjusted for matching factors, baseline BMI, baseline Charlson Comorbidity Index, and race

The following outcomes were evaluated but no elevated risk was observed: cervicitis and endocervicitis, pelvic inflammatory disease, and prolapse of the female genital organs

Table 5

Risk factors for urinary and genital organ disorders among endometrial cancer survivors

	Urinary System Disorders				Genital Organ Disorders			
	1–5 Years		5–10 Years		1–5 Years		5–10 Years	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Treatment Type[a]								
Surgery only								
Surgery and radiation	1.46	(1.26–1.69)	1.24	(1.03–1.49)	1.26	(1.08–1.47)	1.09	(0.88–1.35)
Surgery and chemotherapy	2.99	(2.21–4.04)	0.74	(0.31–1.80)	1.62	(1.14–2.28)	1.81	(0.99–3.31)
Surgery, radiation, and chemotherapy	2.34	(1.81–3.02)	1.51	(0.98–2.32)	1.52	(1.14–2.03)	1.02	(0.61–1.71)
Stage[b]								
Local								
Regional	1.45	(1.24–1.70)	1.3	(1.04–1.61)	1.17	(0.98–1.39)	1.02	(0.79–1.32)
Advanced	3.43	(2.57–4.57)	1.49	(0.70–3.17)	1.37	(0.92–2.02)	0.62	(0.23–1.68)
Grade[b]								
Grade I (Well differentiated)								
Grade II (Moderately differentiated)	1.20	(1.04–1.39)	1.07	(0.90–1.27)	1.04	(0.90–1.20)	1.06	(0.87–1.28)
Grade III (Poorly differentiated)	1.57	(1.32–1.88)	0.86	(0.66–1.13)	1.13	(0.93–1.37)	1.21	(0.92–1.59)
Grade IV (Undifferentiated)	2.78	(1.97–3.94)	0.89	(0.40–2.00)	1.83	(1.22–2.75)	0.56	(0.18–1.76)
Year of Diagnosis[c]								
1997–2000								
2001–2004	1.35	(1.12–1.64)	1.15	(0.95–1.41)	1.15	(0.96–1.38)	0.91	(0.73–1.13)
2005–2010	1.21	(1.02–1.44)	0.92	(0.75–1.12)	0.97	(0.82–1.15)	0.82	(0.66–1.01)
2011–2012	1.19	(0.94–1.49)			0.78	(0.61–1.00)		
Age at Diagnosis[d]								
<50								
50–59	1.19	(0.96–1.47)	1.18	(0.91–1.52)	1.09	(0.91–1.31)	0.93	(0.73–1.18)
60–69	1.39	(1.12–1.72)	1.55	(1.20–2.01)	0.98	(0.81–1.18)	0.97	(0.76–1.24)
70–79	1.70	(1.35–2.14)	1.90	(1.44–2.52)	0.77	(0.61–0.96)	0.64	(0.46–0.88)
80+	2.20	(1.68–2.87)	2.67	(1.89–3.79)	0.53	(0.37–0.74)	0.34	(0.18–0.63)

	Urinary System Disorders				Genital Organ Disorders			
	1–5 Years		5–10 Years		1–5 Years		5–10 Years	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Charlson Comorbidity Index[e]								
0								
1	1.40	(1.19–1.64)	1.83	(1.51–2.21)	1.23	(1.05–1.45)	1.10	(0.88–1.37)
2+	2.10	(1.80–2.46)	2.40	(1.95–2.95)	1.18	(0.99–1.41)	1.14	(0.88–1.49)
Baseline BMI[f]								
<18 kg/m^2	0.83	(0.34–2.01)	1.48	(0.61–3.63)	1.05	(0.50–2.23)	1.30	(0.53–3.18)
18–24.9 kg/m^2								
<25–29.9 kg/m^2	1.07	(0.90–1.27)	1.16	(0.93–1.44)	1.10	(0.92–1.30)	1.18	(0.94–1.49)
>30 kg/m^2	1.01	(0.86–1.19)	1.19	(0.97–1.47)	0.98	(0.83–1.15)	1.02	(0.81–1.27)

Models adjusted for

[a] CCI, BMI, race, year of diagnosis, and age at diagnosis;

[b] age at diagnosis, diagnosis year, BMI, CCI, Race;

[c] BMI, CCI, race, endometrial cancer type;

[d] BMI, race, diagnosis year, CCI;

[e] age at diagnosis, diagnosis year, race;

[f] CCI, age at diagnosis, race