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Genitourinary disease risks among ovarian cancer survivors in a population-based cohort study

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Abstract

Objective.—While genitourinary complications during treatment for ovarian cancer are well known, long-term adverse outcomes have not been well characterized. The number of ovarian cancer survivors has been increasing. The aim of this study was to investigate long-term adverse genitourinary outcomes in a population-based cohort.

Methods.—We identified a cohort of 1,270 ovarian cancer survivors diagnosed between 1996–2012 from the Utah Cancer Registry, and 5,286 cancer-free women were matched on birth year

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Authors' contributions:

C. C., M.H. wrote, reviewed, and revised the manuscript; C.C. and Y.C. contributed to the analysis, B.B. and S.A. performed statistical support; B.B., J.B.S., J.O., J.D., D.G., M.H. revised the manuscript; K.R, J.S., M.D., V.D., M.N, A.F. prepared and provided study data; M.H. obtained grant funding, designed the study, planned the analyses; all authors approved the final version of the manuscript.

and state from the Utah Population Database. Genitourinary disease diagnoses were identified through ICD-9 codes from electronic medical records and statewide healthcare facilities data. Cox proportional hazards models were used to estimate hazard ratios (HR) for genitourinary outcomes at 1 to <5 years and 5+ years after ovarian cancer diagnosis.

Results.—Ovarian cancer survivors had increased risks for urinary system disorders (HR: 2.53, 95% CI: 2.12–3.01) and genital organ disorders (HR: 1.88, 95% CI: 1.57–2.27) between 1 and <5 years after cancer diagnosis compared to the general population cohort. Increased risks were observed for acute renal failure, chronic kidney disease, calculus of kidney, hydronephrosis, pelvic peritoneal adhesions, and pelvic organ inflammatory conditions. Increased risks of several of these diseases were observed 5+ years after cancer diagnosis.

Conclusions.—Ovarian cancer survivors experience increased risks of various genitourinary diseases compared to women in the general population in the long-term. Understanding the multimorbidity trajectory among ovarian cancer survivors is important to improve clinical care after cancer treatment is completed.

Keywords

cancer survivorship; genital organ disorders; genitourinary diseases; ovarian cancer; urinary system disorders

Introduction

In the United States, ovarian cancer accounts for 2.5% of new cancer cases and 5% of cancer deaths [1]. In 2019, there were an estimated 22,530 new ovarian cancer cases diagnosed and 13,980 ovarian cancer deaths [1]. Despite the high mortality rate, five-year survival rates for ovarian cancer have increased from 36% for women diagnosed in 1975–1977 to 48% for women diagnosed between 2008–2014, due to earlier diagnosis and advances in treatment [2]. The number of ovarian cancer survivors is estimated to increase from 249,230 in 2019 to 297,580 in 2030 [3].

While the number of ovarian cancer survivors is increasing, there are few long-term follow-up studies among ovarian cancer survivors that have examined health outcomes in a population-based cohort. Previous survivorship studies on ovarian cancer survivors largely focused on quality of life, surveillance, physical activity, and side effects after treatment [2, 4–11]. A few studies investigated adverse outcomes but the follow up was usually short. Based on Surveillance, Epidemiology, and End Results program (SEER)-Medicare linked data, higher rates of hypertension, thromboembolic events, congestive heart failure, infection, and anemia were observed among ovarian cancer survivors ≥ 66 years of age at 12 months after cancer diagnosis compared to cancer-free women [12]. In another study including 390 gynecologic cancer patients, patients reported high prevalence of cognitive changes (66.7%), peripheral neuropathy (61.3%), and sexual changes (50.9%) within a median time of one year since cancer diagnosis [13]. A cohort study in Sweden including 616 gynecological cancer survivors treated with pelvic radiation therapy reported higher prevalence of several self-reported urinary tract and pelvic symptoms after 2 years of cancer treatment compared to the general population [14]. Ovarian cancer survivors also

experienced a higher risk of second primary cancer diagnoses, with a 20-year cumulative risk of 4.5% according to SEER cancer registry data [15].

We previously reported that endometrial cancer survivors had higher risks of genitourinary outcomes compared to a general population of women (HR: 1.64, 95% CI: 1.50 – 1.78) [16]. Genitourinary complications during treatment are well-known among ovarian cancer patients [14]. However, to our knowledge, the risk of long-term genitourinary outcomes diagnosed >5 years after cancer diagnosis have not been investigated comprehensively with a population-based cohort design. With the continued increase in the number of ovarian cancer survivors and their longer survival times, population-based cohort studies are needed to better understand the impact of long-term adverse outcomes among ovarian cancer survivors. The aim of our study was to estimate the incidence of genitourinary diseases among ovarian cancer survivors at 1 to <5 years and 5+ years after ovarian cancer diagnosis, compared to a general population of women.

Methods

Data collection

Women diagnosed with invasive ovarian cancer at 18 years of age or older in Utah between 1996 and 2012 (N=2,113) were identified by the Utah Cancer Registry (UCR). Ovarian cancer diagnosis was classified according to the International Classification of Diseases for Oncology, version 3 (ICD-O-3 code: C56.9). We followed the 2014 World Health Organization (WHO) classification guidelines to categorize the histotypes of ovarian cancer [17–19]. Cases were excluded if: 1) the cancer diagnosis was not the first primary cancer (N=320), 2) cancer stage was missing or unknown (N=104), or 3) the patient died within a year after cancer diagnosis (N=419), leaving 1,270 ovarian cancer survivors. We restricted the diagnoses years from 1996 to 2012 because of the availability of high-quality electronic medical record (EMR) data, which was necessary to calculate baseline comorbidity scores, and because outcome data were available up to 2016.

The Utah Population Database (UPDB) links data from the UCR, hospital EMR, statewide healthcare facilities data, driver licenses, voter registration, family history records, and Utah vital records. The ovarian cancer survivors were matched with up to five women without cancer from the general population by birth year and birth state. We identified 5,286 women from the Utah general population through the UPDB who met the following eligibility criteria at baseline: 1) 18+ years old, 2) cancer-free, and 3) living in Utah. The last known date of residence in Utah was determined by whether the individual was observed in one of the UPDB records.

Information on date of cancer diagnosis, tumor characteristics, and first course cancer treatment for the ovarian cancer survivors were obtained from the UCR. Information about comorbidities and outcomes of interest were obtained from Utah statewide healthcare facilities data as well as linkage to EMR data from the two largest healthcare systems in Utah: Intermountain Health Care and the University of Utah Health Science Center. We used International Classification of Diseases, 9th Revision (ICD-9) diagnosis or procedure codes to identify the comorbidities and outcomes. The ICD-9 codes were processed with the

Healthcare Cost and Utilization Project's Clinical Classifications Software (CCS) [20] to group the diseases into discrete diagnosis categories with four levels, with level 1 covering broad disease categories and level 4 covering the most specific conditions within these categories. A total of 38 genitourinary diseases were identified as outcomes of interest (please refer to the supplemental materials, Supplementary Table 1, for the complete list of CCS diagnosis categories and corresponding ICD-9 codes). Individuals diagnosed with level three and four outcomes before the start of each analysis time period were considered as prevalent cases and were excluded for that specific outcome. Since levels one and two were broader and contained multiple conditions, individuals diagnosed with level one or two outcomes before baseline were included.

Statistical analysis

We compared demographic factors between the ovarian cancer survivors and the general population, and described clinical characteristics of the ovarian cancer survivors. The baseline date was the date of cancer diagnosis for ovarian cancer patients. For the general population cohort, the baseline date was the date of cancer diagnosis for the cancer patient that the individual was matched to. Individuals who did not develop diseases of the genitourinary system were censored at death, or at the date of last known residence in Utah. We used two follow-up time periods to evaluate the long-term risk of genitourinary outcomes, 1 to <5 years and >=5 years after the baseline date.

Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for genitourinary outcomes at 1 to <5 years and 5+ years with adjustment for matching factors (birth year and birth state), and potential confounders, such as race, baseline body mass index (BMI), and baseline Charlson Comorbidity Index (CCI). The potential confounders were chosen a priori based on the three properties of confounders using causal diagrams [21]. The CCI was calculated using all medical record data prior to the baseline [22]. The proportional hazards assumption was tested for each Cox proportional hazards model by including interactions of the predictors and time in the model. For models where the assumption was violated, we used flexible parametric survival models with restricted cubic splines [23, 24].

Height and weight were obtained from the Utah driver license data at least one year prior to the baseline, and used to calculate baseline BMI. Approximately 31.1% of the ovarian cancer survivors and 27.3% of the general population had missing information for baseline BMI. Thus, for individuals with missing BMI, we imputed the value using a linear regression model with cancer diagnosis, baseline CCI, race, and age at baseline as covariates. Hazard ratios with and without the imputed BMI were compared to assure that the inferences did not change. We excluded women > 50 years old as a proxy for menopausal status when estimating the risk of menstrual disorders. Sensitivity analyses were conducted by excluding subjects who had hysterectomy and/or oophorectomy for estimating the risk of genital organ diseases, including pelvic peritoneal adhesions, endometriosis, ovarian cyst, and other inflammatory diseases of female pelvic organs. For ovarian cancer survivors, the history of hysterectomy and/or oophorectomy was obtained from the cancer registry surgery variables, including surgery with hysterectomy, debulking of ovarian cancer

mass, and pelvic exenteration. For women from the general population, we used Utah data from the Behavioral Risk Factor Surveillance System (BRFSS) [25] to imputed the history of hysterectomy by a regression model with race and age at baseline as covariates [26]. Limited surgery was defined as total removal of tumor or unilateral/bilateral oophorectomy (with or without hysterectomy). Aggressive surgery was defined as receiving omentectomy, debulking, or pelvic exenteration. Analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC).

Results

The final cohort included 1,270 ovarian cancer cases and 5,286 women from the general population. A higher proportion of ovarian cancer survivors had higher baseline comorbidity score (CCI >=1: 32.7% vs. 28%) than the general population (Table 1). Nearly 60.6% of the ovarian cancer survivors were diagnosed at late stage (Table 2). About 63% of ovarian cancer survivors received both surgery and chemotherapy as treatment for cancer. Among ovarian cancer patients who received surgery, 947 patients had aggressive surgery, such as surgery with omentectomy, debulking, pelvic exenteration (Table 2). Ovarian cancer patients who received surgery only (N=333) were more likely to be diagnosed at localized stage (49.8%) and less likely to be diagnosed with high-grade serous histology (41.1%) compared with ovarian cancer survivors overall (N=1270) (Supplementary Table 2). In addition, they were younger at cancer diagnosis and diagnosed in earlier years (35.4% diagnosed between 1996–2000). When we stratified cancer stage by chemotherapy, 53.4% of ovarian cancer survivors (249 out of 466) had chemotherapy at stage I or II and 81.8% (618 out of 756) at stage III or IV (data not shown).

Ovarian cancer survivors had a 2.41-fold increased risk of genitourinary diseases compared to women from the general population in year 1–5 of follow up (95% CI:1.98–2.94, data not shown). Specifically, ovarian cancer survivors had a higher incidence of urinary system diseases compared to the general population 1 to <5 years after cancer diagnosis (HR: 2.53, 95% CI: 2.12–3.01, Table 3). More than 15% of ovarian cancer survivors had urinary tract infections with a HR of 2.39 (95% CI: 1.93–2.95) compared to the general population cohort. Ovarian cancer survivors had an elevated risk of hydronephrosis (HR: 35.94, 95% CI: 18.78–68.80), unspecified diseases of kidney and ureters (HR: 5.95, 95% CI: 4.65–7.63), and retention of urine (HR: 5.74, 95% CI: 2.98–11.06) 1 to <5 years after cancer diagnosis. After 5 years since the cancer diagnosis, ovarian cancer survivors had a higher risk of hydronephrosis compared to the general population (HR: 9.10, 95% CI: 4.29–19.33). The risks of acute renal failure (HR: 2.42, 95% CI: 1.59–3.69), unspecified diseases of kidney and ureters (HR: 2.62, 95% CI: 1.76–3.88), and unspecified diseases of bladder and urethra (HR: 2.32, 95% CI: 1.33–4.04) were also higher among ovarian cancer survivors compared to the general population 5+ years after cancer diagnosis.

Ovarian cancer survivors had a higher incidence of genital organ diseases compared to the general population 1 to <5 years after cancer diagnosis (HR: 1.88, 95% CI: 1.57–2.27, Table 4). The risk of pelvic peritoneal adhesions was highest 1 to <5 years after cancer diagnosis (HR: 16.59, 95% CI: 7.00–39.34) and persisted 5+ years after cancer diagnosis (HR: 8.88, 95% CI: 1.88–41.91). Ovarian cancer survivors were at a higher risk for menopausal

disorders, female genital pain, other inflammatory diseases of female pelvic organs, and unspecified female genital disorders between 1 and <5 years after diagnosis. Among women ≤ 50 years of age, the risk of menstrual disorders was inversely associated with ovarian cancer diagnosis (HR: 0.25, 95% CI: 0.11–0.59, 1 to <5 years after cancer diagnosis). Among ovarian cancer patients diagnosed with “other inflammatory diseases of female pelvic organs”, 80% were diagnosed with vaginitis and vulvovaginitis. After excluding the subjects who had hysterectomy and/or oophorectomy, the increased risks among ovarian cancer survivors were still observed for genital organ diseases (HR: 2.10, 95% CI:1.43–3.08), pelvic peritoneal adhesions (HR: 6.13, 95% CI:1.15–32.75), “other inflammatory diseases of female pelvic organs” (HR: 4.29, 95% CI:1.76–10.41), and ovarian cyst (HR: 8.41, 95% CI: 2.07–34.06) 1 to <5 years after cancer diagnosis (data not shown).

Ovarian cancer patients treated with a combination of surgery and chemotherapy or with other treatments were at higher risk for urinary system disorders compared to those treated with surgery alone at 1 to <5 years after diagnosis (Table 5). Individuals who received aggressive surgery had an elevated risk of urinary system disorders compared to those with limited surgery at 1 to <5 years after diagnosis (HR: 3.34, 95% CI: 2.14–5.22, Table 5). When we further adjusted for cancer stage and histotype; the positive association between other treatment and urinary system disorders remained similar ($HR_{\text{other treatment vs. surgery only}}$: 1.89, 95% CI: 1.05–3.41; $HR_{\text{surgery and chemotherapy vs. surgery only}}$: 1.36, 95% CI: 0.98–1.89, respectively, data not shown). Individuals diagnosed with an advanced stage of ovarian cancer had an increased risk of urinary system disorders compared to those with a localized stage at 1 to <5 years after diagnosis (HR: 3.11, 95% CI: 2.18–4.45). In addition, individuals >80 years of age or had a high baseline comorbidity score (baseline CCI greater than 2) had an increased risk of urinary system disorders 1 to <5 years after cancer diagnosis. The associations remained similar when we restricted the analyses to ovarian cancer survivors with high-grade serous ovarian cancer (Supplementary Table 3). For genital organ disorders, ovarian cancer patients who were overweight were at higher risk compared to those with a normal weight 1 to <5 years after diagnosis. We did not observe meaningful differences between year of diagnosis and the risk of genitourinary diseases. The results were similar whether we estimated HRs excluding individuals who had missing BMI or used the BMI imputation.

Discussion

In this population-based cohort study, we observed that ovarian cancer survivors had an increased risk of several genitourinary diseases 1 to <5 years after cancer diagnosis compared to the general population. The long-term adverse genitourinary health outcomes associated with ovarian cancer survivors 5+ years after cancer diagnosis included acute renal failure (HR: 2.42, 95% CI: 1.59–3.69), chronic kidney disease (HR: 2.24, 95% CI: 1.40–3.57), calculus of kidney (HR: 2.28, 95% CI: 1.18–4.43), hydronephrosis (HR: 9.10, 95% CI: 4.29–19.33), and pelvic peritoneal adhesions (HR: 8.88, 95% CI: 1.88–41.91). Increased risks of urinary system disorders among ovarian cancer patients were associated with cancer treatment, advanced stage, serous histology, age at cancer diagnosis, and higher baseline comorbidity scores 1 to <5 years after cancer diagnosis. However, at 5+ years after cancer

diagnosis, age and serous histology were the only risk factors associated with urinary system disorder risks.

According to a SEER patterns of care report, the percentage of ovarian cancer patients who received chemotherapy was 64% for stage I or II and 80% for stage III or IV [27]. In our study, the percentage of receiving chemotherapy in ovarian cancer patients was similar for stage III or IV (82%) but slightly lower for stage I or II (53%). Chemotherapy could be misclassified due to incomplete records/ascertainment; that is, some ovarian cancer patients who received chemotherapy may be classified as having received surgery only. Ovarian cancer patients who had surgery only were more likely to be diagnosed with localized stage, diagnosed in earlier time periods, and less likely to be diagnosed with high-grade serous histology. Since treatment depends on cancer stage, an increased risk of urinary system disorders due to cancer stage is likely due to cancer treatment. After additionally adjusting for cancer stage and histotype, the positive association between other treatment and urinary system disorders remained similar. A few clinical studies reported that intraperitoneal cisplatin chemotherapy could be associated with acute renal failure in ovarian cancer patients during cancer treatment due to the toxicity of paclitaxel and carboplatin [27–29]. A SEER Medicare study including 5,087 ovarian cancer survivors ≥ 66 years reported higher incidence of renal disease 3- and 12-months after cancer diagnosis compared with cancer-free women [12]. In our study, which had a longer follow-up time and included women of all ages, we also observed a higher risk of renal failure among ovarian cancer survivors compared with women from the general population, and an elevated risk of acute renal failure remained high 5+ years after cancer diagnosis (HR: 2.42, 95% CI: 1.59–3.69).

An additional important finding from our study is the elevated risk of a number of urinary system conditions, including hydronephrosis and calculus of kidney, which has not been previously reported. We also observed that women diagnosed with ovarian cancer at >50 years had a higher risk of urinary system disorders. A systematic review, including data from 31 publications, reported that gynecologic cancer survivors had a higher prevalence of pelvic floor disorders (which include urinary incontinence, fecal incontinence, and pelvic organ prolapse) compared to the general population [30]. We observed a high risk of unspecified bladder and urethra diseases among ovarian cancer survivors compared to the general population in both the 1 to <5 years and 5+ years time periods after cancer diagnosis. When we evaluated the risk factors of urinary system disorders, the positive associations at 1 to < 5 years after cancer diagnosis were attenuated for cancer treatment, cancer stage, and baseline comorbidity scores at 5+ years after cancer diagnosis. We may have had less statistical power due to the smaller sample size of ovarian cancer patients diagnosed with urinary system disorders at 5+ years after cancer diagnosis (N=91). The proportion of urinary system disorders among ovarian cancer survivors was higher than the general population (35.8% vs. 27.1%, respectively). Another potential reason for the attenuation in risk is that the influence of cancer treatment on urinary organs may have decreased over time.

Women diagnosed with ovarian cancer at >50 years did not have an associated risk of genital organ disorders. A potential explanation for this could be that women who were >50 years of age had completed menopause, after which there is less hormonal and metabolic activity associated with the female reproductive organs, and they were not at risk of certain genital

organ disorders, such as menstrual disorders and infertility [31]. We further observed that ovarian cancer survivors had a lower risk of menstrual disorders compared to women in the general population (HR: 0.25, 95% CI: 0.11–0.59). It is likely that many ovarian cancer survivors received cancer treatment that included surgically-induced or chemotherapy-induced menopause [32], and therefore, they were less likely to experience menstrual disorders. Since the information of menopausal status was not available in our study, the age of 50 years was used as a proxy. Women who had hysterectomy or oophorectomy would not be at risk of genital organ disorders, such as endometriosis, menstrual disorders, menopausal disorders, and ovarian cyst. The percentage of having hysterectomy and/or oophorectomy was 79.2% among ovarian cancer survivors. However, the percentage of hysterectomy and/or oophorectomy among ovarian cancer patients could be underestimated since some procedures did not specify if the uterus or ovaries were removed during surgery or not. We used an external source, the BRFSS, to impute hysterectomy for the women from the general population. We estimated that the proportion of women who had hysterectomy among the general population was 18.3%, which was similar to the result from Cancer Prevention Study-II Nutrition Cohort study [33]. After the exclusion of hysterectomy and/or oophorectomy, the conclusion at 1–5 years after cancer diagnosis remained the same. However, the increased risks of pelvic peritoneal adhesions and other inflammatory diseases of female pelvic organs were not observed 5+ years after cancer diagnosis.

A limitation of the study is that ovarian cancer survivors are more likely to visit a clinic for follow-up care than women without cancer, leading to increased surveillance. According to the National Comprehensive Cancer Network guidelines for ovarian cancer patients, follow-up is recommended every 2 to 4 months during the first two years, every 3 to 6 months during the following three years after cancer treatment and once per year after 3 years [34]. Therefore, ovarian cancer survivors may be more likely to be diagnosed earlier with their adverse health outcomes compared with women from the general population. However, the frequency of clinic visits likely decreases over time, and the follow-up period of >5 years after cancer diagnosis should be less affected by increased surveillance. In addition, treatment data were limited to broad categories and did not include specific chemotherapy agent names or doses to assess possible dose-response associations between specific agents and genitourinary diseases. More detailed treatment data, from claims data or abstraction, is warranted to further examine the associations between specific cancer treatments and genitourinary diseases. Although our results support the association between cancer treatment type and the risk of urinary system disorders 1 to <5 years after cancer diagnosis, we were not able to represent the results stratified by surgery and chemotherapy status because among 50 ovarian cancer patients who did not have surgery, 18 patients developed urinary system disorders 1 to <5 years after cancer diagnosis. Among 245 ovarian cancer patients who did not have chemotherapy, 60 patients developed urinary system disorders 1 to <5 years after cancer diagnosis. Future studies with a larger sample size are needed for this stratified analysis. Another limitation is that our study population was not racially or ethnically diverse, though 7% of ovarian cancer survivors and 6% of women from the general population were of Hispanic ethnicity. Lastly, ovarian cancer diagnosis was based on ICD-O-3 code (C56.9), which does not include fallopian tube (ICD-O-3 code: C57.0) or primary peritoneal cancers (ICD-O-3 code: C48.1). Ovarian, fallopian tube, and primary

peritoneal cancers are likely highly similar [34]. However, since only 55 women with fallopian tube cancer and 87 with primary peritoneal cancer would have been included in our study, it is unlikely that excluding them influenced our findings.

The strengths of our study included the relatively large sample size (> 1,200 ovarian cancer survivors and > 5,000 women from the general population), the population-based design, and the use of ICD coding that provided a full spectrum of diagnosed genitourinary outcomes. The EMR and statewide healthcare facilities data also provided valuable information in terms of baseline comorbidities. The sources of EMR data in this study were the state's two largest healthcare systems as well as from statewide healthcare facilities data. In addition, more than 40% of ovarian cancer survivors (N=602) were followed >10 years, allowing for risk estimation for long-term health outcomes.

In conclusion, we observed that ovarian cancer survivors experienced increased risks of various genitourinary diseases 1 to <5 year and 5+ years after cancer diagnosis compared to the general population. Understanding the multimorbidity trajectory for ovarian cancer survivors after their cancer treatment is completed is of vital importance to improve clinical care after cancer diagnosis. Further, these results point to the need to consider monitoring for genitourinary diseases among ovarian cancer survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

Ovarian cancer survivors had a 2-fold increased risk of genitourinary diseases compared to women from the general population.

Urinary system disorders were diagnosed more frequently in ovarian cancer survivors (34.6%) compared to women without cancer.

Genital organ disorders were more common among ovarian cancer survivors (22.1%) compared to women in the general population.

Table 1.

Demographic characteristics of the ovarian cancer survivor and general population cohorts

	Ovarian cancer survivors N=1270		General population N=5286	
	N	**%**	**N**	**%**
Birth year				
<1930	198	15.6%	788	14.9%
1930 to 1949	561	44.2%	2259	42.7%
1950 to 1969	417	32.8%	1826	34.5%
1970+	94	7.4%	413	7.8%
Race				
White	1218	95.9%	4822	91.2%
Black	2	0.2%	13	0.3%
American Indian	6	0.5%	32	0.6%
Asian or Pacific Islander	9	0.7%	123	2.3%
More than one race	31	2.4%	115	2.2%
Missing	4	0.3%	181	3.4%
Ethnicity				
Non-Hispanic	1176	92.6%	4967	94.0%
Hispanic	94	7.4%	319	6.0%
Vital status				
Alive	555	43.7%	4531	85.7%
Dead	715	56.3%	755	14.3%
Follow up period (years)				
1 to 4	226	17.8%	86	1.6%
5 to 9	442	34.8%	1183	22.4%
10 to 14	325	25.6%	1800	34.1%
15+	277	21.8%	2217	41.9%
Baseline CCI				
0	855	67.3%	3807	72.0%
1	254	20.0%	844	16.0%
2+	161	12.7%	635	12.0%
Baseline BMI[a]				
<18.5 kg/m^2	32	2.5%	154	2.9%
18.5 to 24.9 kg/m^2	625	49.2%	2575	48.7%
25 to 29.9 kg/m^2	357	28.1%	1594	30.2%
30+ kg/m^2	256	20.2%	963	18.2%

Abbreviation: CCI, Charlson Comorbidity Index.

[a]Imputed BMI

Table 2.

Clinical characteristics of ovarian cancer survivors

	Ovarian cancer survivors (N=1270)	
	N	**%**
Year of diagnosis		
1996–2000	341	26.9%
2001–2005	372	29.3%
2006–2012	557	43.9%
Age at diagnosis		
18–49	346	27.2%
50–59	323	25.4%
60–69	286	22.5%
70–79	243	19.1%
80–93	72	5.7%
Stage		
Localized	282	22.2%
Regional	219	17.2%
Distant	769	60.6%
Treatment		
Surgery only	333	26.2%
Surgery and chemotherapy	800	63.0%
Other treatment[a]	88	6.9%
Missing	49	3.9%
Surgery type[b]		
Limited surgery	194	17.0%
Aggressive surgery	947	83.0%
Histology		
High-grade serous	714	56.2%
Low-grade serous	15	1.2%
Endometrioid	136	10.7%
Mucinous	88	6.9%
Clear Cell	75	5.9%
Carcinosarcoma	17	1.3%
Carcinoma, NOS	114	9.0%
Other type[c]	111	8.7%

[a] Includes chemotherapy only, surgery and radiation, chemotherapy and radiation, surgery and radiation and chemotherapy.

[b] Limited surgery: removal of tumor or unilateral/bilateral oophorectomy (with or without hysterectomy). Aggressive surgery: surgery with omentectomy, debulking, pelvic exenteration. Total N=1141.

[c] Malignant Brenner, mixed, sarcoma, non-specific

Table 3.

Urinary system disease risks among ovarian cancer survivors compared to a general population of women, by years since cancer diagnosis

	1 to <5 years after cancer diagnosis					5+ years after cancer diagnosis				
	Ovarian cancer survivors		General population			Ovarian cancer survivors		General population		
	N	%	N	%	HR (95% CI)[a]	N	%	N	%	HR (95% CI)[a]
Diseases of the urinary system	245	34.6%	511	19.3%	2.53 (2.12, 3.01)	91	35.8%	207	27.1%	1.30 (0.97, 1.73)
Nephritis; nephrosis; renal sclerosis	17	1.4%	24	0.5%	4.54 (1.95, 10.58)	11	2.0%	30	1.5%	1.20 (0.51, 2.81)
Acute and unspecified renal failure	77	6.4%	117	2.5%	4.23 (2.97, 6.02)	49	9.2%	104	5.3%	2.35 (1.57, 3.52)
Acute renal failure	71	5.9%	107	2.2%	4.26 (2.94, 6.16)	46	8.6%	94	4.7%	2.42 (1.59, 3.69)
Unspecified renal failure	21	1.7%	34	0.7%	4.94 (2.46, 9.91)	10	1.8%	38	1.8%	1.27 (0.54, 2.97)
Chronic kidney disease	36	2.9%	95	1.9%	2.45 (1.54, 3.90)	36	6.6%	106	5.2%	2.24 (1.40, 3.57)
Urinary tract infections	160	18.5%	312	10.6%	2.39 (1.93, 2.95)	74	21.0%	199	18.7%	1.33 (0.99, 1.78)
Infections of kidney	28	2.3%	46	1.0%	2.95 (1.75, 4.99)	9	1.7%	59	3.0%	0.64 (0.32, 1.29)*
Cystitis and urethritis	30	2.5%	78	1.6%	2.26 (1.41, 3.63)	16	3.0%	36	1.8%	1.53 (0.74, 3.16)
Urinary tract infection; site not specified	155	17.3%	302	9.8%	2.46 (1.98, 3.05)	69	18.8%	195	17.3%	1.28 (0.95, 1.74)
Calculus of urinary tract	35	2.9%	82	1.7%	2.01 (1.30, 3.10)	24	4.6%	43	2.3%	2.23 (1.28, 3.89)
Calculus of kidney	27	2.2%	46	1.0%	2.80 (1.63, 4.82)	18	3.4%	30	1.5%	2.28 (1.18, 4.43)
Calculus of ureter	9	0.7%	34	0.7%	1.21 (0.55, 2.62)	7	1.3%	27	1.3%	1.23 (0.50, 3.05)
Other and unspecified urinary calculus	13	1.1%	36	0.7%	1.69 (0.86, 3.32)	6	1.1%	20	1.0%	0.83 (0.30, 2.33)
Other diseases of kidney and ureters	148	15.6%	126	3.4%	2.19 (1.88, 2.55)*	56	14.0%	93	6.4%	2.76 (1.90, 4.01)
Hydronephrosis	97	8.3%	16	0.3%	35.94 (18.78, 68.80)	25	5.0%	15	0.8%	9.10 (4.29, 19.33)
Other and unspecified diseases of kidney and ureters	134	13.7%	121	3.2%	5.95 (4.65, 7.63)*	50	12.0%	87	5.7%	2.62 (1.76, 3.88)
Other diseases of bladder and urethra	36	3.0%	63	1.3%	3.15 (1.98, 5.02)	25	4.8%	51	2.6%	2.32 (1.33, 4.04)
Bladder neck obstruction	2	0.2%	1	0.0%	---	1	0.2%	0	0.0%	---
Other and unspecified diseases of bladder and urethra	34	2.8%	63	1.3%	2.75 (1.81, 4.18)*	24	4.6%	51	2.6%	2.29 (1.31, 3.99)
Genitourinary symptoms and ill-defined conditions	135	15.5%	272	8.8%	2.35 (1.87, 2.96)	69	19.3%	176	15.6%	1.50 (1.09, 2.07)
Hematuria	39	3.3%	92	2.0%	1.87 (1.25, 2.78)	28	5.5%	69	3.8%	1.43 (0.88, 2.33)
Retention of urine	24	2.0%	22	0.5%	5.74 (2.98, 11.06)	11	2.0%	31	1.5%	1.62 (0.74, 3.55)

	1 to <5 years after cancer diagnosis					5+ years after cancer diagnosis				
	Ovarian cancer survivors		General population			Ovarian cancer survivors		General population		
	N	%	N	%	HR (95% CI)[a]	N	%	N	%	HR (95% CI)[a]
Other and unspecified genitourinary symptoms	132	14.1%	261	7.6%	2.72 (2.15, 3.45)	72	18.5%	171	13.4%	1.72 (1.25, 2.37)

Abbreviation: HR, hazard ratio; CI, confident interval.

[a.] Models adjusted for matching factors, race, baseline BMI, baseline Charlson Comorbidity Index.

[*] Proportional hazards assumption not met; flexible model used.

Table 4.

Genital organ disease risks among ovarian cancer survivors in comparison to the general population of women, by years since cancer diagnosis

	1 to <5 years after cancer diagnosis					5+ years after cancer diagnosis				
	Ovarian cancer survivors		General population			Ovarian cancer survivors		General population		
	N	%	N	%	HR (95% CI)[a]	N	%	N	%	HR (95% CI)[a]
Diseases of female genital organs	156	22.1%	433	16.4%	1.88 (1.57, 2.27)*	26	14.6%	93	17.4%	0.96 (0.60, 1.54)
Inflammatory diseases of female pelvic organs	57	5.9%	78	2.2%	3.58 (2.45, 5.24)	19	5.1%	45	3.5%	1.52 (0.85, 2.72)
Pelvic peritoneal adhesions	33	2.9%	12	0.3%	16.59 (7.00, 39.34)	9	1.9%	5	0.3%	8.88 (1.88, 41.91)
Cervicitis and endocervicitis	3	0.3%	23	0.5%	0.62 (0.18, 2.11)	2	0.4%	8	0.4%	1.11 (0.21, 5.81)
Pelvic inflammatory disease	2	0.2%	1	0.0%	6.43 (0.15, 271.97)	---	---	---	---	---
Other inflammatory diseases of female pelvic organs	37	3.2%	64	1.4%	2.86 (1.83, 4.46)	22	4.4%	53	2.9%	1.80 (1.06, 3.07)
Endometriosis	4	0.4%	26	0.6%	0.88 (0.29, 2.64)	4	0.8%	18	1.1%	0.95 (0.30, 3.05)
Menstrual disorders[b]	6	2.1%	92	9.3%	0.25 (0.11, 0.59)	12	2.6%	52	4.0%	0.71 (0.38, 1.34)*
Ovarian cyst	19	1.8%	51	1.3%	1.85 (1.09, 3.13)*	7	1.6%	17	1.1%	1.29 (0.49, 3.41)
Menopausal disorders	88	8.8%	240	6.9%	1.61 (1.24, 2.10)	38	9.8%	139	11.5%	1.06 (0.72, 1.58)
Female infertility	2	0.2%	10	0.2%	0.64 (0.11, 3.76)	3	0.5%	2	0.1%	7.71 (0.84, 70.89)
Other female genital disorders	81	12.7%	149	7.1%	2.38 (1.76, 3.21)	20	8.7%	66	10.0%	0.97 (0.59, 1.61)*
Female genital pain and other symptoms	62	6.9%	128	3.9%	2.32 (1.71, 3.15)*	25	6.8%	72	5.9%	1.37 (0.85, 2.21)
Other and unspecified female genital disorders	61	7.5%	117	4.2%	2.26 (1.62, 3.15)	13	4.2%	38	4.0%	1.16 (0.62, 2.19)*

Abbreviation: HR, hazard ratio; CI, confident interval.

[a] Models adjusted for matching factors, race, baseline BMI, baseline Charlson Comorbidity Index.

[b] Women > 50 years old were excluded.

* Proportional hazards assumption not meant; flexible model used.

Table 5.

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

	Urinary system disorders		Genital organ disorders	
	1 to <5 years HR (95% CI)	5+ years HR (95% CI)	1 to <5 years HR (95% CI)	5+ years HR (95% CI)
Cancer Treatment[a]				
Surgery only	Reference	Reference	Reference	Reference
Surgery and chemotherapy	1.81 (1.33, 2.46)	0.89 (0.57, 1.38)	1.27 (0.85, 1.88)	1.39 (0.58, 3.35)
other treatment[e]	2.76 (1.58, 4.82)	1.01 (0.23, 4.43)	1.26 (0.62, 2.60)	2.62 (0.31, 22.23)
Surgery Type[a]				
Limited surgery[g]	Reference	Reference	Reference	Reference
Aggressive surgery[g]	3.34 (2.14, 5.22)	1.32 (0.80, 2.16)	1.53 (0.88, 2.65)	2.74 (0.80, 9.47)
Cancer Stage[a]				
Localized	Reference	Reference	Reference	Reference
Regional	1.39 (0.88, 2.22)	1.05 (0.59, 1.88)	1.01 (0.55, 1.84)*	0.71 (0.15, 3.49)
Advanced	3.11 (2.18, 4.45)	1.21 (0.73, 2.00)	1.27 (0.82, 1.97)*	2.10 (0.86, 5.12)
Histology[a]				
High-grade serous	Reference	Reference	Reference	Reference
Low-grade serous	0.67 (0.21, 2.13)	8.9 (2.99, 26.5)	---	0.76 (0.09, 6.79)
Endometrioid	0.38 (0.23, 0.64)	0.91 (0.47, 1.77)	0.83 (0.44, 1.56)	1.57 (0.52, 4.76)
Mucinous	0.51 (0.29, 0.88)	1.07 (0.55, 2.09)	1.01 (0.55, 1.87)	1.35 (0.36, 5.04)
Clear Cell	0.57 (0.32, 1.02)	1.58 (0.71, 3.52)	1.16 (0.59, 2.26)	---
Carcinosarcoma	2.00 (0.79, 5.08)	---	0.51 (0.07, 3.74)	---
Carcinoma, NOS	0.75 (0.44, 1.25)	0.74 (0.28, 1.91)	0.83 (0.38, 1.81)	2.52 (0.50, 12.60)
Other type[f]	0.54 (0.32, 0.91)	0.34 (0.13, 0.92)	0.70 (0.36, 1.37)	1.96 (0.55, 6.94)
Baseline BMI[b]				
<18 kg/m^2	1.31 (0.61, 2.83)	1.11 (0.27, 4.61)	1.48 (0.53, 4.14)	---
18 to 24 kg/m^2	Reference	Reference	Reference	Reference
25 to 29 kg/m^2	1.11 (0.81, 1.53)	0.79 (0.45, 1.37)	1.54 (1.05, 2.24)	1.08 (0.41, 2.89)
30+ kg/m^2	1.15 (0.82, 1.63)	1.50 (0.87, 2.60)	1.03 (0.65, 1.64)	2.01 (0.74, 5.45)
Age at Cancer Diagnosis[c]				
18–49	Reference	Reference	Reference	Reference
50–59	1.48 (1.03, 2.12)	1.55 (0.87, 2.75)	0.82 (0.53, 1.27)	0.46 (0.15, 1.35)
60–69	1.43 (0.97, 2.11)	2.89 (1.59, 5.24)	0.59 (0.36, 0.96)	0.71 (0.24, 2.10)
70–79	1.31 (0.87, 1.98)	5.45 (2.86, 10.38)	0.48 (0.28, 0.84)	0.81 (0.25, 2.66)
80+	2.85 (1.62, 5.01)	4.89 (0.65, 36.98)	0.76 (0.35, 1.66)	---
Baseline CCI[d]				
0	Reference	Reference	Reference	Reference

	Urinary system disorders		Genital organ disorders	
	1 to <5 years	5+ years	1 to <5 years	5+ years
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
1	1.31 (0.93, 1.83)	1.22 (0.64, 2.31)	0.82 (0.52, 1.29)	0.50 (0.11, 2.21)
2+	2.71 (1.84, 3.99)	0.72 (0.21, 2.45)	1.44 (0.89, 2.34)	0.34 (0.04, 2.76)

Abbreviation: HR, hazard ratio; CI, confident interval; CCI, Charlson Comorbidity Index.

Model adjusted for

[a] age at diagnosis, baseline BMI, baseline CCI, race;

[b] age at diagnosis, baseline CCI, race;

[c] baseline BMI, baseline CCI;

[d] age at diagnosis, baseline BMI, race.

[e] Chemotherapy only, surgery and radiation only, chemotherapy and radiation only, surgery and radiation and chemotherapy only.

[f] Malignant Brenner, mixed, sarcoma, non-specific.

[g] Limited surgery: removal of tumor or unilateral/bilateral oophorectomy (with or without hysterectomy).

Aggressive surgery: surgery with omentectomy, debulking, pelvic exenteration.

[*] Proportional hazards assumption not met; flexible model used.