Gynecologic Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

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

Sean Soisson [a,b], Patricia A. Ganz [c], David Gaffney [b,d], Kerry Rowe [e], John Snyder [e], Yuan Wan [f], Vikrant Deshmukh [g], Mike Newman [g], Alison Fraser [f], Ken Smith [f], Kimberly Herget [h], Heidi A. Hanson [f,i], Yelena P. Wu [b,j], Joseph Stanford [a], Theresa L. Werner [b,k], Veronica Wendy Setiawan [l], Mia Hashibe [a,b,*]

[a] Division of Public Health, Department of Family and Preventive Medicine, University of Utah School of Medicine, Salt Lake City, UT, United States
[b] Huntsman Cancer Institute, Salt Lake City, UT, United States
[c] Department of Health Policy and Management, UCLA Fielding School of Public Health, Los Angeles, CA, United States
[d] Department of Radiation Oncology, University of Utah School of Medicine, Salt Lake City, UT, United States
[e] Intermountain Healthcare, Salt Lake City, UT, United States
[f] Pedigree and Population Resources, Population Sciences, Huntsman Cancer Institute, Salt Lake City, UT, United States
[g] University of Utah Health Sciences Center, Salt Lake City, UT, United States
[h] Utah Cancer Registry, Salt Lake City, UT, United States
[i] Department of Surgery, University of Utah School of Medicine, Salt Lake City, UT, United States
[j] Department of Dermatology, University of Utah School of Medicine, Salt Lake City, UT, United States
[k] Division of Oncology, Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT, United States
[l] Department of Preventive Medicine, Keck School of Medicine of USC, Los Angeles, CA, United States

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.

ARTICLE INFO

Article history:
Received 10 October 2017
Received in revised form 20 December 2017
Accepted 22 December 2017
Available online xxxx

Keywords:
Endometrial cancer survivors
Cancer survivorship
Genitourinary toxicities
Genitourinary adverse events

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 2648 endometrial cancer survivors diagnosed in the state of Utah between 1997 and 2012 and 10,503 general population women were identified. All ICD-9 diagnosis codes 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 and 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 and 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 and 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

* Corresponding author at: Division of Public Health, Department of Family and Preventive Medicine, Huntsman Cancer Institute, 2000 Circle of Hope, Salt Lake City, UT 84112, United States.
E-mail address: mia.hashibe@utah.edu (M. Hashibe).

https://doi.org/10.1016/j.ygyno.2017.12.025
0090-8258/

monitoring and counseling for genitourinary disorders for endometrial cancer patients both immediately after treatment cessation and for years afterwards.

1. 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.

2. Methods

2.1. Data collection

Using the Utah Population database (UPDB), we identified women diagnosed with endometrial cancer in the state of Utah between 1997 and 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.

2.2. 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.

2.3. 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. non-white). 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

Please cite this article as: S. Soisson, et al., Long-term, adverse genitourinary outcomes among endometrial cancer survivors in a large, population-based cohort study, Gynecol Oncol (2017), https://doi.org/10.1016/j.ygyno.2017.12.025