LONG-TERM, ADVERSE CARDIOVASCULAR, GENITOURINARY, AND GASTROINTESTINAL OUTCOMES AMONG ENDOMETRIAL CANCER SURVIVORS IN A POPULATION-BASED COHORT STUDY

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ABSTRACT

Endometrial cancer is the second most common cancer among female cancer survivors in the United States. A variety of long-term, adverse health effects have been observed among endometrial cancer survivors but the relationship between endometrial cancer diagnosis and treatment and these outcomes among survivors, years after diagnosis remains poorly understood. Because of the high survival rate and the increasing rate at which new cases are being diagnosed, examining the risk for long-term, adverse health effects among endometrial cancer survivors is essential.

Cohorts of 2,648 endometrial cancer survivors diagnosed in Utah between 1997 and 2012 and 10,503 age-matched, cancer-free women from the general population were identified. Electronic medical record data including all International Classification of Diseases , 9th revision (ICD-9) diagnosis codes from Utah's two largest healthcare providers as well as statewide ambulatory surgery and inpatient records were used to capture all available cardiovascular, genitourinary, and gastrointestinal outcomes. Cox regression models were used to estimate risk for outcomes between survivors and individuals in the general population at 1-5 and >5-10 years after diagnosis. Cox regression models were also used to examine potential risk factors for various conditions among endometrial cancer survivors.

Endometrial cancer survivors were at elevated risk for cardiovascular, genitourinary, and gastrointestinal disorders overall and for dozens of more specific outcomes within these broader categories compared to the general population. Between 1-5 years after diagnosis,

endometrial cancer survivors treated with surgery in conjunction with chemotherapy and/or radiation were at elevated risk for heart, circulatory system, urinary system, genital organ, upper gastrointestinal, lower gastrointestinal, abdominal hernia, and liver disorders compared to those treated with surgery alone. Elevated risk for abdominal hernias and lower gastrointestinal disorders persisted between >5-10 years after diagnosis.

These results present sufficient evidence that endometrial cancer survivors experience a greater burden of adverse cardiovascular, genitourinary, and gastrointestinal outcomes many years after diagnosis compared to the general population and that these outcomes may be related to cancer treatment. Many of these conditions contribute to increased morbidity and mortality and adversely affect quality of life. For these reasons, greater attention should be focused both on long-term surveillance and prevention of these conditions among endometrial cancer survivors.

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CHAPTER 1

INTRODUCTION

1.1 Endometrial Cancer Incidence and Survival Statistics

Endometrial cancer is the second most common cancer among female cancer survivors in the United States, the fourth most commonly diagnosed cancer among women, and the 10th most commonly diagnosed cancer overall.[1] Endometrial cancer was the 8th most common cause of death from cancer among women in 2013, 7th in 2015, and the 6th in 2016, responsible for an estimated 10,470 deaths.[2] The majority (75-80%) of women diagnosed with endometrial cancer are diagnosed with stage I disease. The rate of death from endometrial cancer has increased by >1% per year since 2003, but the current 5-year survival rate is relatively high at 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]

The median age for endometrial cancer diagnosis is 62, and the majority of cases are diagnosed between 45 and 74 years of age.[3] Women with a family history of Lynch Syndrome-related disease (2-5% of all cases) are often diagnosed at an earlier age.[4-6] Incidence rates of newly diagnosed endometrial cancers among women under the age of 50 have increased by 1.3% per year since 1988 and by 1.9% per year among women over the age of 55 since 2005.[2] The increasing rate of newly diagnosed cases and high overall survival rate has led to a steadily growing number of endometrial cancer survivors in the United States, from 556,640 in 2006 to

an estimated 757,000 in 2016.[3,7]

1.2 Endometrial Cancer Type and Treatment Indication

Endometrial cancer was thought to be a single disease prior to the early 1980s, when clinicians observed that histologic, molecular, and behavioral characteristics suggested two distinct subtypes with differing etiologies.[8-10] Broadly, well differentiated endometrioid adenocarcinomas (with or without squamous differentiation) were labeled Type I; while those that are higher grade papillary serous, clear cell, or several additional types of carcinoma were labeled Type II.[11] Type I tumors comprise 80-90% of all endometrial cancer diagnoses while Type II tumors comprise 10-20%.[11,12]

After the FIGO staging criteria was revised in 2009, these prognostic factors were used to further classify tumors into low, intermediate, and high risk groups for metastases to lymph nodes, the abdominal cavity, and to distant sites.[13] Low risk endometrial cancers are endometrioid histology, stage IA, low grade tumors with <50% myometrial invasion; other stage I tumors are intermediate risk; and high risk tumors are those that are nonendometrioid histology, stage IB or higher, grade 3, and >50% myometrial invasion.[13,14]

Treatment for endometrial cancer in almost all cases involves total hysterectomy (usually with bilateral salpingo-oophorectomy).[15] The use of adjuvant radiation therapy, either external beam and/or brachytherapy, or chemotherapy varies by stage, grade, and histology at diagnosis; and lymphadenectomy is performed depending on grade, depth of myometrial invasion, and tumor size.[16] Using data from SEER and the National Cancer Database in 2013, it was estimated that 69% of those diagnosed with stage I or II endometrial cancer were treated with surgery alone, while 17% were treated with surgery and radiation therapy, 5% with surgery and chemotherapy, 6% with surgery, radiation therapy and chemotherapy, and 1% with

chemotherapy and radiation therapy.[17] For those diagnosed with stage III and IV endometrial cancer, 16% were treated with surgery alone, 28% with surgery and radiation therapy, 33% with surgery and chemotherapy, 5% with surgery, radiation therapy, and chemotherapy, and 12% with chemotherapy and radiation therapy.

1.3 Long-Term, Adverse Health Effects Among Endometrial Cancer Survivors

The majority of studies that have examined long-term adverse health outcomes among endometrial cancer survivors have focused primarily on health-related quality of life, mental health, obesity, and adverse sexual side effects. The studies that have measured specific cardiovascular, genitourinary, and gastrointestinal outcomes often include small numbers of individuals, lack control groups, lack validated outcome measures, measure symptoms that are secondary to an underlying cause, or suffer from loss to follow-up, making risk for these conditions difficult to quantify. The use of self-reported data from questionnaires to measure gastrointestinal and genitourinary outcomes may include questions about conditions that patients are reluctant to report.

1.3.1 Cardiovascular Outcomes

A study using Surveillance, Epidemiology, and End Results Program (SEER) data between 1973 and 1988 reported that cardiovascular disease was the leading cause of death among 33,233 endometrial cancer survivors.[18] The proportion of women diagnosed with Type I endometrial cancer in this cohort who died of cardiovascular disease (42.1%) was higher than the proportion of all women who died of cardiovascular disease during that same time period (35%).[19] This observation was supported in a subsequent study using SEER data between 1988

and 2002 that reported that the proportion of endometrial cancer survivors who died of cardiovascular disease was greater than those who died of any other cause.[20]

The relationship between endometrial cancer and cardiovascular disease is complicated due to shared risk factors.[21] The proportion of the American population that is obese has more than doubled since 1960, from 15.8% to 36.6%; and the proportion that is extremely obese is more than 6 times greater than in 1960, from 1.4% to 8.6%.[22] Heart disease and hypertension are likely common among endometrial cancer survivors[23] due to obesity, but there have been few studies sufficiently powered to examine the risk for more specific cardiovascular outcomes among endometrial cancer populations compared to the general population. The relationship between treatment with radiation therapy and cardiovascular disease is poorly understood, but there is evidence that treatment with chemotherapy can increase the risk of heart failure and cardiomyopathy.[24]

1.3.2 Genitourinary Outcomes

Adverse genitourinary conditions due to treatment for endometrial cancer are among the most commonly reported complications reported among endometrial cancer survivors. Long-term surveillance of surgically treated patients has suggested that regional complications due to surgery are usually resolved within 1 year, while treatment with radiation therapy can cause damage to tissue architecture of the genital and urinary systems that can persist for years after treatment cessation.[25-27]

In a comparison of urinary incontinence among survivors of several different cancer types, 40.2% of endometrial cancer survivors experienced urinary incontinence, which was higher than any of the other cancers examined (breast, prostate, bladder, colorectal, and lung), which ranged from 27.1%-35.2%.[28] Survivors of endometrial and cervical cancer also experience

urinary urgency, daytime leakage at least once a day, bladder pain, and nocturia. They are 2-5 times more likely to experience symptoms of urinary incontinence after 1 year of treatment cessation.[29] Endometrial cancer patients treated with external beam radiation therapy were at higher risk for urinary incontinence compared to those treated with brachytherapy at 7 and 10 years after diagnosis.[30] Additionally, there is evidence that the combination of external beam radiation therapy and brachytherapy increases the risk of long-term urinary complications compared to external beam radiation therapy or brachytherapy alone.[31]

There is evidence that individuals treated with radiation therapy for gynecologic malignancies may experience renal toxicity,[32] but very few studies have examined the relationship between radiation therapy therapy and specific renal outcomes among endometrial cancer survivors; and they have produced mixed results.

1.3.3 Gastrointestinal Outcomes

In a retrospective study that examined treatment related complications among high-risk endometrial cancer patients (*n*=109), 66% of individuals who experienced any complications had either adverse gastrointestinal or genitourinary outcomes.[33] Among those who experienced GI complications, 14% were short term (<6 months) and 29% were long-term (>6 months). Increased risk for diarrhea, pain, nausea, bloating, bowel obstructions, rectal bleeding, fecal incontinence, and urgency due to radiation therapy induced bowel damage has been observed among endometrial cancer patients years after diagnosis[34-36]. Adverse gastrointestinal outcomes among cancer survivors are often overlooked due to the priority of surveillance for disease recurrence, but gastrointestinal symptoms remain among the most common complications of treatment and have the greatest impact on quality of life.[37]

Treatment with external beam radiation therapy has been associated with adverse gastrointestinal outcomes among endometrial cancer survivors.[38,39] However, gastrointestinal outcomes have typically been measured in broad categories in populations <1,000 endometrial cancer survivors with broad variation in the length of time since diagnosis. Individuals treated with external beam radiation therapy have been observed to have more gastrointestinal complications within 5 years after diagnosis than those treated with brachytherapy, including diarrhea, leakage, and the need to stay within close proximity to a toilet, all of which limit daily activities.[40]

1.4 The Current Study

The three specific aims of this study are to compare the risk of a wide range of long-term (1) cardiovascular, (2) genitourinary, and (3) gastrointestinal outcomes between endometrial cancer survivors and individuals from the general population, as well as examine risk factors for a number of specific long-term outcomes among endometrial cancer survivors 1-5 years and >5-10 years after diagnosis. These risk factors include treatment type, stage, grade, and age at diagnosis, baseline body mass index, and baseline Charlson Comorbidity Index.

Cohorts of 2,648 women diagnosed with endometrial cancer and 10,503 matched individuals from the general population were identified using the Utah Population Database. Electronic medical record data containing all ICD-9 diagnosis codes from Utah's two largest healthcare providers as well as statewide ambulatory surgery and inpatient records were used to capture outcomes. The current study is one of the largest population-based cohort studies intended to quantify risk for adverse health outcomes among endometrial cancer survivors.

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CHAPTER 2

LONG-TERM CARDIOVASCULAR OUTCOMES AMONG ENDOMETRIAL CANCER SURVIVORS

2.1 Abstract

Endometrial cancer is the second most common cancer among female cancer survivors in the US, with an estimated 757,000 endometrial cancer survivors in 2016. Cardiovascular disease is the leading cause of death among endometrial cancer survivors. Risk for cardiovascular disease may be increased among endometrial cancer survivors due to shared risk factors such as obesity or due to the effects of cancer treatment. Because of the high overall survival rate and the large number of endometrial cancer survivors, studies that examine late effects among endometrial cancer survivors are critical.

Cohorts of 2,648 endometrial cancer survivors diagnosed in the state of Utah between 1997 and 2012, and 10,503 age-matched women from the general population were identified using the Utah Population Database. All ICD-9 diagnosis codes were collected from Utah's two largest healthcare systems in addition to statewide ambulatory surgery and inpatient visits. Cox regression models were used to estimate hazard ratios (HR) at 1-5 years and >5-10 years after cancer diagnosis. Models were adjusted for matching factors, race/ethnicity, baseline body mass index (BMI), and baseline Charlson Comorbidity Index.

Between 1-5 years after diagnosis, the some of the highest cardiovascular risks among endometrial cancer survivors were observed for phlebitis, thrombophlebitis and

thromboembolism (HR: 2.24, 99% CI: 1.63-3.08), lymphatic diseases (HR: 1.86, 99% CI: 1.62-2.14), pulmonary heart disease (HR: 1.82, 99% CI: 1.36-2.43), hypotension (HR: 1.85, 99% CI: 1.29-2.65), and atrial fibrillation (HR: 1.44, 99% CI: 1.02-2.02). At >5-10 years, elevated risk persisted for many of these diseases and other cardiovascular disease outcomes among the endometrial cancer survivors. In comparison to endometrial cancer patients who had surgery, patients who additionally had radiation therapy and/or chemotherapy were at increased risks for heart and circulatory system disorders at 1-5 years, but not at >5-10 years after cancer diagnosis. Obesity at cancer diagnosis contributed to increased risks of hypertension and diseases of the heart.

Endometrial cancer survivors in this population are at higher risk for various adverse long-term cardiovascular outcomes compared to women from the general population. This study suggests that increased monitoring for diseases of the cardiovascular system may be necessary for women diagnosed with endometrial cancer during the first several years after diagnosis and continued care throughout the life course.

2.2 Introduction

Endometrial cancer is the 4th most commonly diagnosed cancer among women in the United States and the second most common cancer among female cancer survivors.[1] Incidence rates among women under the age of 50 have been increasing by 1.3% per year since 1988 and by 1.9% among women over the age of 50 since 2005.[2] It was the 6th most common cause of death from cancer among women in the United States in 2016, with an estimated 10,470 deaths, having been 7th most common in 2015 and 8th most common in 2013.[2] Since 2003, rates of death due to endometrial cancer have increased by 1.1% per year. As of 2016, there were an estimated 757,000 endometrial cancer survivors in the United States.[3]

Endometrial cancer survivors are a relatively young population with high survival rates. The average age at diagnosis is 62, with the majority of endometrial cancers being diagnosed in women over the age of 55.[3,4] Women with a family history of hereditary nonpolyposis colon cancer (Lynch syndrome) are often diagnosed at an earlier age[5-7]. 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 stage IV.[2] However, little is known about the long-term health effects associated with endometrial cancer and whether treatment type moderates these effects.

Previous studies on the long-term health effects among endometrial cancer survivors have focused largely on quality of life, mental health, obesity, and adverse sexual side effects; though there have been several studies that have examined long-term cardiovascular outcomes among endometrial cancer survivors.[8-10] A 2015 study among long-term survivors of breast, prostate, colorectal, ovarian, and endometrial cancers found that endometrial cancer survivors (*n*=194) were diagnosed with an average of 2.4 comorbid conditions after their cancer diagnosis, which was second only to breast cancer survivors (with 2.9 comorbid conditions).[4] In addition, 21.2% of endometrial cancer survivors in their cohort experienced at least 1 adverse cardiovascular outcome after cancer diagnosis, a proportion that was higher than that of survivors of any of the other cancer sites.

Based on SEER data, cardiovascular disease was reported to be the leading cause of death greater than 5 years after cancer diagnosis among 33,233 endometrial cancer survivors diagnosed between 1973 and 1988.[8] The proportion of women diagnosed with localized, low grade endometrial cancer who died of cardiovascular disease in this population (42.1%) was higher than the proportion of all women who died of cardiovascular disease during that same time period (35%).[9] For individuals diagnosed with either high or low grade localized

endometrial cancer, the proportion of individuals who died of cardiovascular disease was greater than that of endometrial cancer, other malignancies, and other causes of death. Similarly, a study published in 2017 that examined mortality among endometrial cancer survivors diagnosed between 1988 and 2002 reported that between 5 and 10 years after diagnosis, endometrial cancer survivors were more likely to die of cardiovascular disease than of endometrial cancer, other malignancies, and other causes.[10]

Obesity is a risk factor for both endometrial cancer and cardiovascular disease.[8] The proportion of the American population that is obese has more than doubled since 1960, from 15.8% to 36.6%; and the proportion that is extremely obese is more than 6 times greater than in 1960, from 1.4% to 8.6%.[9] This increase in the prevalence of obesity in conjunction with changes in other endometrial cancer risk factors such as diabetes,[13] fertility,[14] intrauterine device use,[15,16] hormone therapy use,[17] and elective hysterectomy[18] may contribute to the increased incidence of endometrial cancer observed over the past several decades.

While there have been a number of studies that have examined long-term cardiovascular outcomes among endometrial cancer survivors, many of these have included small sample sizes, lacked control groups, measured broad outcome categories, or lacked validated outcome measures.

Studies that examine risk for long-term cardiovascular outcomes among endometrial cancer survivors using reliable data from electronic medical records are becoming increasingly more critical because of the high overall survival rate among individuals diagnosed with endometrial cancer, the large number of endometrial cancer survivors, the projected increase in the number of endometrial cancer diagnoses over the next several decades,[19] the introduction of more complex therapies, and the high mortality due to cardiovascular disease among endometrial cancer survivors.

2.3 Methods

2.3.1 Data Collection

An initial cohort of 3,624 endometrial cancer survivors was identified using the Utah Population Database. Diagnosis data were available from the statewide SEER Utah Cancer Registry for women aged 18 and over, diagnosed with invasive first primary endometrial cancer between 1997 and 2012 in the state of Utah (SEER International Classification of Diseases for Oncology (ICD-O-3) codes: C54.0-C55.9). Endometrial cancer histological subtypes adenocarcinoma, endometrioid, mucinous adenocarcinoma, and adenocarcinoma with squamous differentiation were classified as Type I (ICD-O-3 morphology codes: 8140, 8260, 8380, 8382, 8480, 8482, 8560, and 8570) and clear-cell carcinomas and papillary serous carcinomas as Type II (ICD-O-3 morphology codes: 8310, 8441, and 8460)[20]. Survivors were matched on birth year and birth state with up to 5 women from the general population.

Outcome data used for this study included statewide ambulatory and inpatient data from the Utah Department of Health and Electronic Data Warehouse data from Intermountain Health Care and the University of Utah Health Sciences Center. The Utah Population Database data included records from the Utah Cancer Registry, Utah Driver's License, vital records, and the Utah Department of Health. Statewide ambulatory and inpatient records as well as those from the University of Utah and Intermountain Healthcare systems were linked via the Utah Population Database.

Electronic medical record data was available prior to 1992, but all three major sources did not have comprehensive electronic medical record data for individuals in these cohorts until 1996. Individuals diagnosed with endometrial cancer between 1997 and 2012 were included in this analysis to allow adequate time prior to cancer diagnosis to capture prior diagnoses of the cardiovascular outcomes of interest. A total of 153 endometrial cancer patients were excluded

because their cancer was not staged, 470 because grade was missing, 285 because follow up time did not exceed 1 year, 65 because their Utah residence did not exceed 1 year. The stage and grade were necessary for our sample because we were interested in their potential role in risk for the outcomes measured in this study. There were a total of 2,648 endometrial cancer survivors included in the final sample.

2.3.2 Categorization of Outcomes

Outcome data from the statewide, University of Utah Health Sciences Center, and Intermountain Healthcare systems included all available ICD-9 diagnosis codes, as well as diagnosis date which allowed for time to outcome to be calculated). The Clinical Classification Software developed by the Health Cost and Utilization Project was used to categorize ICD-9 codes into 4 levels of specificity (Levels 1-4).[21] Diseases of the cardiovascular system (level 1) according to the Clinical Classification Software were used in this analysis. Level 2 outcomes included hypertension, diseases of the heart, cerebrovascular diseases, diseases of the arteries, arterioles, and capillaries, and diseases of the veins and lymphatics. More specific outcomes within these categories were analyzed as level 3 and 4 outcomes. Examples of this hierarchy include diseases of the heart (level 2), heart valve disorders (level 3), chronic rheumatic disease of the heart valves (level 4), and cerebrovascular disease (level 2), acute cerebrovascular disease (level 3), and intracranial hemorrhage (level 4).

Long-term cardiovascular outcomes were measured 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. Level 3 or 4 outcomes diagnosed prior to the start of each analysis time period were considered prevalent cases of those outcomes and individuals were excluded from the relevant models. Level 1 and 2 outcomes were broader and contained multiple disparate conditions, thus we did not exclude prevalent diagnoses.

2.3.3 Statistical Analysis

Chi-square tests were used to compare baseline characteristics between the cancer and general population cohorts. Univariate and multivariate Cox proportional hazard models were used to calculate hazard ratios for long-term cardiovascular outcomes at 1-5 years and >5-10 years after endometrial cancer diagnosis. We used 99% confidence intervals to account for the penalty imposed by multiple testing due to the large number of outcomes examined in this analysis. Multivariate models were adjusted for matching factors, baseline body mass index (BMI), baseline Charlson Comorbidity Index, and race. 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 hypertension, heart disease, diseases of the arteries, arterioles, and capillaries, and diseases of the veins and lymphatics among endometrial cancer survivors. The proportional hazards assumption was checked for each model using a test for nonzero 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 1 year prior to cancer survivors' endometrial cancer diagnosis were calculated from the driver's license records. For the cancer-free women, the most recent BMI value recorded at least 1 year prior to the endometrial cancer diagnosis date of the matched cancer patient was included. Approximately 35% of the 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 Charlson Comorbidity Index,[22] 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.

2.4 Results

The endometrial cancer survivors cohort had a higher proportion of obese individuals (44.2% vs 19.2%) than the general population cohort (p<0.001; Table 2.1). Approximately 81.53% of the endometrial cancer survivors were diagnosed with low grade tumors, and 80.3% with stage I disease (Table 2.2).

Elevated risks for hypertension were observed among endometrial cancer survivors compared to the general population cohort (Table 2.3) between 1-5 years (HR: 1.51, 99% CI: 1.36-1.67) and between >5-10 years (HR: 1.44, 99% CI: 1.28-1.62) after diagnosis . Approximately 5.5% of endometrial cancer patients were diagnosed with cerebrovascular disease, but an increased risk was not observed compared to the general population cohort.

Increased risks for multiple circulatory system diseases were observed 1-5 years after cancer diagnosis (Table 2.4). Endometrial cancer survivors were 44% more likely to be diagnosed with diseases of arteries, arterioles, and capillaries during both time periods. Elevated risk during both the 1-5 year and >5-10 year time periods was observed for peripheral and

vascular atherosclerosis, hypotension, phlebitis, thrombophlebitis, thromboembolism, other circulatory diseases, and other diseases of the veins and lymphatics.

Approximately 25.7% of cancer survivors were diagnosed with diseases of the heart compared to 21.7% of individuals in the general population cohort >5-10 years after cancer diagnosis (Table 2.5). Endometrial cancer survivors were 44% more likely to be diagnosed with a disease of the heart between 1-5 years and 50% more likely between >5-10 years after diagnosis. Elevated risk among endometrial cancer survivors was observed for cardiac dysrhythmias, nonhypertensive congestive heart failure, and congestive heart failure overall at both 1-5 and >5-10 years after diagnosis. Endometrial cancer survivors had a higher risk of developing heart valve disorders, premature beats, and other/ill-defined heart disease at >5-10 years after diagnosis, but not at 1-5 years.

Among endometrial cancer survivors, 68.5% were treated with surgery alone, 21.9% with surgery and radiation therapy, 3.2% with surgery and chemotherapy, and 4.7% with surgery, radiation therapy, and chemotherapy. Among individuals treated with radiation therapy and/or chemotherapy in addition to surgery, elevated risks were observed for diseases of arteries, diseases of veins/lymphatics and heart disease at 1-5 years compared to those treated with surgery alone. These increased risks did not persist in the >5-10 year time period.

Higher BMI was an important risk factor for hypertension and heart disease among endometrial cancer survivors, with both overweight and obese individuals having higher risk at both 1-5 and >5-10 years after cancer diagnosis (Table 2.6). Obese individuals also had elevated risk of diseases of arteries at 1-5 years. Risk for hypertension, heart disease, and diseases of arteries, arterioles, and capillaries increased with each 10-year interval of age at diagnosis compared to those diagnosed prior to age 50 at time period. This association was observed for diseases of the veins and lymphatics at 1-5 years but not at >5-10 years. Stage, grade, and

Charlson Comorbidity Index at baseline also appeared to be important risk factors for these diseases among endometrial cancer survivors.

Figure 2.1 illustrates the comparison of cumulative incidences of newly diagnosed pulmonary heart disease, congestive heart failure, phlebitis and thrombophlebitis, hypertension with complications/secondary complications over the span of 1-10 years after endometrial cancer diagnosis between endometrial cancer survivors and the general population cohort. Stratified analysis comparing risk between those diagnosed with Type I vs Type II endometrial cancer in this cohort showed a clear trend towards larger effect sizes among those diagnosed with Type II endometrial cancer where risk was significantly higher among endometrial cancer survivors overall. These individuals are both more likely to have received radiation therapy and to be treated at a higher dose.

2.5 Discussion

This study is the first to examine risk for all available cardiovascular outcomes in the electronic medical records of several thousand endometrial cancer survivors and matched controls from the general population in a large cohort study. Prior studies that have examined long-term, adverse outcomes among endometrial cancer survivors have tended to focus either on a narrower range of outcomes or have sought to examine the effects related to specific treatments. The results of this study indicate strong evidence that endometrial cancer survivors are at higher risk for a wide range of adverse cardiovascular outcomes years after cancer diagnosis. Of the 5 major cardiovascular disease categories examined, endometrial cancer survivors were at higher risk for hypertension, diseases of the arteries, arterioles and capillaries, diseases of the veins and lymphatics, and diseases of the heart at both 1-5 and >5-10 years after cancer diagnosis after controlling for baseline BMI, Charlson Comorbidity Index and race.

Cerebrovascular disease was the only major category for which no clearly increased risk was observed among survivors. Among endometrial cancer survivors, our results suggest that risk for heart disease is elevated among individuals treated with chemotherapy compared to those who were treated with surgery alone. Similarly, elevated risk was observed for arterial and venous/lymphatic disease among those treated with radiation therapy and/or chemotherapy in conjunction with surgery compared to those treated with surgery alone.

At 1-5 years and >5-10 year after cancer diagnosis, survivors were more likely to be diagnosed with hypertension than individuals from the general population. Additionally, survivors were more than 60% more likely to be diagnosed with secondary hypertension or hypertensive heart or renal disease. Among endometrial cancer survivors, the strongest predictors for increased risk of hypertension were being overweight or obese, increased age, and higher Charlson Comorbidity Index. Risk did not vary by treatment type, stage, or grade. Our findings provide further evidence for the strong association between shared risk factors for both endometrial cancer and hypertension, specifically increased age, higher BMI, and having multiple comorbidities. Prior studies have reported similar proportions of endometrial cancer survivors who have received a diagnosis of hypertension (43-47%),[23,24] but this study is the first to quantify risk for hypertension among endometrial cancer survivors compared to the general population.

The highest risk among endometrial cancer survivors in this study was observed for phlebitis, thrombophlebitis, and thromboembolism. Hypotension can occur in conjunction with pulmonary embolism, deep vein thrombosis, venous thromboembolism, and other circulatory system disorders[25] and the elevated risk of hypotension among endometrial cancer survivors in this study may be related to these conditions. For these circulatory system disorders, it is possible that radiation damage to the endothelial cells of the vascular system could be

implicated.[26] The increased risk for circulatory system disorders among survivors treated with radiation therapy and/or chemotherapy support previous findings that risk for these conditions is elevated among survivors of lymphoma, breast cancer, and head and neck cancer who were treated with radiation therapy[27] and among individuals treated with chemotherapy for a variety of cancers.[28]

For diseases of the heart, elevated risk for chest pain and pulmonary heart disease was observed at 1-5 years but not at >5-10 years. Individuals diagnosed with endometrial cancer were approximately 50% more likely to be diagnosed with cardiac dysrhythmias and congestive heart failure than individuals in the general population at both 1-5 years and >5-10 years after cancer diagnosis. Both have well established associations with obesity and a number of additional cardiovascular diseases, including hypertension, myocarditis, myocardial infarction, and cardiomyopathy.[29,30] While cardiomyopathy and myocardial infarction risk was similar to that of the general population, other peri/endo/myocarditis diseases were more common in endometrial cancer survivors. Cardiac dysrhythmias and congestive heart failure as a result of cancer treatment have more often been associated with pharmacologic interventions than with radiation therapy,[31,32] and the increased risk for heart disease overall among survivors treated with chemotherapy, in conjunction with surgery and/or radiation therapy compared to those treated with surgery alone support this evidence. Our results suggest that cancer treatment increasing the risk of cardiovascular disease was largely confined to the 1-5 years after cancer diagnosis and that treatment with chemotherapy was an important factor.

This study has a number of significant strengths. The large sample size (>2,500 endometrial cancer survivors and >10,000 cancer free women) provides a study population large enough to be sufficiently powered to examine a large number of potential outcomes without being overburdened by the penalty imposed by multiple comparisons. This is a critical feature in

a study intended to encapsulate the experience of endometrial cancer survivors over a long period of time. The data used in this study incorporates medical records from the state's two largest healthcare providers (Intermountain Healthcare and University of Utah Health Sciences Center) as well as statewide ambulatory surgery and inpatient data, which provides comprehensive medical record data for a large number of individuals. In addition to the large sample size, these data contain a large amount of follow-up time for individuals in both cohorts. The mean follow-up time among survivors is 8.5 years. Approximately 27% have total follow-up time between 1 and 5 years, 39% between 5 and 10 years, and 34% in excess of 10 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 are comprised of comprehensive electronic medical record 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 98.5% 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 10 years is limited due to lack of follow-up time for this proportion of the study population. However, with the Utah Population Database as a data source, we are able to update our analysis on a regular basis. Another limitation of this study concerns the lack of baseline BMI data. It was required that baseline BMI be recorded at least 1 year prior to the survivor's cancer diagnosis. This decision was made to avoid potential bias introduced by including BMI values recorded during a time

period when BMI could be affected by development of endometrial cancer in the cancer survivors cohort. This issue was addressed by imputing baseline BMI for those individuals with missing values using endometrial cancer status, age at diagnosis, and baseline Charlson Comorbidity Index. We assured that the inferences for our results did not change whether we used the original BMI variable or the BMI variable with subjects with missing BMI having imputed values.

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 radiation therapy type and dosage, specific chemotherapy agents, and duration of treatment. However, the treatment data that were available did provide evidence that risk for several cardiovascular outcomes vary by treatment type. Additional research is also needed to determine the contribution of diet and physical activity to these outcomes to better understand the causal relationship between treatment type and the outcomes examined in this study.

In conclusion, endometrial cancer survivors in this cohort were at higher risk for a number of long-term cardiovascular outcomes. These results present a wide range of outcomes encompassing hypertension, diseases of the heart, cerebrovascular diseases, diseases of the arteries, arterioles, and capillaries, and diseases of the veins and lymphatics. 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. Despite this, it is clear from these results that the survivors of endometrial cancers in this cohort experienced a high burden of cardiovascular events. These results highlight the importance of placing greater emphasis on survivorship and that increased monitoring for cardiovascular disease over long periods of time among endometrial cancer survivors is warranted.

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Table 2.1: 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	4.38	473	4.50	
1920-1929	310	11.71	1,192	11.35	
1930-1939	541	20.43	2,015	19.18	
1940-1949	787	29.72	3,085	29.37	
1950-1959	591	22.32	2,444	23.27	
>1960	303	11.44	1,294	12.32	0.54
Race					
White	2,525	95.35	9,617	91.56	
Black	10	0.38	29	0.28	
American Indian/Alaskan Native	111	1.06	32	1.21	
Asian	277	2.64	19	0.72	
Pacific Islander	60	0.57	48	1.81	
Unknown	14	0.53	409	3.89	*<0.001*
Vital Status					
Alive	1,924	72.66	8,906	84.79	
Dead	724	27.34	1,597	15.21	*<0.001*
Baseline BMI					
<18 kg/m^2	18	0.68	307	2.92	
18-24.9 kg/m^2	645	24.36	4,994	47.55	
25-29.0 kg/m^2	814	30.74	3,190	30.74	
>30 kg/m^2	1,171	44.22	2,012	19.16	*<0.001*
Age Attained at the End of Follow-up					
<50	161	6.08	697	6.64	
50-59	389	14.69	1,697	16.16	
60-69	826	31.19	3,142	29.92	
70-79	692	26.13	2,637	25.11	
80-89	442	16.69	1,787	17.01	
90+	138	5.21	543	5.17	0.303
Follow up Period					
1-5 years	726	27.42	2,742	26.11	
>5-10 years	1,028	38.82	4,062	38.67	
>10-15 years	595	22.47	2,576	24.53	
15+ years	299	11.29	1,123	10.69	0.122

Table 2.2: Clinical characteristics among endometrial cancer survivors

	Endometrial Cancer (n=2,648)	
Diagnosis Year	n	%
1997-2000	563	21.26
2001-2003	471	17.79
2004-2006	483	18.24
2007-2009	572	21.60
2010-2012	559	21.11
Age at Diagnosis		
<40	140	5.29
40-49	307	11.59
50-59	786	29.68
60-69	758	28.63
70-79	451	17.03
80+	206	7.78
Grade		
Grade I (Well differentiated)	1,314	49.62
Grade II (Moderately differentiated)	845	31.91
Grade III (Poorly differentiated)	421	15.90
Grade IV (Undifferentiated)	68	2.57
Stage		
Local	10,565	80.34
Regional	2,154	16.38
Advanced	432	3.28
Histology		
Endometrioid adenocarcinoma	1,853	69.98
Adenocarcinoma with squamous differentiation	56	2.11
Serous adenocarcinoma	87	3.29
Clear cell adenocarcinoma	17	0.64
Mixed cell adenocarcinoma	47	1.77
Mucinous adenocarcinoma	45	1.70
Carcinosarcoma	26	0.98
Stromal sarcoma	44	1.66
Leiomyosarcoma	41	1.55
Other	432	16.31
Endometrial Cancer Type		
Type I	2,300	86.86
Type II	87	3.29
Unknown	261	9.86
Treatment Type		
Surgery only	1,813	68.47
Surgery and radiation	579	21.87
Surgery and chemotherapy	84	3.17
Surgery, radiation, and chemotherapy	124	4.68
No available treatment information	48	1.81

Table 2.3: Hypertension and cerebrovascular 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					
	Survivors		General Population			
	n	%	n	%	HR	99% CI
Hypertension	1,237	46.7	3,431	32.7	**1.51***	**(1.36-1.67)**
Essential hypertension	202	17.3	1,165	16.1	0.99	(0.78-1.26)
Hypertension with comp./secondary hypertension	106	4.2	241	2.4	**1.66**	**(1.17-2.35)**
Hypertensive heart and/or renal disease	90	3.5	213	2.1	**1.60**	**(1.10-2.33)**
Cerebrovascular disease	145	5.5	560	5.3	1.02	(0.78-1.33)
Acute cerebrovascular disease	56	2.2	212	2.1	1.17	(0.77-1.80)
Occlusion of cerebral arteries	32	1.2	125	1.2	1.04	(0.59-1.81)
Occlusion or stenosis of precerebral arteries	27	1.0	127	1.2	0.77	(0.42-1.41)
Transient cerebral ischemia	35	1.4	149	1.5	0.81	(0.47-1.37)
	5-10 Years					
	Survivors		General Population			
	n	%	n	%	HR	99% CI
Hypertension	874	33.0	2,906	27.7	**1.44**	**(1.28-1.62)**
Essential hypertension	137	14.2	814	13.5	0.96	(0.70-1.32)
Hypertension with comp./secondary hypertension	101	4.2	241	2.4	**1.65**	**(1.15-2.37)**
Hypertensive heart and/or renal disease	95	3.9	218	2.2	**1.80**	**(1.24-2.63)**
Cerebrovascular disease	124	4.7	494	4.7	1.27	(0.94-1.70)
Acute cerebrovascular disease	47	1.9	203	2.0	1.20	(0.75-1.92)
Occlusion of cerebral arteries	32	1.7	101	1.3	1.19	(0.67-2.12)
Occlusion or stenosis of precerebral arteries	26	1.0	112	1.1	1.09	(0.56-2.13)
Transient cerebral ischemia	34	1.3	106	1.1	1.48	(0.82-2.66)

Models adjusted for baseline BMI, baseline Charlson Comorbidity Index, and race.

*Models in violation of the proportional hazards assumption that were evaluated using flexible parametric survival models with restricted cubic splines. The following outcomes were evaluated but no elevated risk was observed: other hypertensive complications, intracranial hemorrhage, acute but ill-defined cerebrovascular event, other and ill-defined cerebrovascular disease, late effects of cerebrovascular disease.

Table 2.4: Circulatory system disease risks at 1-5 and >5-10 years after diagnosis among endometrial cancer survivors in comparison to a general population cohort of women.

	1-5 Years					
	Survivors		General Population			
	n	%	n	%	HR	99% CI
Diseases of arteries; arterioles; and capillaries	495	18.7	1,366	13.0	**1.44**	**(1.24-1.68)**
Peripheral and visceral atherosclerosis	108	4.2	256	2.5	**1.77**	**(1.27-2.48)**
Atherosclerosis of arteries of extremities	17	0.6	52	0.5	1.75	(0.76-4.02)
Peripheral vascular disease unspecified	39	1.5	103	1.0	**1.75**	**(1.01-3.01)**
Other peripheral and visceral atherosclerosis	70	2.7	163	1.6	**1.69**	**(1.12-2.56)**
Aortic; peripheral; and visceral artery aneurysms	17	0.7	63	0.6	1.15	(0.53-2.50)
Aortic and peripheral arterial embolism or thrombosis	10	0.4	24	0.2	1.73*	(0.59-5.10)
Other circulatory disease	262	12.7	779	8.4	**1.47**	**(1.19-1.83)**
Hypotension	99	3.9	237	2.3	**1.85**	**(1.29-2.65)**
Other and unspecified circulatory disease	223	10.5	681	7.3	**1.33**	**(1.06-1.68)**
Diseases of veins and lymphatics	615	23.2	1,380	13.1	**1.86***	**(1.62-2.14)**
Phlebitis; thrombophlebitis and thromboembolism	134	5.7	248	2.5	**2.24***	**(1.63-3.08)**
Phlebitis and thrombophlebitis	53	2.1	82	0.8	**3.11**	**(1.83-5.28)**
Other venous embolism and thrombosis	124	5.2	225	2.2	**2.19***	**(1.57-3.05)**
Hemorrhoids	206	9.1	680	7.4	**1.26**	**(1.00-1.58)**
Other diseases of veins and lymphatics	120	4.8	119	1.2	**4.47***	**(3.03-6.59)**

Table 2.4 Continued

	5-10 Years					
	Survivors		General Population			
	n	%	n	%	HR	99% CI
Diseases of arteries; arterioles; and capillaries	372	14.1	1,244	11.8	**1.44**	**(1.21-1.73)**
Peripheral and visceral atherosclerosis	64	2.6	233	2.3	**1.59**	**(1.04-2.44)**
Atherosclerosis of arteries of extremities	14	0.5	37	0.4	1.76	(0.63-4.89)
Peripheral vascular disease unspecified	22	0.9	93	0.9	1.16	(0.57-2.36)
Other peripheral and visceral atherosclerosis	46	1.8	161	1.6	1.63	(0.99-2.69)
Aortic; peripheral; and visceral artery aneurysms	12	0.5	61	0.6	1.23	(0.46-3.29)
Aortic and peripheral arterial embolism or thrombosis	7	0.3	20	0.2	1.53	(0.45-5.23)
Other circulatory disease	175	9.7	671	7.9	**1.36**	**(1.04-1.77)**
Hypotension	73	3.0	227	2.3	**1.51**	**(1.01-2.26)**
Other and unspecified circulatory disease	144	7.6	593	6.8	1.22*	(0.92-1.63)
Diseases of veins and lymphatics	380	14.4	1,098	10.5	**1.60**	**(1.35-1.91)**
Phlebitis; thrombophlebitis and thromboembolism	64	2.9	205	2.1	**1.61**	**(1.05-2.48)**
Phlebitis and thrombophlebitis	18	0.7	64	0.6	1.92	(0.84-4.38)
Other venous embolism and thrombosis	55	2.4	183	1.9	1.40	(0.88-2.23)
Hemorrhoids	125	6.0	481	5.7	1.25	(0.93-1.68)
Other diseases of veins and lymphatics	45	1.9	120	1.2	**1.84**	**(1.06-3.18)**

Models adjusted for baseline BMI, baseline Charlson Comorbidity Index, and race. The following outcomes were evaluated but no elevated risk was observed: abdominal aortic aneurysm; without rupture, other aneurysm, arterial embolism and thrombosis of lower extremity artery, other arterial embolism and thrombosis, varicose veins of lower extremity.

*Models in violation of the proportional hazards assumption that were evaluated using flexible parametric survival models with restricted cubic splines.

Table 2.5: Heart disease risk at 1-5 and >5-10 years after diagnosis among endometrial cancer survivors in comparison to a general population cohort of women.

	1-5 Years					
	Survivors		General Population			
	n	%	n	%	HR	99% CI
Diseases of the heart	962	36.3	2,742	26.1	**1.44**	**(1.29-1.61)**
Heart valve disorders	129	5.5	425	4.3	1.19	(0.88-1.60)
Peri-; endo-; and myocarditis; cardiomyopathy	48	1.9	157	1.5	1.23	(0.76-2.01)
Cardiomyopathy	28	1.1	104	1.0	0.99	(0.54-1.85)
Other peri-; endo-; and myocarditis	25	1.9	69	0.7	**2.11**	**(1.02-4.37)**
Acute myocardial infarction	41	1.6	113	1.1	1.50	(0.87-2.58)
Coronary atherosclerosis and other heart disease	130	5.5	454	4.7	1.32*	(0.98-1.77)
Angina pectoris	27	1.1	114	1.1	0.70	(0.37-1.33)
Coronary atherosclerosis	114	4.7	381	3.9	1.27	(0.93-1.75)
Nonspecific chest pain	222	10.6	724	8.3	**1.26**	**(1.00-1.57)**
Pulmonary heart disease	130	5.3	266	2.6	**1.71**	**(1.24-2.36)**
Other and ill-defined heart disease	113	4.6	319	3.1	1.23	(0.89-1.71)
Conduction disorders	62	2.5	204	2.0	1.29	(0.83-1.99)
Cardiac dysrhythmias	225	10.8	704	7.7	**1.51**	**(1.19-1.90)**
Paroxysmal supraventricular tachycardia	16	0.6	57	0.6	1.11	(0.49-2.47)
Paroxysmal ventricular tachycardia	17	0.7	46	0.4	2.18	(0.83-5.72)
Atrial fibrillation	101	4.1	295	2.9	**1.44**	**(1.02-2.02)**
Atrial flutter	28	1.1	70	0.7	1.44	(0.75-2.77)
Premature beats	49	1.9	142	1.4	1.54	(0.94-2.54)
Other cardiac dysrhythmias	194	8.7	566	6.0	**1.50**	**(1.17-1.92)**
Cardiac arrest and ventricular fibrillation	17	0.7	47	0.5	1.99	(0.81-4.88)
Congestive heart failure; nonhypertensive	127	5.2	382	3.8	**1.43**	**(1.06-1.95)**
Congestive heart failure	121	5.0	350	3.5	**1.50**	**(1.09-2.06)**

Table 2.5 Continued

	Survivors		>5-10 Years General Population			
	n	%	n	%	HR	99% CI
Diseases of the heart	680	25.7	2,275	21.7	**1.50**	**(1.31-1.71)**
Heart valve disorders	100	4.5	346	3.7	**1.43**	**(1.02-2.03)**
sPeri-; endo-; and myocarditis; cardiomyopathy	44	1.7	123	1.2	1.63	(0.94-2.80)
Cardiomyopathy	31	1.2	91	0.9	1.48	(0.75-2.90)
Other peri-; endo-; and myocarditis	20	0.8	41	0.4	**2.61**	**(1.12-6.07)**
Acute myocardial infarction	26	1.0	104	1.0	0.98	(0.48-2.00)
Coronary atherosclerosis and other heart disease	98	4.4	367	4.0	1.09	(0.75-1.57)
Angina pectoris	34	1.3	99	1.0	1.19	(0.62-2.30)
Coronary atherosclerosis	85	3.6	298	3.1	1.13	(0.75-1.69)
Nonspecific chest pain	131	7.0	527	6.6	1.24	(0.92-1.67)
Pulmonary heart disease	63	2.7	245	2.5	1.26	(0.83-1.92)
Other and ill-defined heart disease	97	4.2	293	3.0	**1.47***	**(1.01-2.13)**
Conduction disorders	48	1.9	208	2.1	1.05	(0.64-1.73)
Cardiac dysrhythmias	160	8.6	572	6.8	**1.53**	**(1.16-2.04)**
Paroxysmal supraventricular tachycardia	11	0.4	37	0.4	0.92	(0.30-2.81)
Paroxysmal ventricular tachycardia	17	0.7	54	0.5	1.49	(0.64-3.49)
Atrial fibrillation	75	3.2	296	3.0	1.25	(0.85-1.84)
Atrial flutter	24	0.9	78	0.8	1.26	(0.61-2.57)
Premature beats	36	1.4	123	1.2	**1.92**	**(1.06-3.48)**
Other cardiac dysrhythmias	142	6.0	444	5.0	**1.76**	**(1.31-2.37)**
Cardiac arrest and ventricular fibrillation	16	0.6	49	0.5	1.38	(0.57-3.38)
Congestive heart failure; nonhypertensive	100	4.3	326	3.4	**1.58**	**(1.08-2.31)**
Congestive heart failure	91	3.9	305	3.2	**1.53***	**(1.03-2.28)**

Models adjusted for baseline BMI, baseline Charlson Comorbidity Index, and race.

*Models in violation of the proportional hazards assumption that were evaluated using flexible parametric survival models with restricted cubic splines

Table 2.6: Risk factor for hypertension, heart disease, and vascular diseases among endometrial cancer survivors

	Hypertension			
	1-5 Years		>5-10 Years	
	HR	**95% CI**	**HR**	**95% CI**
Treatment Type[a]				
Surgery only		*Reference*		
Surgery and radiation	**1.14**	**(1.00-1.30)**	1.1	(0.93-1.29)
Surgery and chemotherapy	1.27	(0.90-1.80)	1.26	(0.67-2.36)
Surgery, radiation, and chemotherapy	1.18	(0.89-1.55)	1.19	(0.79-1.77)
Stage[b]				
Local		*Reference*		
Regional	1.02	(0.88-1.19)	1.07	(0.88-1.30)
Advanced	0.93	(0.64-1.36)	0.73	(0.30-1.77)
Grade[b]				
Grade I (Well differentiated)		*Reference*		
Grade II (Moderately differentiated)	0.95	(0.84-1.08)	0.94	(0.82-1.09)
Grade III (Poorly differentiated)	1.05	(0.89-1.23)	**0.79**	**(0.63-0.99)**
Grade IV (Undifferentiated)	1.10	(0.74-1.63)	0.71	(0.33-1.49)
Year of Diagnosis[c]				
1997-2000		*Reference*		
2001-2004	**1.27**	**(1.08-1.51)**	1.17	(0.99-1.39)
2005-2010	**1.18**	**(1.02-1.38)**	**0.84**	**(0.70-0.99)**
2011-2012	1.08	(0.88-1.33)	.	.
Age at Diagnosis[d]				
<50		*Reference*		
50-59	**1.64**	**(1.32-2.03)**	**1.67**	**(1.32-2.11)**
60-69	**2.31**	**(1.87-2.85)**	**2.27**	**(1.80-2.86)**
70-79	**2.84**	**(2.27-3.55)**	**2.63**	**(2.04-3.39)**
80+	**3.42**	**(2.64-4.43)**	**3.26**	**(2.36-4.51)**
Charlson Comorbidity Index[e]				
0		*Reference*		
1	**1.52**	**(1.32-1.76)**	**1.73**	**(1.47-2.05)**
2+	**2.78**	**(2.41-3.20)**	**2.82**	**(2.36-3.37)**
Baseline BMI[f]				
<18 kg/m^2	1.02	(0.45-2.29)	1.72	(0.76-3.90)
18-24.9 kg/m^2		*Reference*		
<25-29.9 kg/m^2	**1.69**	**(1.43-2.00)**	**1.46**	**(1.20-1.78)**
>30 kg/m^2	**1.82**	**(1.55-2.13)**	**1.75**	**(1.45-2.10)**

Table 2.6 Continued

	Heart Disease			
	1-5 Years		>5-10 Years	
	HR	95% CI	HR	95% CI
Treatment Type[a]				
Surgery only			*Reference*	
Surgery and radiation	1.12	(0.96-1.30)	1.08	(0.90-1.29)
Surgery and chemotherapy	**2.29**	**(1.62-3.23)**	1.32	(0.65-2.66)
Surgery, radiation, and chemotherapy	**1.91**	**(1.44-2.54)**	1.19	(0.75-1.90)
Stage[b]				
Local			*Reference*	
Regional	1.02	(0.88-1.19)	1.06	(0.85-1.33)
Advanced	0.93	(0.64-1.36)	**2.10**	**(1.03-4.26)**
Grade[b]				
Grade I (Well differentiated)			*Reference*	
Grade II (Moderately differentiated)	1.06	(0.92-1.23)	1.05	(0.89-1.24)
Grade III (Poorly differentiated)	**1.56**	**(1.31-1.86)**	1.00	(0.78-1.28)
Grade IV (Undifferentiated)	**2.35**	**(1.63-3.40)**	0.62	(0.25-1.49)
Year of Diagnosis[c]				
1997-2000			*Reference*	
2001-2004	1.02	(0.85-1.23)	0.96	(0.79-1.16)
2005-2010	0.89	(0.75-1.05)	**0.72**	**(0.59-0.87)**
2011-2012	**0.70**	**(0.55-0.89)**	.	.
Age at Diagnosis[d]				
<50			*Reference*	
50-59	**1.44**	**(1.13-1.84)**	**1.41**	**(1.08-1.83)**
60-69	**1.99**	**(1.57-2.53)**	**1.86**	**(1.44-2.41)**
70-79	**2.65**	**(2.06-3.39)**	**2.40**	**(1.81-3.18)**
80+	**4.01**	**(3.03-5.30)**	**3.92**	**(2.79-5.49)**
Charlson Comorbidity Index[e]				
0			*Reference*	
1	**1.75**	**(1.48-2.06)**	**1.71**	**(1.41-2.07)**
2+	**3.05**	**(2.61-3.57)**	**3.13**	**(2.57-3.81)**
Baseline BMI[f]				
<18 kg/m^2	0.67	(0.25-1.81)	0.86	(0.27-2.69)
18-24.9 kg/m^2			*Reference*	
<25-29.9 kg/m^2	**1.26**	**(1.06-1.51)**	**1.27**	**(1.02-1.57)**
>30 kg/m^2	**1.23**	**(1.04-1.46)**	**1.22**	**(1.00-1.50)**

Table 2.6 Continued

	Diseases of the Arteries			
	1-5 Years		>5-10 Years	
	HR	**95% CI**	**HR**	**95% CI**
Treatment Type[a]				
Surgery only		*Reference*		
Surgery and radiation	**1.26**	**(1.02-1.56)**	1.10	(0.86-1.41)
Surgery and chemotherapy	**3.19**	**(2.10-4.85)**	1.56	(0.64-3.81)
Surgery, radiation, and chemotherapy	**1.99**	**(1.36-2.92)**	1.23	(0.67-2.26)
Stage[b]				
Local		*Reference*		
Regional	1.18	(0.94-1.50)	1.09	(0.81-1.47)
Advanced	**2.90**	**(1.91-4.41)**	1.46	(0.53-4.00)
Grade[b]				
Grade I (Well differentiated)		*Reference*		
Grade II (Moderately differentiated)	1.22	(0.99-1.50)	1.02	(0.82-1.28)
Grade III (Poorly differentiated)	**1.82**	**(1.43-2.32)**	1.03	(0.74-1.43)
Grade IV (Undifferentiated)	**2.97**	**(1.87-4.73)**	0.48	(0.12-1.96)
Year of Diagnosis[c]				
1997-2000		*Reference*		
2001-2004	1.11	(0.85-1.46)	1.03	(0.79-1.33)
2005-2010	1.14	(0.90-1.45)	0.86	(0.66-1.12)
2011-2012	1.08	(0.78-1.50)	.	.
Age at Diagnosis[d]				
<50		*Reference*		
50-59	**1.50**	**(1.06-2.12)**	**1.52**	**(1.05-2.19)**
60-69	**1.77**	**(1.26-2.50)**	**1.98**	**(1.38-2.84)**
70-79	**2.66**	**(1.87-3.78)**	**2.28**	**(1.55-3.37)**
80+	**3.62**	**(2.45-5.37)**	**2.13**	**(1.28-3.54)**
Charlson Comorbidity Index[e]				
0		*Reference*		
1	**1.84**	**(1.46-2.32)**	**2.2**	**(1.70-2.83)**
2+	**2.96**	**(2.37-3.68)**	**3.81**	**(2.92-4.96)**
BMI[f]				
<18 kg/m^2	0.75	(0.18-3.04)	2.25	(0.82-6.15)
18-24.9 kg/m^2		*Reference*		
<25-29.9 kg/m^2	1.17	(0.91-1.52)	1.29	(0.98-1.70)
>30 kg/m^2	**1.31**	**(1.03-1.67)**	0.93	(0.71-1.22)

Table 2.6 Continued

	Diseases of the Veins/Lymphatics			
	1-5 Years		>5-10 Years	
	HR	95% CI	HR	95% CI
Treatment Type[a]				
Surgery only		*Reference*		
Surgery and radiation	**1.29**	**(1.06-1.56)**	1.12	(0.88-1.44)
Surgery and chemotherapy	**2.16**	**(1.44-3.24)**	1.30	(0.54-3.16)
Surgery, radiation, and chemotherapy	**2.29**	**(1.67-3.14)**	1.13	(0.63-2.03)
Stage[b]				
Local		*Reference*		
Regional	**1.34**	**(1.09-1.65)**	1.22	(0.92-1.63)
Advanced	**3.11**	**(2.15-4.48)**	1.67	(0.68-4.09)
Grade[b]				
Grade I (Well differentiated)		*Reference*		
Grade II (Moderately differentiated)	1.19	(1.00-1.43)	1.16	(0.94-1.45)
Grade III (Poorly differentiated)	**1.67**	**(1.34-2.08)**	0.94	(0.67-1.33)
Grade IV (Undifferentiated)	**1.89**	**(1.16-3.09)**	0.24	(0.03-1.75)
Year of Diagnosis[c]				
1997-2000		*Reference*		
2001-2004	0.97	(0.76-1.24)	1.02	(0.79-1.32)
2005-2010	**1.28**	**(1.04-1.59)**	0.94	(0.73-1.22)
2011-2012	0.95	(0.70-1.28)	.	.
Age at Diagnosis[d]				
<50		*Reference*		
50-59	**1.31**	**(1.01-1.70)**	1.06	(0.79-1.42)
60-69	**1.34**	**(1.03-1.74)**	1.00	(0.73-1.35)
70-79	**1.41**	**(1.05-1.89)**	1.03	(0.72-1.48)
80+	1.28	(0.88-1.87)	0.59	(0.32-1.08)
Charlson Comorbidity Index[e]				
0		*Reference*		
1	1.12	(0.91-1.38)	**1.68**	**(1.31-2.14)**
2+	**1.47**	**(1.19-1.80)**	**1.90**	**(1.43-2.52)**
BMI[f]				
<18 kg/m^2	0.49	(0.12-1.98)	2.41	(0.97-5.98)
18-24.9 kg/m^2		*Reference*		
<25-29.9 kg/m^2	1.00	(0.80-1.25)	1.27	(0.95-1.70)
>30 kg/m^2	1.19	(0.97-1.46)	1.28	(0.97-1.68)

Models adjusted for a. Charlson Comorbidity Index, BMI, race, year of diagnosis, and age at diagnosis; b.histology, age at diagnosis, diagnosis year, BMI, Charlson Comorbidity Index, Race; c. BMI, Charlson Comorbidity Index, race, endometrial cancer type; d. BMI, race, diagnosis year, Charlson Comorbidity Index, stage, histology; e.,age at diagnosis, diagnosis year, race; f. Charlson Comorbidity Index, age at diagnosis, race.

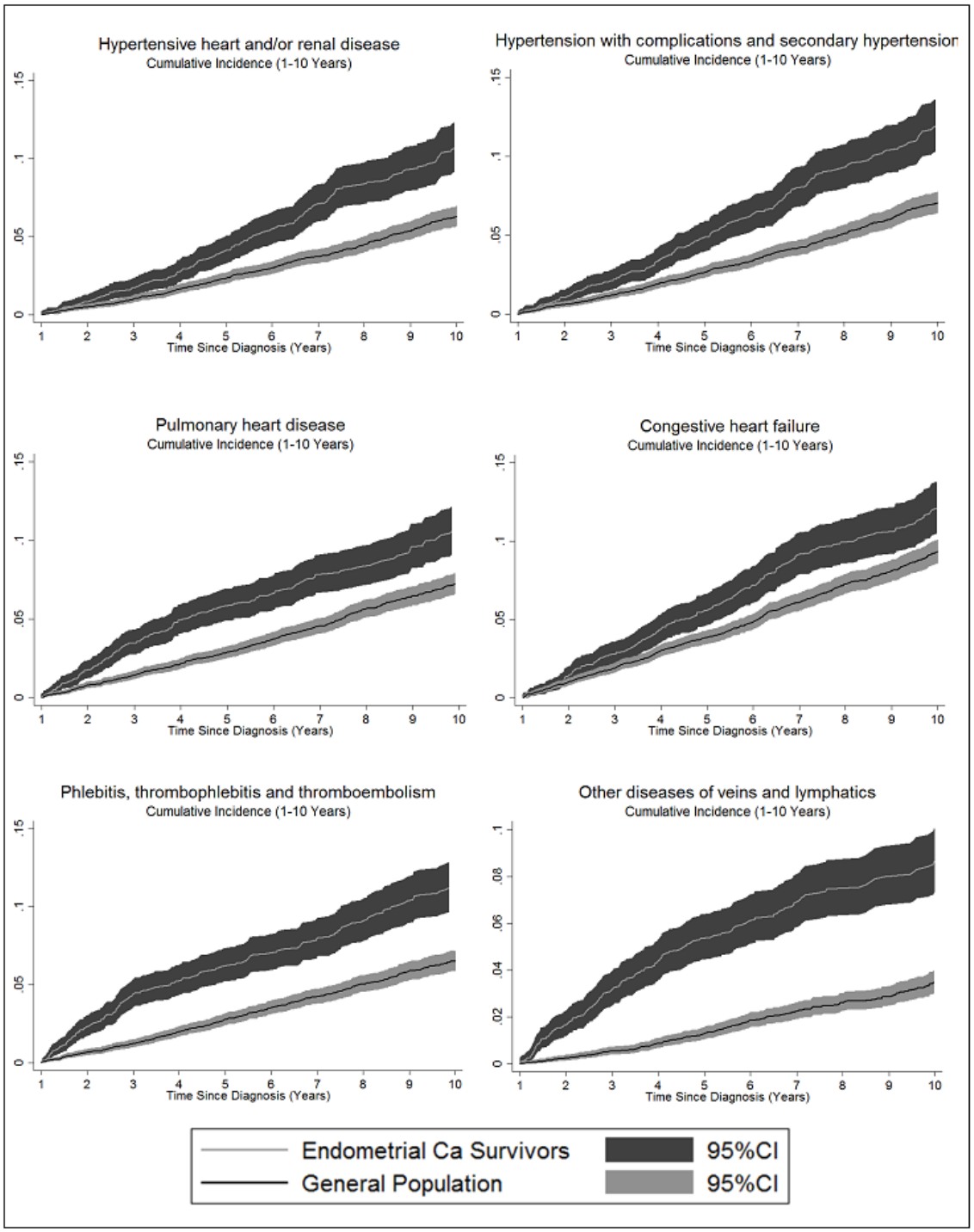

Figure 2.1. Cumulative incidence plots for select cardiovascular disease outcomes

CHAPTER 3

LONG-TERM GENITOURINARY OUTCOMES AMONG ENDOMETRIAL CANCER SURVIVORS

3.1 Abstract

With an estimated 757,000 survivors in 2016, endometrial cancer is the second most common cancer among female cancer survivors in the United States. Endometrial cancer survivors are at increased risk for various adverse genitourinary outcomes. Because of the large number of survivors in the United States as well as the high overall survival rate among endometrial cancer survivors, investigations of long-term adverse health outcomes in proximal bodily regions (such as the genitourinary system) are likely to be affected by disease, treatment, and other comorbidities are important for the management and surveillance of these outcomes among endometrial cancer survivors.

Cohorts of 2,648 endometrial cancer survivors diagnosed in the state of Utah between 1997 and 2012, and 10,503 age-matched women from the general population were identified using the Utah Population Database. All ICD-9 diagnosis codes were collected from the state's two largest healthcare systems and statewide ambulatory surgery and inpatient visits. Multivariate Cox regression models were used to estimate hazard ratios (HR) at 1-5 years and >5-10 years after cancer diagnosis.

Endometrial cancer survivors were at elevated risk for urinary system disorders between 1-5 years (HR: 1.64, 99% CI: 1.47-1.83) and >5-10 years (HR: 1.40, 99% CI: 1.22-1.61) and genital organ disorders between 1-5 years (HR: 1.71, 99% CI: 1.54-1.91) and >5-10 years (HR: 1.33, 99% CI: 1.15-1.54). The highest risks among endometrial cancer survivors were observed between 1-5 years for hydronephrosis (HR: 5.74, 99% CI: 3.40-9.69), nephritis, nephrosis, and renal sclerosis (HR: 3.53, 99% CI: 1.85-6.74), calculus of the kidneys (HR: 2.97, 99% CI: 1.74-5.08), and acute and unspecified renal failure (HR: 2.21, 99% CI: 1.60-3.06). Between 1-5 years after cancer diagnosis, elevated risk for urinary disorders was observed among cancer survivors who were treated with different combinations of radiation therapy, chemotherapy, and/or surgery compared to those who received surgery alone.

Endometrial cancer survivors in this population were at higher risk for genitourinary outcomes compared to women from the general population in the state of Utah, especially between 1 and 5 years after cancer diagnosis. This study presents evidence to suggest that increased monitoring for diseases of the genitourinary system is necessary for women diagnosed with endometrial cancer both immediately after treatment cessation and for several years afterwards.

3.2 Introduction

In the United States, endometrial cancer is the second most common cancer among female cancer survivors, the fourth most commonly diagnosed cancer among women, and the tenth most commonly diagnosed cancer overall.[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. In 2006, there were an estimated 556,640 endometrial cancer survivors in

the United States, which increased to 635,437 in 2013, and it is projected that there were 757,000 endometrial cancer survivors in 2016.[3,4] 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. Following treatment with radiation therapy therapy, long-term damage to the genital organs has been well documented.[8,9] radiation therapy can induce damage to connective tissue of the vagina, chronic vaginal discharge, necrosis, ulceration, fistula formation, thinning and atrophy of the vaginal epithelium, fibrosis, loss of elasticity of the vagina have also been observed. Individuals treated with external beam radiation therapy suffer chronic bony pain secondary to hip fracture that affects locomotion.[10] After abdominal surgery patients are at increased risk for a bowel obstruction and this is increased with external beam radiation therapy.

In a study that measured short term vaginal and urinary toxicity due to interstitial brachytherapy for locally advanced endometrial, cervical, vulvar, or vaginal cancer, 17.8% of the population experienced grade 3 vaginal toxicity and 15.1% experienced grade 3 urinary toxicity within 1 year, resulting in symptoms that can persist more than a year after the completion of treatment.[11] While this study suggests that grade 3 vaginal and urinary toxicity are likely to occur in individuals treated with interstitial brachytherapy, no patients experienced grade 4 or 5 toxicity. Both vaginal and urinary toxicity may contribute to many of the adverse genitourinary complications observed among endometrial cancer survivors treated with radiation therapy.

In a prospective study of individuals diagnosed with endometrial cancer, 30% had urinary complications, 9.2% had genital complications, and 2.3% had pelvic soft tissue complications within 1 year after diagnosis.[12] In this population, a higher proportion of individuals treated with surgery alone reported urinary complications than those treated with surgery and radiation therapy, surgery and chemotherapy, and surgery, radiation therapy, and chemotherapy. After 5 years postdiagnosis, urinary symptoms remained the most common.

Urinary incontinence is one of the most common long-term effects among endometrial cancer survivors.[13-21] In a comparison of urinary incontinence among survivors of several different cancer types, 40.2% of endometrial cancer survivors experienced urinary incontinence, which was higher than any of the other cancers examined (breast, prostate, bladder, colorectal, and lung), which ranged from 27.1%-35.2%.[13] Long-term stress urinary incontinence and voiding dysfunction have also been observed to be higher among endometrial cancer survivors treated with radical hysterectomy compared to total abdominal hysterectomy[16] and in women treated with radiation therapy compared to surgery alone.[17] However, in a comparison of adverse urinary outcomes between recurrence-free survivors of gynecologic cancers and controls from the general population, no elevated risk was observed among those treated with radiation therapy.[22]

Survivors of endometrial and cervical cancer also experience urinary urgency, daytime leakage at least once a day, bladder pain, and nocturia. They are 2-5 times more likely to experience symptoms of urinary incontinence after 1 year of treatment cessation.[18] Endometrial cancer patients treated with external beam radiation therapy were at higher risk for urinary incontinence compared to those treated with brachytherapy at 7 and 10 years after diagnosis.[19] Additionally, there is evidence that the combination of external beam radiation therapy and brachytherapy increases the risk of long-term urinary complications compared to external beam

radiation therapy or brachytherapy alone.[20]

Long-term surveillance of surgically treated patients has suggested that regional complications due to surgery are usually resolved within 1 year, while treatment with radiation therapy can cause damage to tissue architecture of the genital and urinary systems that can persist for years after treatment cessation.[21,23]

Many prior investigations of genitourinary outcomes among endometrial cancer survivors have often lack objective measures to capture outcomes, examine symptoms that are secondary to more clinically relevant genitourinary conditions, or are conducted using small sample sizes. 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.

3.3 Methods

3.3.1 Data Collection

An initial cohort of 3,624 endometrial cancer survivors was identified using the Utah Population Database. Diagnosis data were available from the statewide SEER Utah Cancer Registry for women aged 18 and over, diagnosed with invasive first primary endometrial cancer between 1997 and 2012 in the state of Utah (SEER ICD-O-3 codes: C54.0-C55.9). Endometrial cancer histological subtypes adenocarcinoma, endometrioid, mucinous adenocarcinoma, and adenocarcinoma with squamous differentiation were classified as Type I (ICD-O-3 morphology codes: 8140, 8260, 8380, 8382, 8480, 8482, 8560, and 8570) and clear-cell carcinomas and

papillary serous carcinomas as type II (ICD-O-3 morphology codes: 8310, 8441, and 8460).[24] Eligible survivors were required to have stage and grade included in diagnosis records from the Utah Cancer Registry and to have lived in the state of Utah for at least 1 year after diagnosis. Survivors were matched with up to 5 women from the general population on birth year and birth state.

Outcome data used for this study included statewide ambulatory and inpatient data from the Utah Department of Health and Electronic Data Warehouse data from Intermountain Health Care and the University of Utah Health Sciences Center. The Utah Population Database data included records from the Utah Cancer Registry, Utah Driver's License, vital records, and the Utah Department of Health. Statewide ambulatory and inpatient records as well as those from the University of Utah and Intermountain Healthcare systems were linked via the Utah Population Database.

Electronic medical record data was available prior to 1992, but all three major sources did not have comprehensive electronic medical record data for individuals in these cohorts until 1996. Individuals diagnosed with endometrial cancer between 1997 and 2012 were included in this analysis to allow adequate time prior to cancer diagnosis to capture prior diagnoses of the genitourinary outcomes of interest. A total of 153 endometrial cancer patients were excluded because their cancer was not staged, 470 because grade was missing, 285 because follow up time did not exceed 1 year, 65 because their Utah residence did not exceed 1 year. The stage and grade were necessary for our sample because we were interested in their potential role in risk for the outcomes measured in this study. There were a total of 2,648 endometrial cancer survivors and 10,503 individuals from the general population included in the final sample.

3.3.2 Categorization of Outcomes

Outcome data from the statewide, University of Utah Health Sciences Center, and Intermountain Healthcare systems included all available ICD-9 diagnosis codes, as well as diagnosis date which allowed for time to outcome to be calculated. The Clinical Classification Software developed by the Health Cost and Utilization Project was used to categorize ICD-9 codes into 4 levels of specificity (Levels 1-4).[25] Diseases of the genitourinary system (level 1) according to the Clinical Classification Software were used in this analysis. Level 2 outcomes included diseases of the urinary system and disease of the genital organs. More specific outcomes within these categories were analyzed as level 3 and 4 outcomes. Examples of this hierarchy include diseases of the urinary system (level 2), acute and unspecified renal failure (level 3), acute renal failure (level 4).

Long-term genitourinary outcomes were measured 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 3 or 4 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 1 and 2 outcomes were broader, thus we did not exclude prevalent diagnoses.

3.3.3 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 for long-term genitourinary outcomes at 1-5 years and >5-10 years after endometrial cancer diagnosis. We used 99% confidence intervals to account for the penalty imposed by multiple testing due to the large number of outcomes examined in this analysis. Multivariate models were adjusted for matching factors, baseline body mass index (BMI), baseline Charlson Comorbidity Index,[26] and race. 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 hypertension, heart disease, diseases of the arteries, arterioles, and capillaries, and diseases of the veins and lymphatics among endometrial cancer survivors. The proportional hazards assumption was checked for each model using a test for nonzero 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 1 year prior to cancer survivors' endometrial cancer diagnosis were calculated from the driver's license records. For the cancer-free women, the most recent BMI value recorded at least 1 year prior to the endometrial cancer diagnosis date of the matched cancer patient was included. Approximately 35% of the 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 Charlson Comorbidity Index, 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 (data not shown).

3.4 Results

The endometrial cancer survivors cohort had a higher proportion of obese individuals (44.2% vs 19.2%) than the general population cohort (p<0.001, Table 3.1). 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). Nearly 81.5% of the endometrial cancer survivors were diagnosed with grade I or II and 80.3% with stage I disease (Table 3.2). The majority (86.9%) were diagnosed with type I endometrial cancer, 3.3% with type II, and 9.9% were unknown. Among endometrial cancer survivors, 68.5% were treated with surgery alone, 21.9% with surgery and radiation therapy, 3.2% with surgery and chemotherapy, and 4.7% with surgery, radiation therapy, and chemotherapy. The mean follow-up time among survivors is 8.5 years. Approximately 27% have total follow-up time between 1-5 years, 39% between >5-10 years, and 34% in excess of 10 years.

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 3.3). More than 37% of survivors were diagnosed with a urinary system disorder compared to 24% 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. The highest risk among endometrial cancer survivors was observed for hydronephrosis at 1-5 years (HR: 5.74,

99% CI: 3.40-9.69). After 5 years, endometrial cancer patients were 2.4 times more likely to be diagnosed with hydronephrosis (99% CI: 1.22-4.73). Survivors were 2-3 times more likely to be diagnosed with calculus of the kidneys or ureters, other diseases of the bladder and urethra, and other and ill-defined genitourinary symptoms between 1-5 years but not between >5-10 years. Survivors were at higher risk for chronic kidney disease at 1-5 years but not at >5-10 years after diagnosis.

Between 1-5 years after diagnosis, 36.9% of survivors were diagnosed with a genital organ disorder compared to 26.2% of individuals in the general population (Table 3.4). Survivors were at elevated risk of genital organ disorders overall at both 1-5 years (HR: 1.71, 99% CI: 1.54-1.91) and at >5-10 years (HR: 1.33, 99% CI: 1.15-1.54). Additionally, endometrial cancer survivors were at higher risk for nonmalignant 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 nonmalignant breast conditions.

Individuals treated with surgery in combination with radiation therapy 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 radiation therapy 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 associated with urinary system or genital organ disorders. Figure 3.1 shows the cumulative incidence of select genitourinary outcomes between cancer survivors and individuals from the general population.

3.5 Discussion

These results present an important addition to the body of literature concerning long-term, adverse genitourinary outcomes among endometrial cancer survivors. The majority of investigations into these associations have 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 electronic medical record data between endometrial cancer survivors and matched individuals from the general population. This analysis supports many of the findings of prior investigations by showing an association between endometrial cancer diagnosis and several of the underlying conditions that might result in urinary incontinence, daytime leakage, nocturia, voiding difficulty, and bladder, genital, and pelvic pain. In this 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. These results also provide evidence that those treated with radiation therapy 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.

Endometrial cancer survivors were 64% more likely to be diagnosed with a urinary system disorder between 1-5 years and 40% more likely between >5-10 years compared to individuals in the general population. The majority of studies that have examined urinary system disorders due to cancer treatment in women have focused on cervical cancer.[17] Those that have examined long-term urinary system disorders among endometrial cancer survivors have had

mixed results[14,17,22] and have largely focused on conditions such as urinary incontinence that may be secondary to many of the outcomes that were measured in the study. 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 electronic medical records provides a more objective 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 conditions including acute renal failure, chronic kidney disease, calculus of the kidneys, hydronephrosis, and nephritis, nephrosis and renal sclerosis. These conditions are often associated with obesity and advanced age, which are shared risk factors for endometrial cancer. We adjusted for BMI and age at diagnosis and found a significant association between endometrial cancer diagnosis and these conditions, while the case-only risk factor analysis suggested that elevated BMI was not associated with urinary system disorders overall among endometrial cancer survivors compared to those in the normal BMI range prior to endometrial cancer diagnosis. However, survivors diagnosed at a later age were more likely to be diagnosed with urinary system disorders. Our results suggest that elevated risk for urinary system disorders may be the result of radiation therapy and/or chemotoxicity, limited to the 1-5 years after diagnosis. This is further supported by the observation that elevated risk for many of the outcomes measured was not observed after 5 years since cancer diagnosis, though there is evidence that damage to the urinary system related to treatment can cause severe long-term renal damage that can result in acute renal failure.

While we observed elevated risk for genital organ disorders among endometrial cancer survivors, the risks for specific outcomes were largely confined to the 1-5 year range. As with

urinary system disorders, elevated risk for genital organ disorders among those treated with radiation therapy and/or chemotherapy compared to those treated with surgery alone was also observed only in the 1-5 year period after cancer diagnosis. There was a higher level of granularity for urinary system disorders than for genital organ disorders. The level 3 genital organ disorders include nonmalignant breast conditions, inflammatory diseases of female pelvic organs, endometriosis, prolapse of female genital organs, menstrual disorders, ovarian cyst, menopausal disorders, female infertility, and other female genital disorders. Only two of these categories contain more specific diagnoses and include a category of "other" which may include disparate conditions. Further, several of these are of no relevance in individuals who have undergone hysterectomy or bilateral salpingo-oophorectomy, leaving only a few clinically meaningful or easily interpretable genital organ outcomes for analysis. Despite this, our results support previous findings that risk for pelvic pain and inflammatory diseases of the pelvic organs are common among endometrial cancer survivors and we were able to quantify risk for these conditions compared to the general population.

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 electronic medical record data provides a more objective measure of the experience of endometrial cancer survivors with respect to genitourinary outcomes. In addition, the electronic medical record data used in this study come 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 is 8.5 years. Approximately 27% have total follow-up time between 1 and 5 years, 39% between 5 and 10 years, and 34% in excess of 10 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 electronic medical record 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 10 years is limited due to lack of follow-up time for this proportion of the study population. However, with the Utah Population Database 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 radiation therapy 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.

Future research is necessary to more accurately assess causal relationships between treatment for endometrial cancer and the outcomes measured in this study. While the mechanisms of damage to the genitourinary system due to surgery, chemotherapy and radiation therapy have been investigated more completely for cervical cancer, more studies that examine these associations among endometrial cancer survivors are necessary. Further analysis that incorporates more specific treatment related factors are also needed. Additionally, because

electronic medical record data are 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 a number of long-term genitourinary outcomes. 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 control for many of these risk factors provides a clearer picture than has been previously available. It is clear from these results that the survivors of endometrial cancers in this cohort experienced a high burden of adverse genitourinary outcomes, especially urinary system disorders. These results suggest that increased monitoring for genitourinary disease over long periods of time among endometrial cancer survivors is warranted. Further, these result 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.

3.6 References

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Table 3.1: 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 kg/m^2	18	0.7	307	2.9	
18-24.9 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	
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 3.2: Clinical characteristics among endometrial cancer survivors

	Endometrial Cancer (n=2,648)	
Diagnosis Year	n	%
1997-2000	563	21.26
2001-2003	471	17.79
2004-2006	483	18.24
2007-2009	572	21.60
2010-2012	559	21.11
Age at Diagnosis		
<40	140	5.29
40-49	307	11.59
50-59	786	29.68
60-69	758	28.63
70-79	451	17.03
80+	206	7.78
Grade		
Grade I (Well differentiated)	1,314	49.62
Grade II (Moderately differentiated)	845	31.91
Grade III (Poorly differentiated)	421	15.90
Grade IV (Undifferentiated)	68	2.57
Stage		
Local	10,565	80.34
Regional	2,154	16.38
Advanced	432	3.28
Histology		
Endometrioid adenocarcinoma	1,853	69.98
Adenocarcinoma with squamous differentiation	56	2.11
Serous adenocarcinoma	87	3.29
Clear cell adenocarcinoma	17	0.64
Mixed cell adenocarcinoma	47	1.77
Mucinous adenocarcinoma	45	1.70
Carcinosarcoma	26	0.98
Stromal sarcoma	44	1.66
Leiomyosarcoma	41	1.55
Other	432	16.31
Endometrial Cancer Type		
Type I	2,300	86.86
Type II	87	3.29
Unknown	261	9.86
Treatment Type		
Surgery only	1,813	68.47
Surgery and radiation	579	21.87
Surgery and chemotherapy	84	3.17
Surgery, radiation, and chemotherapy	124	4.68
No available treatment information	48	1.81

Table 3.3: 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					
	Survivors		General Population			
Outcome	n	%	n	%	HR	99% CI
Diseases of the urinary system	991	37.4	2,572	24.5	**1.64***	**(1.47-1.83)**
Nephritis; nephrosis; renal sclerosis	46	1.7	52	0.5	**3.53**	**(1.85-6.74)**
Acute and unspecified renal failure	139	5.3	249	2.4	**2.21**	**(1.60-3.06)**
Acute renal failure	112	4.2	219	2.1	**2.04**	**(1.42-2.93)**
Unspecified renal failure	50	1.9	81	0.8	**2.52**	**(1.43-4.44)**
Chronic kidney disease	104	3.9	218	2.1	**1.78**	**(1.25-2.54)**
Urinary tract infections	268	10.1	831	7.9	**1.52**	**(1.23-1.88)**
Infections of kidney	41	1.6	135	1.3	1.14	(0.68-1.90)
Cystitis and urethritis	51	1.9	121	1.2	**1.79**	**(1.12-2.85)**
Urinary tract infection; site not specified	252	9.5	800	7.6	**1.50**	**(1.21-1.86)**
Calculus of urinary tract	76	2.9	140	1.3	**1.95**	**(1.30-2.94)**
Calculus of kidney	52	2.0	79	0.8	**2.97**	**(1.74-5.08)**
Calculus of ureter	38	1.4	62	0.6	**1.97**	**(1.09-3.57)**
Other and unspecified urinary calculus	24	0.9	62	0.6	1.39	(0.73-2.67)
Other diseases of kidney and ureters	211	8.0	376	3.6	**2.25***	**(1.75-2.90)**
Hydronephrosis	79	3.0	47	0.5	**5.74**	**(3.40-9.69)**
Other diseases of kidney and ureters	196	7.4	360	3.4	**2.26***	**(1.74-2.94)**
Other diseases of bladder and urethra	66	2.5	142	1.4	**1.97**	**(1.27-3.05)**
Other diseases of bladder and urethra	64	2.4	141	1.3	**1.93**	**(1.24-3.01)**
Genitourinary symptoms and ill-defined conditions	248	9.4	811	7.7	**1.65**	**(1.33-2.06)**
Hematuria	102	3.9	204	1.9	**2.16**	**(1.52-3.06)**
Retention of urine	27	1.0	73	0.7	1.16	(0.61-2.22)
Other and unspecified genitourinary symptoms	223	8.4	735	7.0	**1.66**	**(1.32-2.09)**

Table 3.3 Continued

	Survivors		5-10 Years General Population			
Outcome	n	%	n	%	HR	99% CI
Diseases of the urinary system	638	24.1	2,169	20.7	**1.40**	**(1.22-1.61)**
Nephritis; nephrosis; renal sclerosis	26	1.0	48	0.5	**2.84***	**(1.30-6.22)**
Acute and unspecified renal failure	95	3.6	254	2.4	**1.61**	**(1.12-2.31)**
Acute renal failure	96	3.6	234	2.2	**1.82**	**(1.26-2.63)**
Unspecified renal failure	27	1.0	72	0.7	1.52	(0.76-3.01)
Chronic kidney disease	88	3.3	257	2.5	1.40	(0.96-2.04)
Urinary tract infections	177	6.7	678	6.5	**1.45**	**(1.11-1.89)**
Infections of kidney	33	1.3	107	1.0	1.25	(0.68-2.28)
Cystitis and urethritis	32	1.2	102	1.0	**1.83**	**(1.01-3.33)**
Urinary tract infection; site not specified	185	7.0	660	6.3	**1.47**	**(1.13-1.91)**
Calculus of urinary tract	45	1.7	129	1.2	1.35	(0.81-2.25)
Calculus of kidney	25	0.9	91	0.9	1.24	(0.65-2.38)
Calculus of ureter	18	0.7	60	0.6	1.36	(0.65-2.87)
Other and unspecified urinary calculus	21	0.8	53	0.5	1.61	(0.73-3.53)
Other diseases of kidney and ureters	107	4.0	327	3.1	**1.56**	**(1.12-2.17)**
Hydronephrosis	25	0.9	51	0.5	**2.40**	**(1.22-4.73)**
Other diseases of kidney and ureters	103	3.9	302	2.9	**1.62**	**(1.15-2.29)**
Other diseases of bladder and urethra	45	1.7	122	1.2	1.69	(0.99-2.87)
Other diseases of bladder and urethra	44	1.7	120	1.1	1.71	(1.00-2.92)
Genitourinary symptoms and ill-defined conditions	112	4.2	596	5.7	1.18	(0.86-1.63)
Hematuria	38	1.4	170	1.6	1.17	(0.69-1.98)
Retention of urine	15	0.6	76	0.7	0.71	(0.30-1.66)
Other and unspecified genitourinary symptoms	106	4.0	559	5.3	1.12	(0.81-1.55)

Adjusted for baseline BMI, baseline Charlson Comorbidity Index, and race

*Models in violation of the proportional hazards assumption that were evaluated using flexible parametric survival models with restricted cubic splines

Table 3.4: 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					
	Survivors		General Population			
Outcome	n	%	n	%	HR	99% CI
Diseases of female genital organs	976	36.9	2,756	26.2	**1.71***	**(1.54-1.91)**
Nonmalignant breast conditions	240	9.1	682	6.5	**1.70***	**(1.35-2.14)**
Inflammatory diseases of female pelvic organs	78	3.0	210	2.0	**1.88**	**(1.27-2.80)**
Pelvic peritoneal adhesions	9	0.3	25	0.2	1.27	(0.41-4.00)
Other inflammatory diseases of pelvic organs	88	3.3	166	1.6	**2.16**	**(1.48-3.17)**
Endometriosis	15	0.6	47	0.5	2.05	(0.78-5.40)
Menstrual disorders	14	0.5	175	1.7	0.80	(0.36-1.80)
Ovarian cyst	12	0.5	92	0.9	0.58*	(0.24-1.36)
Menopausal disorders	108	4.1	604	5.8	1.30	(0.95-1.78)
Other female genital disorders	107	4.0	487	4.6	**1.97***	**(1.41-2.76)**
Female genital pain and other symptoms	107	4.0	326	3.1	**1.51***	**(1.09-2.08)**
Other and unspecified female genital disorders	81	3.1	281	2.7	**2.21***	**(1.49-3.29)**

Table 3.4 Continued

	Survivors		5-10 Years General Population			
Outcome	n	%	n	%	HR	99% CI
Diseases of female genital organs	531	20.1	1,895	18.0	**1.33**	**(1.15-1.54)**
Nonmalignant breast conditions	146	5.5	445	4.2	**1.47**	**(1.09-1.99)**
Inflammatory diseases of female pelvic organs	24	0.9	115	1.1	1.20	(0.63-2.28)
Pelvic peritoneal adhesions	2	0.1	9	0.1	1.57	(0.12-20.09)
Other inflammatory diseases of pelvic organs	27	1.0	95	0.9	1.59	(0.84-2.99)
Endometriosis	2	0.1	14	0.1	0.84	(0.08-8.78)
Menstrual disorders	5	0.2	111	1.1	0.40	(0.12-1.38)
Ovarian cyst	1	0.0	46	0.4	0.09	(0.01-1.44)
Menopausal disorders	44	1.7	364	3.5	0.80	(0.50-1.29)
Other female genital disorders	25	0.9	245	2.3	1.07	(0.57-2.02)
Female genital pain and other symptoms	36	1.4	212	2.0	1.06	(0.63-1.78)
Other and unspecified female genital disorders	13	0.5	125	1.2	0.87	(0.37-2.04)

Models adjusted for 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.

*Models in violation of the proportional hazards assumption that were evaluated using flexible parametric survival models with restricted cubic splines.

Table 3.5: Risk factors for urinary and genital organ disorders among endometrial cancer survivors

	Urinary System Disorders			
	1-5 Years		5-10 Years	
	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)**
Surgery and chemotherapy	**2.99**	**(2.21-4.04)**	0.74	(0.31-1.80)
Surgery, radiation, and chemotherapy	**2.34**	**(1.81-3.02)**	1.51	(0.98-2.32)
Stage[b]				
Local				
Regional	**1.45**	**(1.24-1.70)**	**1.3**	**(1.04-1.61)**
Advanced	**3.43**	**(2.57-4.57)**	1.49	(0.70-3.17)
Grade[b]				
Grade I (Well differentiated)				
Grade II (Moderately differentiated)	**1.20**	**(1.04-1.39)**	1.07	(0.90-1.27)
Grade III (Poorly differentiated)	**1.57**	**(1.32-1.88)**	0.86	(0.66-1.13)
Grade IV (Undifferentiated)	**2.78**	**(1.97-3.94)**	0.89	(0.40-2.00)
Year of Diagnosis[c]				
1997-2000				
2001-2004	**1.35**	**(1.12-1.64)**	1.15	(0.95-1.41)
2005-2010	**1.21**	**(1.02-1.44)**	0.92	(0.75-1.12)
2011-2012	1.19	(0.94-1.49)	.	.
Age at Diagnosis[d]				
<50				
50-59	1.19	(0.96-1.47)	1.18	(0.91-1.52)
60-69	**1.39**	**(1.12-1.72)**	**1.55**	**(1.20-2.01)**
70-79	**1.70**	**(1.35-2.14)**	**1.90**	**(1.44-2.52)**
80+	**2.20**	**(1.68-2.87)**	**2.67**	**(1.89-3.79)**
Charlson Comorbidity Index[e]				
0				
1	**1.40**	**(1.19-1.64)**	**1.83**	**(1.51-2.21)**
2+	2.10	(1.80-2.46)	2.40	(1.95-2.95)
Baseline BMI[f]				
<18 kg/m^2	0.83	(0.34-2.01)	1.48	(0.61-3.63)
18-24.9 kg/m^2				
<25-29.9 kg/m^2	1.07	(0.90-1.27)	1.16	(0.93-1.44)
>30 kg/m^2	1.01	(0.86-1.19)	1.19	(0.97-1.47)

Table 3.5 Continued

	Genital Organ Disorders			
	1-5 Years		5-10 Years	
	HR	95% CI	HR	95% CI
Treatment Type[a]				
Surgery only				
Surgery and radiation	**1.26**	**(1.08-1.47)**	1.09	(0.88-1.35)
Surgery and chemotherapy	**1.62**	**(1.14-2.28)**	1.81	(0.99-3.31)
Surgery, radiation, and chemotherapy	**1.52**	**(1.14-2.03)**	1.02	(0.61-1.71)
Stage[b]				
Local				
Regional	1.17	(0.98-1.39)	1.02	(0.79-1.32)
Advanced	1.37	(0.92-2.02)	0.62	(0.23-1.68)
Grade[b]				
Grade I (Well differentiated)				
Grade II (Moderately differentiated)	1.04	(0.90-1.20)	1.06	(0.87-1.28)
Grade III (Poorly differentiated)	1.13	(0.93-1.37)	1.21	(0.92-1.59)
Grade IV (Undifferentiated)	**1.83**	**(1.22-2.75)**	0.56	(0.18-1.76)
Year of Diagnosis[c]				
1997-2000				
2001-2004	1.15	(0.96-1.38)	0.91	(0.73-1.13)
2005-2010	0.97	(0.82-1.15)	0.82	(0.66-1.01)
2011-2012	0.78	(0.61-1.00)	.	.
Age at Diagnosis[d]				
<50				
50-59	1.09	(0.91-1.31)	0.93	(0.73-1.18)
60-69	0.98	(0.81-1.18)	0.97	(0.76-1.24)
70-79	**0.77**	**(0.61-0.96)**	**0.64**	**(0.46-0.88)**
80+	**0.53**	**(0.37-0.74)**	**0.34**	**(0.18-0.63)**
Charlson Comorbidity Index[e]				
0				
1	**1.23**	**(1.05-1.45)**	1.10	(0.88-1.37)
2+	1.18	(0.99-1.41)	1.14	(0.88-1.49)
Baseline BMI[f]				
<18 kg/m^2	1.05	(0.50-2.23)	1.30	(0.53-3.18)
18-24.9 kg/m^2				
<25-29.9 kg/m^2	1.10	(0.92-1.30)	1.18	(0.94-1.49)
>30 kg/m^2	0.98	(0.83-1.15)	1.02	(0.81-1.27)

Models adjusted for a. Charlson Comorbidity Index, BMI, race, year of diagnosis, and age at diagnosis; b. age at diagnosis, diagnosis year, BMI, Charlson Comorbidity Index, Race; c. BMI, Charlson Comorbidity Index, race, endometrial cancer type; d. BMI, race, diagnosis year, Charlson Comorbidity Index; e.,age at diagnosis, diagnosis year, race; f. Charlson Comorbidity Index, age at diagnosis, race.

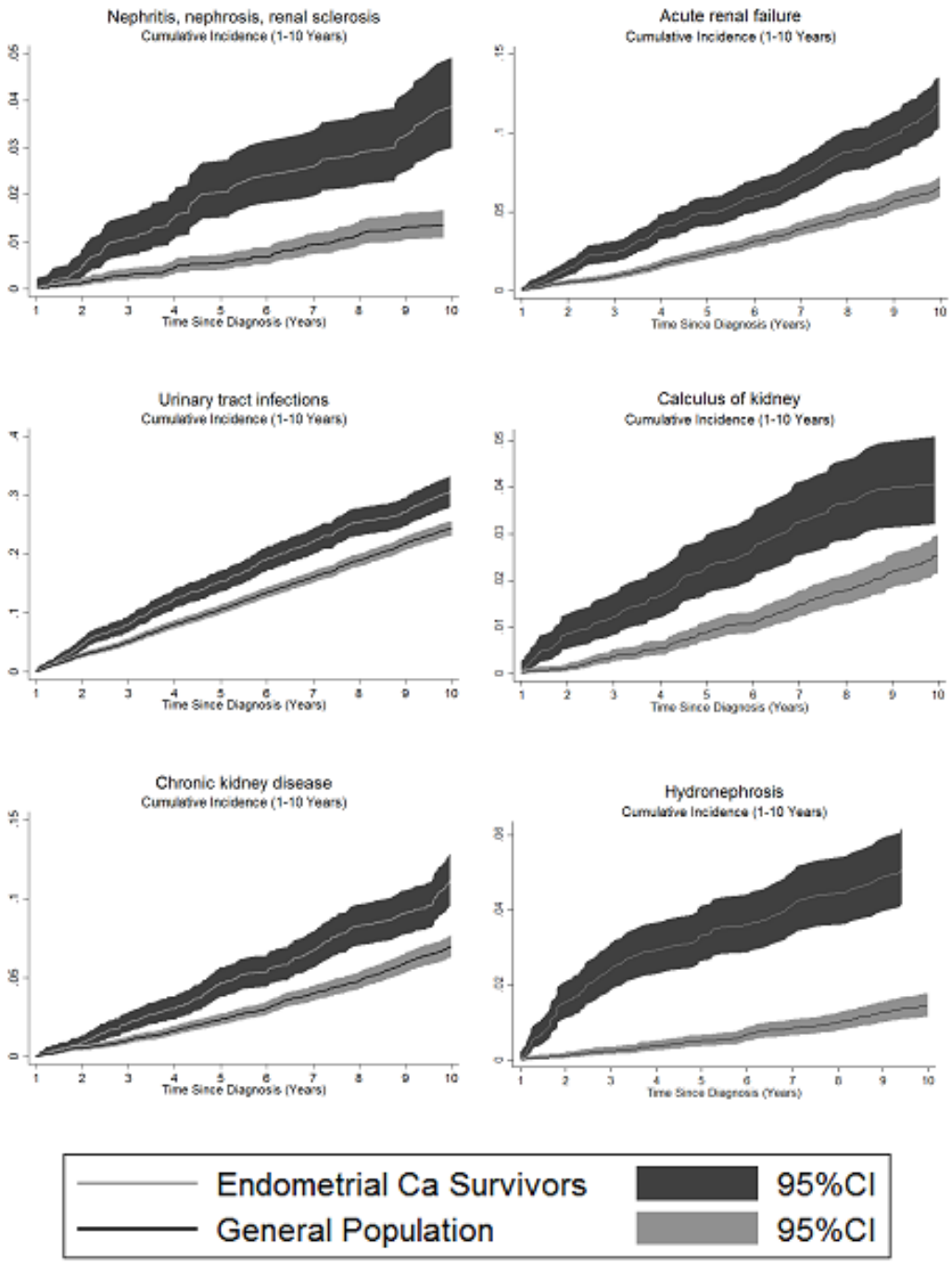

Figure 3.1. Cumulative incidence plots for select genitourinary outcomes

CHAPTER 4

LONG-TERM GASTROINTESTINAL OUTCOMES AMONG ENDOMETRIAL CANCER SURVIVORS

4.1 Abstract

Endometrial cancer is the second most common cancer among female cancer survivors in the United States. There are an estimated 757,000 survivors in currently living in the United States. Endometrial cancer survivors experience a wide range of acute and long-term adverse gastrointestinal outcomes that vary by treatment type. Because of the increasing number of survivors in the United States as well as the high overall survival rate among those diagnosed with endometrial cancer, investigations of long-term adverse health outcomes in proximal bodily regions (such as the gastrointestinal system) that are likely to be affected by disease, treatment, and other comorbidities are important for the management and surveillance of these outcomes among endometrial cancer survivors.

Cohorts of 2,648 endometrial cancer survivors diagnosed in the state of Utah between 1997 and 2012, and 10,503 age-matched women from the general population were identified using the Utah Population Database. All ICD-9 diagnosis codes for gastrointestinal outcomes were collected from the state's two largest healthcare systems, and statewide ambulatory surgery and inpatient visits. Multivariate Cox regression models were used to estimate hazard ratios (HR) at 1-5 years and >5-10 years after cancer diagnosis.

Endometrial cancer survivors were at elevated risk for liver disease between 1-5 (HR: 3.10, 99% CI: 2.52-3.87) and between >5-10 (HR: 1.58, 99% CI: 1.20-2.08) years after diagnosis, intestinal obstruction between 1-5 years (HR: 4.16, 99% CI: 2.87-6.04) and >5-10 (HR: 2.14, 99% CI: 1.30-3.52) years after diagnosis, and biliary tract disorders between 1-5 (HR 2.02, 99% CI: 1.58-2.59) and >5-10 (HR: 1.38, 99% CI: 1.00-1.91) years after diagnosis. Survivors were also 3 to 5 times more likely to be diagnosed with an umbilical, ventral, or incisional hernia between 1-5 years after diagnosis, with highly elevated risk persisting >5-10 years after diagnosis for ventral and incisional hernias. Among endometrial cancer survivors, individuals treated with surgery and chemotherapy were 6 times more likely to be diagnosed with liver disease than those treated with surgery alone. Elevated risk was also observed among survivors treated with radiation therapy therapy and/or chemotherapy compared to those treated with surgery alone for upper gastrointestinal disorders, lower gastrointestinal disorders, and abdominal hernias.

Endometrial cancer survivors in this population were at higher risk for many gastrointestinal outcomes compared to women from the general population in the state of Utah between 1-5 and >5-10 years after diagnosis. This study presents strong evidence to suggest that increased monitoring for diseases of the gastrointestinal system is necessary for women diagnosed with endometrial cancer not only during the first several years after diagnosis, but after 5 years as well.

4.2 Introduction

Endometrial cancer is the second most common cancer among female cancer survivors in the United States; and both the rate of diagnosis and the number of survivors have been steadily increasing over the last several decades.[1-4] Individuals diagnosed with endometrial cancer have been observed to experience a wide range of adverse gastrointestinal (GI)

outcomes, both acute and long-term. Risk for GI outcomes varies by treatment type; and investigations into specific gastrointestinal outcomes among individuals treated for endometrial cancer have produced mixed results, with some resolving within several months after treatment cessation and some persisting for years.[5-10] Many of these studies have focused on symptoms that directly affect quality of life but lack validated measures for capturing outcomes, include a small number of individuals, lack control groups, include questions about symptoms that patients are reluctant to report, and suffer from loss to follow-up, making risk for long-term GI outcomes among endometrial cancer survivors difficult to quantify.[5]

Much of the literature regarding GI complications due to radiation therapy has focused on individuals treated for cervical cancer. Individuals treated for endometrial cancer have been observed to have fewer complications severe enough to require surgical intervention compared to those treated for cervical cancer, but are more likely to have long-term complications.[6] However, the proportion of endometrial cancer patients in this study diagnosed with higher grade, type II disease was larger than is typically expected among those diagnosed with endometrial cancer and the sample size was relatively small (*n*=75). In a retrospective study that examined treatment related complications among high-risk endometrial cancer patients (*n*=109), 66% of individuals who experienced any complications had either adverse GI or genitourinary outcomes.[7] Among those who experienced GI complications, 14% were short-term (<6 months) and 29% were long-term (>6 months).

Increased risk for diarrhea, pain, nausea, bloating, bowel obstructions, rectal bleeding, fecal incontinence, and urgency due to RT-induced bowel damage has been observed among endometrial cancer patients years after diagnosis.[8-10] It has been estimated that 90% of those treated with radiation therapy will experience a permanent change in their bowel habit and half of those will have a complication that affects quality of life, though the range of symptoms

included in this estimate is broad.[11,12] Adverse GI outcomes among cancer survivors are often overlooked due to the priority of surveillance for disease recurrence, but GI symptoms remain among the most common complications of treatment and have the greatest impact on quality of life.[13] Individuals with radiation therapy damage to the gastrointestinal tract are more likely to experience protein calorie malnutrition and micronutrient deficiencies similar to those found in individuals with inflammatory bowel disease.[8,14]

In a study that compared gynecologic cancer survivors (*n*=356) in Sweden treated with radiation therapy compared to general population controls, risks for urgency and emptying stools into clothing without warning were elevated among survivors.[15] Treatment with external beam radiation therapy has been associated with adverse GI outcomes among endometrial cancer survivors.[16,17] However, GI outcomes have typically been measured in broad categories in populations <1,000 endometrial cancer survivors with broad variation in the length of time since diagnosis. Individuals treated with external beam radiation therapy have been observed to have more GI complications within 5 years after diagnosis than those treated with brachytherapy, including diarrhea, leakage, and the need to stay within close proximity to a toilet, all of which limit daily activities.[18] In a study that compared rectal bleeding among individuals treated with external beam radiation therapy (*n*=166) and/or brachytherapy (*n*=182), the cumulative incidence of rectal bleeding increased significantly among individuals treated with external beam radiation therapy and external beam radiation therapy and brachytherapy compared to those treated with brachytherapy alone from the time of treatment cessation to 5 years.[19] Nearly 18% of those treated with external beam radiation therapy and brachytherapy experienced rectal bleeding, though the addition of brachytherapy to external beam radiation therapy did not significantly increase risk for rectal bleeding. In a study that compared complications between endometrial cancer survivors treated with external beam radiation

therapy and surgery (*n*=190) and surgery alone (*n*=202), significant differences in both the frequency and severity of GI toxicities have been observed between those treated with external beam radiation therapy and surgery compared to those treated with surgery alone, though no increased risk of bowel obstruction was observed.[20] This study did not differentiate between acute and long-term complications.

In addition to complications due to treatment with radiation therapy, survivors may also experience surgical complications. Risk for incisional hernia among those diagnosed with endometrial cancer varies by surgical procedure. Studies that focus on the immediate complications due to surgery may miss increased long-term risk for incisional hernias. These are common even among women treated with single-port laparoscopy, which generally has fewer complications than laparotomy, including other types of abdominal hernias and bowel injuries.[21,22]

Long-term surveillance of surgically treated patients has suggested that regional complications due to surgery are usually resolved within 1 year. Studies that have investigated the long-term effects of treatment with radiation therapy on the GI system have been mixed, with some resolving within a few years[7] and some providing evidence that treatment with radiation therapy can cause permanent damage to tissue architecture of the GI systems that can persist for years after treatment cessation.[11.12] Large cohort studies that are sufficiently powered to examine a large number of GI 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.

4.3 Methods

4.3.1 Data Collection

An initial cohort of 3,624 endometrial cancer survivors was identified using the Utah Population Database. Diagnosis data were available from the statewide SEER Utah Cancer Registry for women aged 18 and over, diagnosed with invasive first primary endometrial cancer between 1997 and 2012 in the state of Utah (SEER ICD-O-3 codes: C54.0-C55.9). Endometrial cancer histological subtypes adenocarcinoma, endometrioid, mucinous adenocarcinoma, and adenocarcinoma with squamous differentiation were classified as type I (ICD-O-3 morphology codes: 8140, 8260, 8380, 8382, 8480, 8482, 8560, and 8570) and clear-cell carcinomas and papillary serous carcinomas as type II (ICD-O-3 morphology codes: 8310, 8441, and 8460).[23] Eligible survivors were required to have stage and grade included in diagnosis records from the Utah Cancer Registry and to have lived in the state of Utah for at least 1 year after diagnosis. Survivors were matched with up to 5 women from the general population on birth year and birth state.

Outcome data used for this study included statewide ambulatory and inpatient data from the Utah Department of Health and Electronic Data Warehouse data from Intermountain Health Care and the University of Utah Health Sciences Center. The Utah Population Database data included records from the Utah Cancer Registry, Utah Driver's License, vital records, and the Utah Department of Health. Statewide ambulatory and inpatient records as well as those from the University of Utah and Intermountain Healthcare systems were linked via the Utah Population Database.

Electronic medical record data were available prior to 1992, but all three major sources did not have comprehensive electronic medical record data for individuals in these cohorts until 1996. Individuals diagnosed with endometrial cancer between 1997 and 2012 were included in

this analysis to allow adequate time prior to cancer diagnosis to capture prior diagnoses of the GI outcomes of interest. A total of 153 endometrial cancer patients were excluded because their cancer was not staged, 470 because grade was missing, 285 because follow-up time did not exceed 1 year, 65 because their Utah residence did not exceed 1 year. The stage and grade were important for our study because we were interested in investigating Type I and II endometrial cancer subtypes, which are grouped with these variables. There were a total of 2,648 endometrial cancer survivors and 10,503 individuals from the general population included in the final sample.

4.3.2 Categorization of Outcomes

Outcome data from the statewide, University of Utah Health Sciences Center, and Intermountain Healthcare systems included all available ICD-9 diagnosis codes, as well as diagnosis date which allowed for time to outcome to be calculated. The Clinical Classification Software developed by the Health Cost and Utilization Project was used to categorize ICD-9 codes into 4 levels of specificity (Levels 1-4).[24] Diseases of the GI system (level 1) according to the Clinical Classification Software were used in this analysis. Level 2 outcomes included upper GI disorders, lower GI disorders, biliary tract disease, liver disease, pancreatic disorders, intestinal infection, disorders of the teeth and jaw, diseases of the mouth (excluding dental), abdominal hernia, GI hemorrhage, noninfectious gastroenteritis, and other GI disorders. More specific outcomes within these categories were analyzed as level 3 and 4 outcomes. Examples of this hierarchy include upper GI disorders (level two), esophageal disorders (level 3), esophagitis (level 4).

Long-term GI outcomes were measured 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 3 or 4 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 1 and 2 outcomes were broader, thus we did not exclude prevalent diagnoses.

4.3.3 Statistical Analysis

Chi-square tests were used to compare baseline characteristics between the cancer and general population cohorts. Univariate and multivariate Cox proportional hazard models were used to calculate hazard ratios for long-term GI outcomes at 1-5 years and >5-10 years after endometrial cancer diagnosis. We used 99% confidence intervals to account for the penalty imposed by multiple testing due to the large number of outcomes examined in this analysis. Multivariate models were adjusted for matching factors, baseline body mass index (BMI), baseline Charlson Comorbidity Index,[25] and race. 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 upper GI disorders, lower GI disorders, abdominal hernias, and liver disease among endometrial cancer survivors. The proportional hazards assumption was checked for each model using a test for nonzero 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 1 year prior to cancer survivors' endometrial cancer diagnosis were calculated from the driver's license records. For the cancer-free women, the most recent BMI value recorded at least 1 year prior to the endometrial cancer diagnosis date of the matched cancer patient was included. Approximately 35% of the 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 Charlson Comorbidity Index, 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.

4.4 Results

The endometrial cancer survivors cohort had a higher proportion of obese individuals (44.2% vs 19.2%) than the general population cohort ($p<0.001$, Table 4.1). Nearly 81.5% of the endometrial cancer survivors were diagnosed with grade I or II and 80.3% with stage I disease (Table 4.2). Among endometrial cancer survivors, 68.5% were treated with surgery alone, 21.9% with surgery and radiation therapy, 3.2% with surgery and chemotherapy, and 4.7% with surgery, radiation therapy, and chemotherapy.

Endometrial cancer survivors were more likely to be diagnosed with biliary tract, liver, and pancreatic diseases at both 1-5 years and >5-10 years after diagnosis (Table 4.3). Elevated risk for cholelithiasis without cholecystitis was observed at 1-5 years (HR: 1.73, 99% CI: 1.16-2.58) and at >5-10 years (HR: 1.95, 99% CI: 1.21-3.13) after diagnosis. Survivors were 3 times more likely to be diagnosed with liver disease between 1 and 5 years after diagnosis, with elevated risk persisting >5-10 years after diagnosis. Survivors were more than twice as likely to

be diagnosed with acute pancreatitis >5-10 but not between 1-5 years after diagnosis.

Endometrial cancer survivors were 83% more likely to be diagnosed with a lower GI disorder between 1-5 years and 33% more likely between >5-10 years after diagnosis compared to individuals from the general population (Table 4.4). The highest risk was observed for intestinal hernias, with endometrial cancer survivors being 4 times more likely to be diagnosed with an intestinal hernia between 1-5 and twice as likely between >5-10 years after diagnosis. Within this category, survivors were 7 times more likely to be diagnosed with peritoneal or intestinal adhesions between 1-5 years and 3 times more likely between >5-10 years after diagnosis and were three times more likely to be diagnosed with paralytic ileus between 1-5 years after diagnosis, but no elevated risk was observed between>5-10 years after diagnosis. Risk for anal and rectal conditions among endometrial cancer survivors was twice that of general population individuals, but elevated risk did not persist >5-10 years after diagnosis.

Endometrial cancer survivors were at elevated risk for abdominal hernias between 1-5 (HR: 2.18, 99% CI: 1.80-2.65) and >5-10 (HR: 1.44, 99% CI: 1.11-1.87) years after diagnosis (Table 4.5). Survivors were 3 to 5 times more likely to be diagnosed with umbilical, ventral, and incisional hernias without the presence of gangrene between 1-5 years. Elevated risk persisted between >5-10 years after diagnosis for ventral and incisional hernias. Elevated risk for gastrointestinal hemorrhage was observed among survivors between 1-5 years (HR: 1.90, 99% CI: 1.48-2.43) and >5-10 years (HR: 1.43, 99% CI: 1.03-1.99). No elevated risk among endometrial cancer survivors for intestinal infection was observed between 1-5 years after diagnosis; but between >5-10 years, endometrial cancer survivors were more than twice as likely be diagnosed with an intestinal infection. Survivors were at elevated risk for constipation between 1-5 and >5-10 years after diagnosis.

Among endometrial cancer survivors, increased risk for upper GI disorders, lower GI disorders, abdominal hernias, and liver disease was observed for advanced stage and high grade endometrial cancer diagnoses at 1-5 years but not between >5-10 years after diagnosis (Table 4.6). Elevated risk for abdominal hernias and lower GI disorders was observed among individuals treated with chemotherapy and/or radiation therapy compared to those treated with surgery alone between 1-5 years and >5-10 years after diagnosis. Individuals treated with surgery and chemotherapy were 6 times more likely to be diagnosed with liver disease compared to those treated with surgery alone (HR: 6.12, 99% CI: 4.19-8.95) between 1-5 years. No association between obesity and upper GI disorders, lower GI disorders, abdominal hernias, and liver disease compared to normal weight individuals was observed. Survivors who were overweight were at increased risk for upper GI disorders between 1-5 and >5-10 years after diagnosis and for abdominal hernias between >5-10 years after diagnosis compared to normal weight individuals.

Figure 4.1 shows the cumulative incidences of select GI outcomes between 1 and 10 years after diagnosis between endometrial cancer survivors and individuals from the general population cohort.

4.5 Discussion

This is the first large cohort study to compare all available GI outcomes from electronic medical record data between endometrial cancer survivors and matched individuals from the general population. This analysis supports many of the findings of prior investigations by showing an association between endometrial cancer diagnosis and several well-documented conditions related to treatment type. In this population, endometrial cancer survivors were at elevated risk for the majority of broad GI outcomes (upper GI disorders, lower GI disorders,

biliary tract disease, liver disease, pancreatic disorders, abdominal hernia, GI hemorrhage, and other GI disorders) between 1-5 and >5-10 years after diagnosis. These results also provide evidence that those treated with radiation therapy and/or chemotherapy compared to those treated with surgery alone are at higher risk for both upper and lower GI disorders and liver disease within 5 years of diagnosis, with treatment with chemotherapy associated with a six-fold increase in risk for liver disease.

These results present a number of important additions to the body of literature concerning long-term, adverse GI outcomes among endometrial cancer survivors. The majority of investigations into these associations have focused on symptoms that affect health-related quality of life among survivors that were measured using self-report from patients on subjects that are personal and may be less likely to be reported or lack validated measures (such as diagnosis from a clinician) to record outcomes. Studies that measure complications related to treatment are largely focused on acute conditions or those that may indicate disease recurrence at the expense of long-term conditions that can affect quality of life.

Biliary tract disorders such as gallstones have been loosely implicated as potential risk factors for endometrial cancer, though this is likely due to the role of obesity as a shared risk factor.[26,27] We observed that risk for gallstones without gallbladder inflammation and gallbladder inflammation without gallstones were higher among cancer survivors in both time periods, while risk for gallstones with gallbladder inflammation was not elevated among cancer survivors. Our models were adjusted for baseline BMI, but misclassification is possible due to the imputation of BMI values in approximately 38% of the total population. This is the first study to observe elevated risk for a new diagnosis of gallstones and gallbladder inflammation among endometrial cancer survivors years after diagnosis. Pancreatic disorders are also related to BMI, and elevated risk among endometrial cancer survivors compared to general population controls

was observed. Our results suggest that risk for both pancreatic conditions overall and for acute pancreatitis is higher after 5 years than between 1-5 years. Pancreatitis due to chemotherapy is rare (1.4-2%).[28-30] Similarly, evidence for RT-induced pancreatitis is scarce and comes primarily from case reports.[31-33]

In our results, individuals treated with chemotherapy were 6 times more likely to be diagnosed with liver disease compared to those treated with surgery alone between 1-5 years after diagnosis. Risk for liver disease was also highly elevated among survivors compared to individuals in the general population, but calculation of this risk included subcategories for which large effect sizes were observed such as ascites and other and unspecified liver disorders, which may contain multiple conditions with potentially differing etiologies. Regardless, the observation that risk for liver disease overall is higher among those treated with chemotherapy supports prior evidence of toxicity in the liver[34-36] due to treatment with chemotherapy observed among survivors of other cancers. This is the first study to quantify the risk of liver disease overall in endometrial cancer survivors compared to controls from the general population.

Endometrial cancer survivors were at increased risk for lower GI disorders overall during both time periods. The HRs were markedly higher for intestinal obstructions, peritoneal adhesions, and peritonitis and intestinal abscess between 1-5 and >5-10 years after diagnosis, while conditions such as paralytic ileus, anal and rectal conditions, and diverticulosis were much more likely among endometrial cancer survivors between 1-5 years but not >5-10 years after diagnosis. Some prior studies have suggested that RT-induced bowel damage can be permanent.[11,12] These results did not measure outcomes >10 years after diagnosis, but our results suggest that several GI outcomes are more common among endometrial cancer survivors for as many as 10 years after diagnosis, while risk for others was as much as 3 times higher

among survivors between 1-5 years but not significantly elevated between >5-10 years. Prior studies that have examined lower GI disorders among endometrial cancer survivors have primarily relied on patient reported outcomes that may be secondary to other GI conditions, which makes comparisons of risk for the specific outcomes measured in this study difficult. Several studies that have examined risk for anal and rectal conditions and bowel injury found that endometrial cancer survivors are at elevated risk for these conditions,[8,15] but in our population risk was higher than what has been previously observed.

Abdominal hernias, especially incisional hernias are well documented surgical complications, but these are often diagnosed post-operatively. The current study's results suggest that newly diagnosed incisional hernias are more likely to be diagnosed in endometrial cancer survivors even between >5-10 years after diagnosis. Few studies have examined long-term risk for ventral hernias among endometrial cancer survivors, but our results suggest that survivors are more than 5 times more likely to be diagnosed between 1-5 years and 4 times more likely to be diagnosed between >5-10 years. These outcomes are generally thought to be the result of surgical treatment, but our results show elevated risk among survivors treated with surgery and/or chemotherapy compared to those treated with surgery alone during both time periods. This may be explained by the use of chemotherapy and/or radiation therapy in more advanced cases of disease that would also require more aggressive surgeries which could result in more frequent complications, or are due to the use of chemotherapeutic agents that are associated with compromised wound healing.[37]

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 electronic medical record data provide a more objective measure of the experience of endometrial cancer survivors with respect to GI outcomes. In addition, the electronic medical record data used in

this study came 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 is 8.5 years. Approximately 27% have total follow-up time between 1 and 5 years, 39% between 5 and 10 years, and 34% in excess of 10 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 are comprised of comprehensive electronic medical record 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 10 years is limited due to lack of follow-up time for this proportion of the study population. However, with the Utah Population Database as a data source, we are able to update our analysis on a regular basis for further analysis. 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 radiation therapy type and dosage, specific chemotherapy agents, and duration of treatment. However, the treatment data that were available did provide evidence that risk for several GI outcomes vary by treatment type. It is also possible that there may be surveillance bias among endometrial cancer survivors due to

increased monitoring during routine follow-up in the years following diagnosis.

Future research is necessary to more accurately assess causal relationships between treatment for endometrial cancer and the outcomes measured in this study. While the mechanisms of damage to the GI system due to surgery, chemotherapy and radiation therapy have been investigated more completely for cervical cancer, more studies that examine these associations among endometrial cancer survivors are necessary. Further analysis that incorporates more specific treatment-related factors are also needed. Additionally, because electronic medical record data are 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 a number of long-term GI outcomes. Many of the conditions examined in this study have shared risk factors with endometrial cancer, but the ability to control for many of these risk factors provides a clearer picture than has been previously available. It is evident from these results that the survivors of endometrial cancers in this cohort experienced a high burden of adverse GI outcomes, especially lower GI disorders, abdominal hernias, gastrointestinal hemorrhage, and liver disease. These results suggest that increased monitoring for GI disorders over long periods of time among endometrial cancer survivors may be warranted. Further, these results highlight the need to place more emphasis on survivorship in addition to acute complications of treatment that encompass the majority of the literature on treatment-related effects.

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Table 4.1: 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	4.38	473	4.50	
1920-1929	310	11.71	1,192	11.35	
1930-1939	541	20.43	2,015	19.18	
1940-1949	787	29.72	3,085	29.37	
1950-1959	591	22.32	2,444	23.27	
>1960	303	11.44	1,294	12.32	0.54
Race					
White	2,525	95.35	9,617	91.56	
Black	10	0.38	29	0.28	
American Indian/Alaskan Native	111	1.06	32	1.21	
Asian	277	2.64	19	0.72	
Pacific Islander	60	0.57	48	1.81	
Unknown	14	0.53	409	3.89	*<0.001*
Vital Status					
Alive	1,924	72.66	8,906	84.79	
Dead	724	27.34	1,597	15.21	*<0.001*
Baseline BMI					
<18 kg/m^2	18	0.68	307	2.92	
18-24.9 kg/m^2	645	24.36	4,994	47.55	
25-29.0 kg/m^2	814	30.74	3,190	30.74	
>30 kg/m^2	1,171	44.22	2,012	19.16	*<0.001*
Age Attained at the End of Follow-up					
<50	161	6.08	697	6.64	
50-59	389	14.69	1,697	16.16	
60-69	826	31.19	3,142	29.92	
70-79	692	26.13	2,637	25.11	
80-89	442	16.69	1,787	17.01	
90+	138	5.21	543	5.17	0.303
Follow up Period					
1-5 years	726	27.42	2,742	26.11	
>5-10 years	1,028	38.82	4,062	38.67	
>10-15 years	595	22.47	2,576	24.53	
15+ years	299	11.29	1,123	10.69	0.122

Table 4.2: Clinical characteristics among endometrial cancer survivors

	Endometrial Cancer (n=2,648)	
Diagnosis Year	n	%
1997-2000	563	21.26
2001-2003	471	17.79
2004-2006	483	18.24
2007-2009	572	21.60
2010-2012	559	21.11
Age at Diagnosis		
<40	140	5.29
40-49	307	11.59
50-59	786	29.68
60-69	758	28.63
70-79	451	17.03
80+	206	7.78
Grade		
Grade I (Well differentiated)	1,314	49.62
Grade II (Moderately differentiated)	845	31.91
Grade III (Poorly differentiated)	421	15.90
Grade IV (Undifferentiated)	68	2.57
Stage		
Local	10,565	80.34
Regional	2,154	16.38
Advanced	432	3.28
Histology		
Endometrioid adenocarcinoma	1,853	69.98
Adenocarcinoma with squamous differentiation	56	2.11
Serous adenocarcinoma	87	3.29
Clear cell adenocarcinoma	17	0.64
Mixed cell adenocarcinoma	47	1.77
Mucinous adenocarcinoma	45	1.70
Carcinosarcoma	26	0.98
Stromal sarcoma	44	1.66
Leiomyosarcoma	41	1.55
Other	432	16.31
Endometrial Cancer Type		
Type I	2,300	86.86
Type II	87	3.29
Unknown	261	9.86
Treatment Type		
Surgery only	1,813	68.47
Surgery and radiation	579	21.87
Surgery and chemotherapy	84	3.17
Surgery, radiation, and chemotherapy	124	4.68
No available treatment information	48	1.81

Table 4.3: Biliary, liver, and pancreatic 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					
	Survivors		General Population			
outcome	n	%	n	%	HR	99% CI
Biliary tract disease	206	7.8	385	3.7	**2.02**	**(1.58-2.59)**
Cholelithiasis with acute cholecystitis	15	0.6	46	0.4	1.20	(0.51-2.85)
Cholelithiasis with other cholecystitis	51	1.9	156	1.5	1.08	(0.68-1.71)
Cholelithiasis without mention of cholecystitis	81	3.1	150	1.4	**1.73**	**(1.16-2.58)**
Calculus of bile duct	15	0.6	33	0.3	1.34	(0.53-3.38)
Cholecystitis without cholelithiasis	41	1.6	73	0.7	**2.28**	**(1.32-3.94)**
Other biliary tract disease	57	2.2	114	1.1	**2.05**	**(1.29-3.26)**
Liver disease	353	13.3	470	4.5	**3.10***	**(2.52-3.82)**
Other liver diseases	234	8.8	365	3.5	**2.75***	**(2.13-3.54)**
Cirrhosis of liver without mention of alcohol	6	0.2	27	0.3	0.90	(0.25-3.23)
Liver abscess and sequelae of chronic liver disease	11	0.4	23	0.2	2.61	(0.78-8.67)
Ascites	62	2.3	42	0.4	**6.98***	**(3.73-13.07)**
Other and unspecified liver disorders	217	8.2	340	3.2	**2.65***	**(2.04-3.45)**
Pancreatic disorders (not diabetes)	45	1.7	101	1.0	**1.84**	**(1.11-3.06)**
Acute pancreatitis	24	0.9	67	0.6	1.54	(0.79-3.01)
Chronic pancreatitis	2	0.1	7	0.1	0.58	(0.04-7.91)
Other pancreatic disorders	23	0.9	27	0.3	**3.47**	**(1.50-8.05)**

Table 4.3 Continued

	5-10 Years					
	Survivors		General Population			
	n	%	n	%	HR	99% CI
Biliary tract disease	115	4.3	321	3.1	**1.38**	**(1.00-1.91)**
Cholelithiasis with acute cholecystitis	17	0.6	33	0.3	2.12	(0.86-5.21)
Cholelithiasis with other cholecystitis	35	1.3	114	1.1	1.25	(0.71-2.21)
Cholelithiasis without mention of cholecystitis	61	2.3	118	1.1	**1.95**	**(1.21-3.13)**
Calculus of bile duct	12	0.5	27	0.3	1.86	(0.61-5.60)
Cholecystitis without cholelithiasis	21	0.8	66	0.6	1.21	(0.56-2.59)
Other biliary tract disease	35	1.3	90	0.9	1.58	(0.85-2.94)
Liver disease	164	6.2	428	4.1	**1.58**	**(1.20-2.08)**
Other liver diseases	111	4.2	328	3.1	**1.56**	**(1.12-2.19)**
Cirrhosis of liver without mention of alcohol	4	0.2	23	0.2	0.53	(0.09-3.06)
Liver abscess and sequelae of chronic liver disease	6	0.2	21	0.2	1.49	(0.37-6.01)
Ascites	16	0.6	21	0.2	2.84	(0.95-8.49)
Other and unspecified liver disorders	103	3.9	315	3.0	**1.49**	**(1.06-2.10)**
Pancreatic disorders (not diabetes)	36	1.4	75	0.7	**2.18**	**(1.21-3.92)**
Acute pancreatitis	20	0.8	37	0.4	**2.32**	**(1.04-5.17)**
Chronic pancreatitis	1	0.0	6	0.1	1.52	(0.05-44.86)
Other pancreatic disorders	15	0.6	27	0.3	2.18	(0.84-5.65)

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

*Models in violation of the proportional hazards assumption that were evaluated using flexible parametric survival models with restricted cubic splines

Table 4.4: Lower gastrointestinal 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			
	Survivors		General Population			
outcome	n	%	n	%	HR	99% CI
Lower gastrointestinal disorders	567	21.4	1,329	12.7	**1.82***	**(1.58-2.10)**
Appendicitis and other appendiceal conditions	19	0.7	39	0.4	1.96	(0.88-4.40)
Acute appendicitis with abscess or peritonitis	7	0.3	8	0.1	3.74*	(0.83-16.88)
Acute appendicitis without abscess or peritonitis	4	0.2	27	0.3	0.60	(0.14-2.63)
Acute appendicitis; not otherwise specified	2	0.1	4	0.0	2.43	(0.20-29.32)
Other appendiceal conditions	8	0.3	8	0.1	5.87	(0.93-36.91)
Regional enteritis and ulcerative colitis	14	0.5	36	0.3	1.55	(0.65-3.67)
Intestinal obstruction without hernia	120	4.5	128	1.2	**4.16***	**(2.87-6.04)**
Paralytic ileus	55	2.1	66	0.6	**3.28**	**(1.97-5.48)**
Impaction of intestine	3	0.1	7	0.1	1.78	(0.22-14.43)
Peritoneal or intestinal adhesions	35	1.3	21	0.2	**7.15**	**(3.12-16.40)**
Other intestinal obstruction	96	3.6	67	0.6	**6.64***	**(4.08-10.82)**
Diverticulosis and diverticulitis	249	9.4	728	6.9	**1.51***	**(1.22-1.87)**
Diverticulosis	248	9.4	715	6.8	**1.53***	**(1.24-1.90)**
Diverticulitis	31	1.2	99	0.9	1.21	(0.68-2.13)
Anal and rectal conditions	80	3.0	157	1.5	**2.09**	**(1.40-3.10)**
Peritonitis and intestinal abscess	32	1.2	30	0.3	**4.12**	**(1.93-8.79)**

Table 4.4 Continued

	Survivors		5-10 Years General Population			
	n	%	n	%	HR	99% CI
Lower gastrointestinal disorders	332	12.5	1,117	10.6	**1.33**	**(1.11-1.60)**
Appendicitis and other appendiceal conditions	7	0.3	27	0.3	1.52	(0.44-5.20)
Acute appendicitis with abscess or peritonitis	2	0.1	5	0.1	1.35	(0.13-13.67)
Acute appendicitis without abscess or peritonitis	5	0.2	16	0.2	2.54	(0.47-13.65)
Acute appendicitis; not otherwise specified	3	0.1	4	0.0	2.39	(0.19-30.71)
Other appendiceal conditions	3	0.1	6	0.1	2.97	(0.29-30.31)
Regional enteritis and ulcerative colitis	8	0.3	31	0.3	1.28	(0.43-3.82)
Intestinal obstruction without hernia	51	1.9	109	1.0	**2.14**	**(1.30-3.52)**
Paralytic ileus	26	1.0	60	0.6	1.97	(1.00-3.89)
Impaction of intestine	2	0.1	11	0.1	1.01	(0.12-8.42)
Peritoneal or intestinal adhesions	14	0.5	20	0.2	**3.13**	**(1.17-8.41)**
Other intestinal obstruction	39	1.5	58	0.6	**3.01**	**(1.61-5.63)**
Diverticulosis and diverticulitis	115	4.3	549	5.2	1.04	(0.77-1.42)
Diverticulosis	113	4.3	529	5.0	1.07	(0.79-1.46)
Diverticulitis	19	0.7	93	0.9	0.93	(0.45-1.96)
Anal and rectal conditions	29	1.1	126	1.2	1.12	(0.63-1.99)
Peritonitis and intestinal abscess	20	0.8	29	0.3	**3.01**	**(1.21-7.49)**

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

*Models in violation of the proportional hazards assumption that were evaluated using flexible parametric survival models with restricted cubic splines

Table 4.5: Other gastrointestinal 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					
	Survivors		General Population			
outcome	n	%	n	%	HR	99% CI
Intestinal infection	45	1.7	97	0.9	1.67	(0.97-2.85)
Disorders of teeth and jaw	39	1.5	121	1.2	1.14	(0.67-1.94)
Diseases of mouth; excluding dental	50	1.9	146	1.4	1.36*	(0.86-2.15)
Abdominal hernia	353	13.3	644	6.1	**2.18***	**(1.80-2.65)**
Inguinal hernia	15	0.6	45	0.4	1.39	(0.60-3.21)
Diaphragmatic hernia	140	5.3	334	3.2	**1.67***	**(1.25-2.24)**
Other abdominal hernia	141	5.3	132	1.3	**4.01**	**(2.82-5.70)**
Umbilical hernia without obstruction/gangrene	36	1.4	48	0.5	**3.21**	**(1.71-6.02)**
Ventral hernia without obstruction/gangrene	67	2.5	39	0.4	**5.42**	**(2.96-9.95)**
Incisional hernia with obstruction/gangrene	23	0.9	15	0.1	**4.32**	**(1.62-11.51)**
Incisional hernia without obstruction/gangrene	71	2.7	48	0.5	**5.18***	**(3.04-8.83)**
Other and unspecified hernia	22	0.8	22	0.2	**5.15**	**(1.90-13.96)**
Gastrointestinal hemorrhage	196	7.4	462	4.4	**1.90**	**(1.48-2.43)**
Hemorrhage from gastrointestinal ulcer	18	0.7	46	0.4	**2.37***	**(1.01-5.54)**
Melena	76	2.9	156	1.5	**2.10***	**(1.40-3.16)**
Hemorrhage of rectum and anus	77	2.9	174	1.7	**2.00**	**(1.35-2.96)**
Hemorrhage of gastrointestinal tract	45	1.7	111	1.1	**1.74**	**(1.02-2.96)**
Noninfectious gastroenteritis	101	3.8	272	2.6	**1.44**	**(1.03-2.01)**
Other gastrointestinal disorders	779	29.4	1,816	17.3	**1.86***	**(1.64-2.11)**
Constipation	184	7.0	365	3.5	**2.12**	**(1.63-2.77)**
Other and unspecified gastrointestinal disorders	353	13.3	848	8.1	**2.05**	**(1.69-2.48)**

Table 4.5 Continued

	Survivors		5-10 Years General Population			
	n	%	n	%	HR	99% CI
Intestinal infection	38	1.4	87	0.8	**2.21**	**(1.25-3.93)**
Disorders of teeth and jaw	31	1.2	94	0.9	1.78	(0.96-3.33)
Diseases of mouth; excluding dental	50	1.9	123	1.2	**1.77**	**(1.06-2.94)**
Abdominal hernia	167	6.3	500	4.8	**1.44**	**(1.11-1.87)**
Inguinal hernia	4	0.2	31	0.3	0.63	(0.14-2.80)
Diaphragmatic hernia	63	2.4	249	2.4	1.21	(0.80-1.82)
Other abdominal hernia	44	1.7	102	1.0	**1.77**	**(1.04-3.02)**
Umbilical hernia without obstruction/gangrene	18	0.7	43	0.4	1.68	(0.73-3.88)
Ventral hernia without obstruction/gangrene	26	1.0	23	0.2	**4.24**	**(1.80-9.99)**
Incisional hernia with obstruction/gangrene	8	0.3	9	0.1	2.38	(0.55-10.28)
Incisional hernia without obstruction/gangrene	20	0.8	22	0.2	**3.34**	**(1.32-8.41)**
Other and unspecified hernia	10	0.4	17	0.2	1.50	(0.40-5.67)
Gastrointestinal hemorrhage	98	3.7	328	3.1	**1.43**	**(1.03-1.99)**
Hemorrhage from gastrointestinal ulcer	13	0.5	37	0.4	1.33	(0.52-3.44)
Melena	36	1.4	106	1.0	**1.83**	**(1.03-3.24)**
Hemorrhage of rectum and anus	24	0.9	115	1.1	1.08	(0.58-2.01)
Hemorrhage of gastrointestinal tract	33	1.3	97	0.9	1.78	(0.99-3.20)
Noninfectious gastroenteritis	73	2.8	222	2.1	1.45	(0.98-2.16)
Other gastrointestinal disorders	449	17.0	1,489	14.2	**1.43***	**(1.22-1.68)**
Constipation	93	3.5	304	2.9	**1.44**	**(1.01-2.07)**
Other and unspecified gastrointestinal disorders	131	5.0	598	5.7	1.16	(0.86-1.56)

Models adjusted for baseline BMI, baseline Charlson Comorbidity Index, and race. syndrome, other esophageal bleeding, hematemesis, and dysphagia.

*Models in violation of the proportional hazards assumption that were run using flexible parametric survival models with restricted cubic splines

Table 4.6: Risk factors for upper and lower gastrointestinal disorders among endometrial cancer survivors

	Upper Gastrointestinal Disorders			
	1-5 Years		5-10 Years	
	HR	99% CI	HR	99% CI
Treatment Type[a]				
Surgery only		*Reference*		
Surgery and radiation	**1.27**	**(1.05-1.54)**	1.22	(0.97-1.54)
Surgery and chemotherapy	**1.65**	**(1.04-2.62)**	1.18	(0.48-2.86)
Surgery, radiation, and chemotherapy	**2.17**	**(1.56-3.03)**	**1.76**	**(1.08-2.89)**
Stage[b]				
Local		*Reference*		
Regional	**1.43**	**(1.17-1.76)**	1.02	(0.76-1.35)
Advanced	**1.92**	**(1.23-2.99)**	1.00	(0.37-2.72)
Grade[b]				
Grade I (Well differentiated)		*Reference*		
Grade II (Moderately differentiated)	**1.28**	**(1.06-1.53)**	1.16	(0.94-1.43)
Grade III (Poorly differentiated)	**1.48**	**(1.18-1.87)**	1.10	(0.81-1.51)
Grade IV (Undifferentiated)	1.62	(0.95-2.77)	.	.
Year of Diagnosis[c]				
1997-2000		*Reference*		
2001-2004	1.14	(0.90-1.45)	1.16	(0.91-1.47)
2005-2010	1.09	(0.88-1.35)	0.80	(0.62-1.03)
2011-2012	0.75	(0.54-1.03)	.	.
Age at Diagnosis[d]				
<50		*Reference*		
50-59	1.26	(0.95-1.67)	1.20	(0.88-1.63)
60-69	**1.56**	**(1.18-2.05)**	**1.51**	**(1.12-2.04)**
70-79	**1.63**	**(1.21-2.21)**	1.19	(0.83-1.71)
80+	**1.72**	**(1.19-2.47)**	**1.71**	**(1.08-2.70)**
Charlson Comorbidity Index[e]				
0		*Reference*		
1	**1.44**	**(1.17-1.77)**	**1.58**	**(1.25-2.00)**
2+	**2.30**	**(1.87-2.81)**	**1.88**	**(1.43-2.46)**
Baseline BMI[f]				
<18 kg/m^2	1.91	(0.84-4.34)	1.27	(0.40-4.01)
18-24.9 kg/m^2		*Reference*		
<25-29.9 kg/m^2	**1.30**	**(1.04-1.62)**	**1.42**	**(1.10-1.85)**
>30 kg/m^2	1.05	(0.85-1.31)	1.02	(0.79-1.33)

Table 4.6 Continued

	Lower Gastrointestinal Disorders			
	1-5 Years		5-10 Years	
	HR	99% CI	HR	99% CI
Treatment Type[a]				
Surgery only		*Reference*		
Surgery and radiation	**1.66**	**(1.38-2.00)**	**1.35**	**(1.05-1.74)**
Surgery and chemotherapy	**1.71**	**(1.06-2.76)**	**2.70**	**(1.33-5.49)**
Surgery, radiation, and chemotherapy	**2.38**	**(1.69-3.35)**	1.37	(0.75-2.52)
Stage[b]				
Local		*Reference*		
Regional	**1.72**	**(1.41-2.10)**	1.13	(0.83-1.55)
Advanced	**1.71**	**(1.06-2.77)**	1.25	(0.46-3.41)
Grade [b]				
Grade I (Well differentiated)		*Reference*		
Grade II (Moderately differentiated)	**1.36**	**(1.13-1.64)**	1.04	(0.82-1.32)
Grade III (Poorly differentiated)	**1.62**	**(1.28-2.05)**	1.22	(0.87-1.70)
Grade IV (Undifferentiated)	**2.48**	**(1.55-3.97)**	0.29	(0.04-2.08)
Year of Diagnosis[c]				
1997-2000		*Reference*		
2001-2004	0.97	(0.77-1.24)	1.19	(0.91-1.55)
2005-2010	0.99	(0.80-1.22)	0.85	(0.64-1.12)
2011-2012	0.73	(0.53-1.01)		.
Age at Diagnosis[d]				
<50		*Reference*		
50-59	**1.86**	**(1.37-2.53)**	**1.70**	**(1.21-2.40)**
60-69	**2.22**	**(1.64-3.00)**	**1.75**	**(1.23-2.48)**
70-79	**2.29**	**(1.65-3.19)**	1.44	(0.95-2.19)
80+	**2.18**	**(1.46-3.26)**	1.51	(0.83-2.74)
Charlson Comorbidity Index[e]				
0		*Reference*		
1	0.92	(0.74-1.15)	1.20	(0.92-1.56)
2+	1.05	(0.84-1.32)	1.00	(0.72-1.40)
Baseline BMI[f]				
<18 kg/m^2	1.38	(0.57-3.38)	**2.60**	**(1.05-6.47)**
18-24.9 kg/m^2		*Reference*		
<25-29.9 kg/m^2	1.21	(0.97-1.52)	1.16	(0.87-1.56)
>30 kg/m^2	1.09	(0.87-1.35)	1.05	(0.79-1.39)

Table 4.6 Continued

	Abdominal Hernia			
	1-5 Years		5-10 Years	
	HR	99% CI	HR	99% CI
Treatment Type[a]				
Surgery only		*Reference*		
Surgery and radiation	**1.64**	**(1.29-2.08)**	**1.63**	**(1.15-2.30)**
Surgery and chemotherapy	**2.45**	**(1.45-4.14)**	**3.07**	**(1.12-8.40)**
Surgery, radiation, and chemotherapy	**2.31**	**(1.51-3.54)**	**2.33**	**(1.13-4.81)**
Stage[b]				
Local		*Reference*		
Regional	**1.99**	**(1.55-2.54)**	**1.57**	**(1.05-2.34)**
Advanced	**2.47**	**(1.43-4.28)**	2.34	(0.73-7.51)
Grade[b]				
Grade I (Well differentiated)		*Reference*		
Grade II (Moderately differentiated)	**1.35**	**(1.06-1.72)**	1.19	(0.85-1.66)
Grade III (Poorly differentiated)	**2.13**	**(1.59-2.83)**	1.53	(0.98-2.39)
Grade IV (Undifferentiated)	**3.13**	**(1.74-5.64)**		.
Year of Diagnosis[c]				
1997-2000		*Reference*		
2001-2004	1.26	(0.91-1.75)	0.99	(0.68-1.45)
2005-2010	**1.45**	**(1.08-1.94)**	0.86	(0.58-1.26)
2011-2012	0.97	(0.63-1.48)		.
Age at Diagnosis[d]				
<50		*Reference*		
50-59	1.33	(0.92-1.93)	**2.12**	**(1.21-3.72)**
60-69	**1.87**	**(1.30-2.68)**	**2.72**	**(1.56-4.75)**
70-79	**1.52**	**(1.02-2.29)**	**2.01**	**(1.06-3.82)**
80+	1.44	(0.86-2.39)	**2.56**	**(1.14-5.74)**
Charlson Comorbidity Index[e]				
0		*Reference*		
1	1.18	(0.90-1.55)	1.29	(0.88-1.89)
2+	**1.82**	**(1.40-2.38)**	**1.65**	**(1.09-2.51)**
Baseline BMI[f]				
<18 kg/m^2	0.94	(0.23-3.84)		.
18-24.9 kg/m^2		*Reference*		
<25-29.9 kg/m^2	1.30	(0.97-1.74)	**1.73**	**(1.13-2.65)**
>30 kg/m^2	1.15	(0.86-1.52)	1.25	(0.81-1.91)

Table 4.6 Continued

	Liver Disease			
	1-5 Years		5-10 Years	
	HR	99% CI	HR	99% CI
Treatment Type[a]				
Surgery only		*Reference*		
Surgery and radiation	**1.56**	**(1.21-2.02)**	1.26	(0.87-1.82)
Surgery and chemotherapy	**6.12**	**(4.19-8.95)**	1.96	(0.62-6.21)
Surgery, radiation, and chemotherapy	**3.79**	**(2.65-5.41)**	1.65	(0.77-3.56)
Stage[b]				
Local		*Reference*		
Regional	**1.88**	**(1.46-2.42)**	0.96	(0.60-1.53)
Advanced	**6.18**	**(4.26-8.96)**	1.67	(0.41-6.89)
Grade[b]				
Grade I (Well differentiated)		*Reference*		
Grade II (Moderately differentiated)	**1.49**	**(1.16-1.93)**	0.90	(0.64-1.28)
Grade III (Poorly differentiated)	**3.38**	**(2.58-4.44)**	1.05	(0.64-1.73)
Grade IV (Undifferentiated)	**4.61**	**(2.75-7.74)**		.
Year of Diagnosis[c]				
1997-2000		*Reference*		
2001-2004	**1.79**	**(1.26-2.56)**	1.10	(0.74-1.65)
2005-2010	**1.83**	**(1.32-2.53)**	1.08	(0.72-1.61)
2011-2012	**1.75**	**(1.16-2.64)**		.
Age at Diagnosis[d]				
<50		*Reference*		
50-59	0.77	(0.56-1.06)	0.76	(0.49-1.18)
60-69	0.97	(0.71-1.32)	0.73	(0.46-1.15)
70-79	0.80	(0.55-1.15)	0.88	(0.53-1.49)
80+	0.76	(0.47-1.24)	1.14	(0.58-2.26)
Charlson Comorbidity Index[e]				
0		*Reference*		
1	1.15	(0.87-1.50)	1.17	(0.78-1.74)
2+	**1.64**	**(1.25-2.14)**	**1.94**	**(1.29-2.92)**
Baseline BMI[f]				
<18 kg/m^2	.	.	0.82	(0.11-6.00)
18-24.9 kg/m^2		*Reference*		
<25-29.9 kg/m^2	1.00	(0.75-1.32)	0.94	(0.62-1.44)
>30 kg/m^2	0.94	(0.72-1.23)	0.95	(0.64-1.41)

Models adjusted for a. Charlson Comorbidity Index, BMI, race, year of diagnosis, and age at diagnosis; b. age at diagnosis, diagnosis year, BMI, Charlson Comorbidity Index, Race; c. BMI, Charlson Comorbidity Index, race, endometrial cancer type; d. BMI, race, diagnosis year, Charlson Comorbidity Index; e.,age at diagnosis, diagnosis year, race; f. Charlson Comorbidity Index, age at diagnosis, race

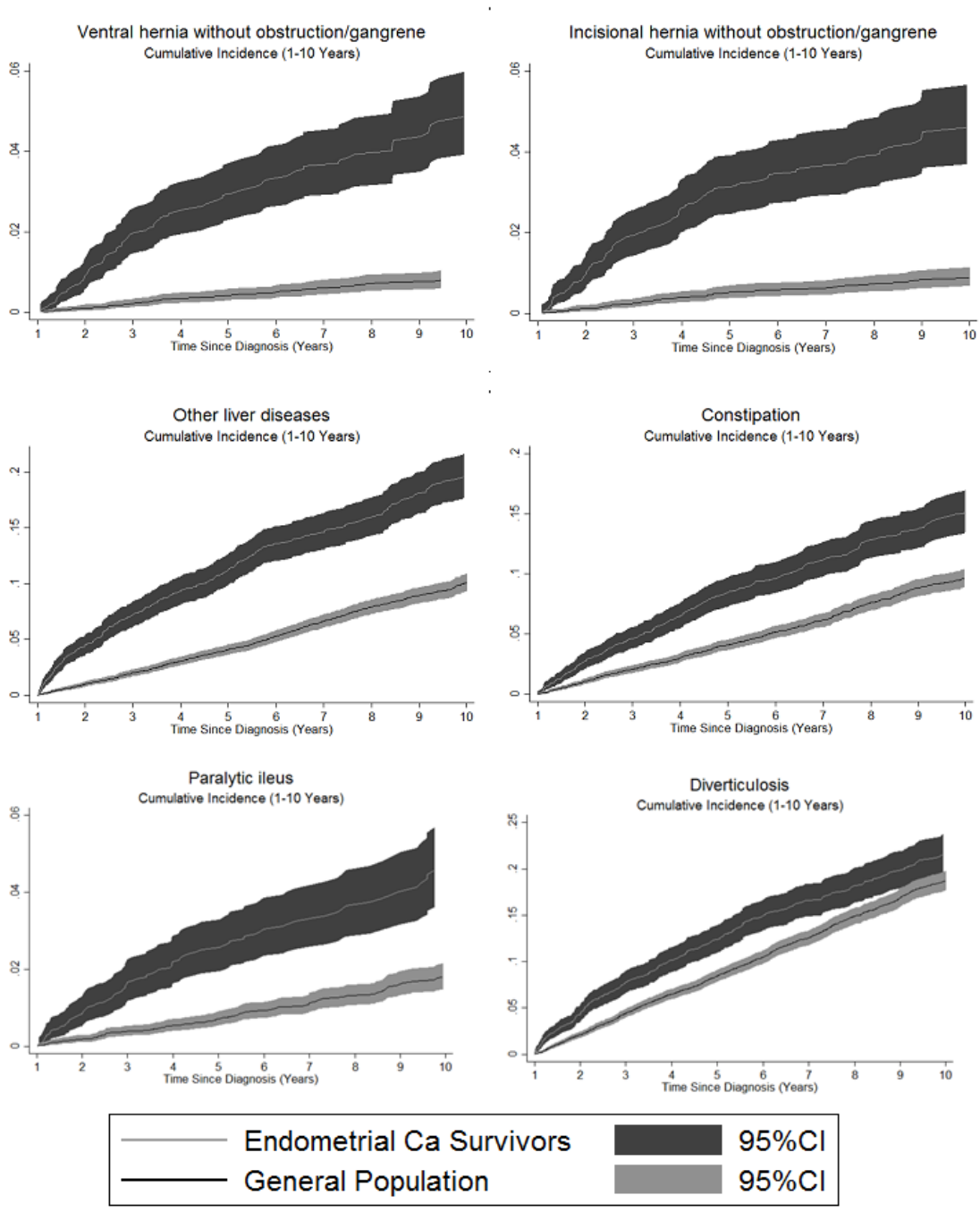

Figure 4.1: Cumulative incidence plots for select gastrointestinal outcomes

Table 4S.1: Upper gastrointestinal 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					
	Survivors		General Population			
outcome	n	%	n	%	HR	99% CI
Upper gastrointestinal disorders	597	22.6	1,997	19.0	**1.19**	**(1.04-1.36)**
Esophageal disorders	247	9.3	848	8.1	**1.25**	**(1.00-1.55)**
Esophagitis	106	4.0	307	2.9	**1.43**	**(1.04-1.96)**
Other esophageal disorders	222	8.4	819	7.8	1.16	(0.93-1.45)
Gastroduodenal ulcer (except hemorrhage)	53	2.0	209	2.0	1.07	(0.70-1.64)
Gastric ulcer	27	1.0	101	1.0	1.14	(0.64-2.04)
Duodenal ulcer	16	0.6	31	0.3	2.36	(1.00-5.57)
Peptic ulcer; site unspecified	30	1.1	129	1.2	0.86	(0.47-1.54)
Gastritis and duodenitis	128	4.8	382	3.6	1.29	(0.96-1.72)
Acute gastritis	18	0.7	42	0.4	1.71	(0.78-3.79)
Other specified gastritis	76	2.9	234	2.2	1.37	(0.95-1.97)
Unspecified gastritis and gastroduodenitis	73	2.8	201	1.9	**1.48***	**(1.03-2.14)**
Duodenitis	18	0.7	50	0.5	1.36	(0.64-2.89)
Other disorders of stomach and duodenum	112	4.2	225	2.1	**2.08**	**(1.49-2.89)**

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

*Models in violation of the proportional hazards assumption that were evaluated using flexible parametric survival models with restricted cubic splines

CHAPTER 5

CONCLUSION

The three aims of this study were to investigate the risk long-term, adverse cardiovascular, genitourinary, and gastrointestinal outcomes among endometrial cancer survivors 1-5 and >5-10 years after diagnosis compared to the general population. Treatment type, stage, grade, and age at diagnosis, baseline body mass index (BMI), and baseline Charlson Comorbidity Index were also examined as risk factors for several cardiovascular, genitourinary, and gastrointestinal outcomes among endometrial cancer survivors.

This study is the first to examine risk for all available cardiovascular, genitourinary, and gastrointestinal outcomes in the electronic medical records of several thousand endometrial cancer survivors and matched controls from the general population in a large cohort study.

5.1 Key Findings

5.1.1 Cardiovascular Outcomes

While endometrial cancer survivors have been observed to be at higher risk for hypertension, this study contributes evidence that endometrial cancer survivors are more likely to develop secondary hypertension and hypertensive heart and/or renal disease years after diagnosis. Those treated with surgery and radiation were only marginally more likely to be diagnosed with hypertension between 1 and 5 years after diagnosis compared to those

treated with surgery alone. Risk for hypertension among endometrial cancer survivors increased with each 10 year interval of age at diagnosis compared to those diagnosed before age 50. Similar proportions of endometrial cancer survivors who have received a diagnosis of hypertension (43-47%) have been previously observed,[1,2] but this study is the first to quantify risk for hypertension among endometrial cancer survivors compared to the general population.

Endometrial cancer survivors were at especially high risk of developing circulatory system disorders between 1-5 and >5-10 years after diagnosis. Survivors were 2-3 times more likely to be diagnosed with phlebitis, thrombophlebitis, or thromboembolism between 1-5 years after diagnosis. It is possible that radiation therapy damage to the endothelial cells of the vascular system could be implicated.[3] The increased risk for circulatory system disorders among survivors treated with radiation therapy and/or chemotherapy support previous findings that risk for these conditions is elevated among survivors of lymphoma, breast cancer, and head and neck cancer who were treated with RT[4] and among individuals treated with chemotherapy for a variety of cancers.[5] Survivors in our study who received radiation therapy and/or chemotherapy in addition to surgery were at higher risk for both venous and arterial disease compared to those treated with surgery alone.

Survivors were at elevated risk for heart disease over all during both time periods and a number of additional heart conditions. They were 43% more likely to be diagnosed with congestive heart failure 1-5 years and 58% more likely between >5-10 years after diagnosis. The 70% elevated risk for pulmonary heart disease was confined to the 1-5 year range and no increased risk was observed >5-10 years after diagnosis. Chemotherapy is often associated with increased risk for heart disease,[6,7] and our findings that endometrial cancer survivors treated with chemotherapy with or without radiation therapy were at elevated risk between 1-5 years after diagnosis supports this. Higher grade at diagnosis was also a strong predictor of heart

disease and is likely related to the treatments indicated for higher grade tumors.

5.1.2 Genitourinary Outcomes

Those that have examined long-term urinary system disorders among endometrial cancer survivors have had mixed results[8-10] and have largely focused on conditions such as urinary incontinence that may be secondary to many of the outcomes that were measured in the study. 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 electronic medical records provides a more objective measure of these conditions which may not have been captured by patient self-report or were not previously measured. Treatment-related risk for urinary system disorders was confined to 1-5 years after diagnosis, but large effect sizes were observed over this time period. Survivors treated with chemotherapy were 3 times more likely to be diagnosed with a urinary system disorder than those treated with surgery alone. Elevated risk was also observed among those treated with radiation therapy and among those diagnosed with higher stage and higher grade tumors.

Survivors were at elevated risk for genital organ disorders between 1-5 and >5-10 years after diagnosis. Between 1-5 years after diagnosis, endometrial cancer survivors were 88% more likely to be diagnosed with an inflammatory disease of the pelvic organs, but no elevated risk was observed after >5-10 years. Unlike urinary system disorders, the number of outcomes available for analysis suffered from a lack of granularity in our outcome classification strategy. Further, there were a number of outcomes that would not have the potential to be diagnosed in endometrial cancer survivors who have undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy, which left only a few clinically meaningful or easily interpretable

genital organ outcomes for analysis. Despite this, elevated risk for genital organ disorders was observed among survivors treated with radiation therapy and/or chemotherapy compared to those treated with surgery alone.

5.1.3 Gastrointestinal Outcomes

This is the first study to observe elevated risk for a new diagnosis of gallstones and gallbladder inflammation among endometrial cancer survivors years after diagnosis. Pancreatic disorders are also related to BMI, and elevated risk among endometrial cancer survivors compared to general population controls was observed. Our results suggest that risk for both pancreatic conditions overall and for acute pancreatitis is higher after 5 years than between 1-5 years. Pancreatitis due to chemotherapy is rare (1.4-2%).[11-13] Similarly, evidence for RT-induced pancreatitis is scarce and comes primarily from case reports.[14-16]

The largest effect size in this study was observed for liver disease among endometrial cancer survivors treated with surgery and chemotherapy compared to those treated with surgery alone. These individuals were more than 6 times more likely to be diagnosed with liver disease. Chemotoxicity in the liver has been observed in those treated for other cancers, but these results are far in excess of what has previously been reported.[17-19] This was also the first study to observe that risk for liver disease overall was elevated among endometrial cancer survivors compared to the general population years after diagnosis.

It was suggested that as many as 90% of those treated with radiation therapy experience permanent bowel damage.[20] The availability of a large amount of GI outcomes in our data allowed us to observe whether or not many of these previously observed conditions are more common in endometrial cancer survivors >5 years after diagnosis. The effect sizes were markedly higher for intestinal obstructions, peritoneal adhesions, and peritonitis and intestinal

abscess between 1-5 and >5-10 years after diagnosis, while conditions such as paralytic ileus, anal and rectal conditions, and diverticulosis were much more likely among endometrial cancer survivors between 1-5 years but not >5-10 years after diagnosis. However, individuals treated with surgery in conjunction with radiation therapy and/or chemotherapy were at significantly elevated risk of lower gastrointestinal conditions between 1-5 and >5-10 years after diagnosis, suggesting long term damage from these treatments is possible.

Abdominal hernias have been previously associated with surgical treatment and are often diagnosed postoperatively, but our results suggest that newly diagnosed ventral and incisional hernias are 3 to 4 times more likely to occur in endometrial cancer survivors even >5 years since diagnosis. Further, we observed that survivors treated with chemotherapy with or without radiation therapy were 2 to 3 times more likely to be diagnosed with an abdominal hernia compared to those treated with surgery alone between 1-5 and >5-10 years after diagnosis. It is possible that this could be related to more aggressive surgeries being performed for higher-risk tumors which might result in more frequent complications or because of the use of chemotherapeutic agents that compromise wound healing.[21]

These results present a number of important additions to the body of literature concerning long-term, adverse cardiovascular, genitourinary, and gastrointestinal outcomes among endometrial cancer survivors. Many of the investigations into genitourinary and gastrointestinal associations have focused on symptoms that affect health-related quality of life among survivors that were measured using self-report from patients on subjects that are personal and may be less likely to be reported or lack validated measures (such as diagnosis from a clinician) to record outcomes. These results utilize clinician-diagnosed outcomes from electronic medical records and contribute to a further understanding of some of the conditions that may cause these symptoms in endometrial cancer survivors.

5.1.4. Public Health and Clinical Impact

Over the last several decades, there has been a focus towards measuring not only the clinical outcomes of cancer treatment but long-term health effects and quality of life.[22] One of the primary risk factors related to both endometrial cancer and long-term adverse health outcomes is obesity. Obese individuals diagnosed with endometrial cancer have poorer overall health outcomes. Interventions intended to reduce the burden of obesity could have a significant effect on the constellation of obesity-related illnesses experienced by survivors of endometrial cancer. These could take the form of dietary and exercise interventions, and many such interventions have been shown to be effective.[23-28]

Ultimately, these results may provide clinicians with information necessary to understand more about many conditions that adversely affect quality of life among survivors and may provide justification for more careful observation and screening for potentially life-threatening conditions that may be related to treatment for endometrial cancer later in life. Results from this study could provide guidance for incorporating information about risk for specific disorders into survivorship care plans by clinicians and others working in cancer survivorship. Care for endometrial cancer patients in the years following diagnosis should be expanded beyond routine surveillance for disease recurrence to include adverse cardiovascular, genitourinary, and gastrointestinal outcomes towards the goal of achieving better quality of life for long-term endometrial cancer survivors.

Future research into long-term, adverse health effects among endometrial cancer survivors should include examining the role of genetic susceptibility in risk for multiple comorbidities. These results could inform future studies by presenting information that may be useful for risk prediction models. In addition, these results could be combined with research into quality of life among endometrial cancer survivors to understand more about the multi-

comorbidity trajectory of cancer survivors.

5.2 References

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