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Long-term Diabetes Risk among Endometrial Cancer Survivors in a Population-Based Cohort Study

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Abstract

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Author Contribution

- Seungmin Kim: The author contributed to writing the manuscript, analyze data, and incorporate comments from co-authors.
- Jihye Park: The author contributed to data analyses and provided overall comments for the manuscript.
- Yuji Chen: The author contributed to create a dataset for the study.
- These authors prepared and provided data and reviewed the manuscript: Kerry Rowe, John Snyder, Alison Fraser, Ken Smith, Vikrant G. Deshmukh, Michael Newman, Kimberley Herget.
- These authors provided scientific input to the study and reviewed the paper: Christina A. Porucznik, Dominik Ose, Mary Playdon, David Gaffney
- Mia Hashibe: The author contributed to obtain grant funding, designed the study, planned the analyses, and wrote parts of the manuscript.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Objective: The majority of endometrial cancer patients are overweight or obese at cancer diagnosis. Obesity is a shared risk factor for both endometrial cancer and diabetes, but it is unknown whether endometrial cancer patients have increased diabetes risks. The aim of our study was to investigate diabetes risk among endometrial cancer patients.

Methods: Endometrial cancer patients diagnosed between 1997 and 2012 in Utah (n=2,314) were identified. Women from the general population (n=8,583) were matched to the cancer patients on birth year and birth state. Diabetes diagnoses were identified from electronic medical records and statewide healthcare facility databases. Cox proportional hazards models were used to estimate hazard ratios for diabetes after cancer diagnosis.

Results: Endometrial cancer survivors had a significantly higher risk of type II diabetes when compared to women from the general population in the first year after cancer diagnosis (HR=5.22, 95% CI=4.05, 6.71), >1–5 years after cancer diagnosis (HR=1.67, 95% CI=1.31, 2.12), and >5 years after cancer diagnosis (HR=1.65, 95% CI=1.29, 2.11). Endometrial cancer patients who were obese at cancer diagnosis had a three-fold increase in type II diabetes risk (HR=2.99, 95% CI=2.59, 3.45). Although endometrial cancer patients diagnosed at distant stage had a higher risk of diabetes, cancer treatment did not appear to contribute to any diabetes risks.

Conclusions: In conclusion, endometrial cancer survivors had a higher risk of diabetes than women in the general population. These results suggest that long term monitoring for diabetes is indicated for endometrial cancer survivors.

Keywords

Endometrial cancer; diabetes; survivorship

Introduction

In the United States, endometrial cancer is the fourth most commonly diagnosed cancer among women, with an estimated 63,230 new cases diagnosed in 2018 [1]. The age-adjusted incidence rate for 2011 to 2015 was 16.9 per 100,000 for women < 65 years of age and 88.6 per 100,000 for women ≥ 65 years of age [2]. Endometrial cancer was the sixth most common cause of cancer death in 2018, with an estimated 11,350 deaths [1]. The death rate has been increasing on average by 1.5% per year among white women and 2.1% per year among black women from 2006 to 2015 [1]. As of 2017, an estimated 757,190 endometrial cancer survivors live in the United States [3]. Long-term chronic disease risks are of concern among endometrial cancer patients, since the majority are obese at diagnosis [4, 5]. We previously reported on increased risks of cardiovascular disease and genitourinary outcomes among endometrial cancer survivors [4, 5].

In the United States, 9.4% of the population had diabetes in 2015 [6]. Diabetes was the seventh leading cause of death in the United States, with 83,564 deaths due to diabetes in 2017 [7]. Diabetes history contributes to an increased risk of all-cause mortality and cancer-related deaths among endometrial cancer survivors [8, 9]. Given that individuals diagnosed with diabetes are likely to spend nearly 2.3 times more on healthcare costs (\$16,752/year vs. \$9,601/year) [10], the economic burden is exacerbated further for cancer patients with

diabetes. Since diabetes is a chronic disease and can lead to complications [10], prevention and control of diabetes among cancer patients is critical.

Hypothesized diabetes-related biological mechanisms driving endometrial cancer etiology and prognosis include increased insulin and insulin-like growth factor (IGF) signaling, dysregulation of ovarian steroid hormones, and chronic inflammation [11]. In addition, previous studies suggest that the association between diabetes and cancer is partly attributable to shared risk factors such as obesity, physical inactivity, and aging [12].

While previous studies suggest an increased risk of endometrial cancer with previous history of diabetes [13–18], limited evidence has been established that the risk for diabetes is increased after diagnosis of endometrial cancer. A recent study in Korea reported no association between endometrial cancer and subsequent diabetes, but the risk of diabetes by diabetes types and risk factors for diabetes were not investigated [19]. Further, there is no previous study, to our knowledge, that examined whether the risk of diabetes after endometrial cancer diagnosis differs in comparison with a general population.

The objectives of this population-based cohort study were to: (1) examine the risk of developing diabetes after cancer diagnosis among endometrial cancer survivors in comparison with a general population, (2) assess risk factors for diabetes among endometrial cancer survivors, (3) examine the risk of developing diabetes stratified by baseline BMI among endometrial cancer survivors in comparison with a general population.

Methods

Women diagnosed with a first primary endometrial cancer from 1997 to 2012 were identified from the statewide Surveillance, Epidemiology, and End Results Program (SEER) Utah Cancer Registry. Additional data for this study were obtained from the Utah Population Database (UPDB), which includes data linked from the Utah Cancer Registry, driver licenses, and birth and death certificates. Additionally, the UPDB links statewide inpatient hospital claims, ambulatory surgery records, and electronic medical records from the two largest healthcare providers in Utah, the University of Utah and Intermountain Healthcare. Utah is considered to have a minimal percentage of residents who seek healthcare out of the state, based on a report by the National Association of Health Data Organizations that reviewed interstate exchange of nonresident data for health research and public health purposes [20]. Also, Utah has a low out migration rate (2.9%) according to the state-to-state migration flow data from the US Census Bureau for 2016 [21].

The eligibility criteria were: 1) women aged ≥18 years at cancer diagnosis, 2) diagnosed with a first primary endometrial cancer (SEER International Classification of Diseases for Oncology, 3rd edition [ICD-O-3] codes: C54.0–C55.9) between 1997 and 2012. The classification of type I endometrial cancer histology was defined as adenocarcinoma, endometrioid, mucinous adenocarcinoma, and adenocarcinoma with squamous differentiation (ICD-O-3 morphology codes: 8140, 8380, 8382, 8480, 8482, 8560, and 8570). Type II endometrial cancer histology was defined as clear-cell carcinomas and papillary serous carcinomas (ICD-O-3 morphology codes: 8310, 8441, and 8460) [22]. Each

endometrial cancer survivor was matched with up to five women from the general population by birth year, and birth state (Utah/non-Utah). Birth state was included in the matching variables because additional information would be available on women born in Utah in the UPDB. Women in the general population comparison group were considered ineligible if they had been diagnosed with any invasive cancer. All research projects using the UPDB were approved by the Utah Resource for Genetic and Epidemiologic Research (RGE) and the Institutional Review Board (IRB) at the University of Utah.

Only new diabetes diagnoses after endometrial cancer diagnoses were considered in this study, thus we excluded diabetes cases before endometrial cancer diagnosis as a prevalent case. All diabetes cases were identified with an ICD-9 diagnosis code and date. Type I and type II diabetes were classified by ICD-9 codes (ICD-9 codes: 250.00 – 250.93). Secondary diabetes mellitus and abnormal findings related to diabetes (ICD-9 codes: 790.2 – 790.29, 791.5, 791.6, V45.85, V53.91, and V65.46) were classified as ‘other’ in the analysis. The majority of other diabetes cases (84% in the cancer patients cohort vs. 83% in the general population cohort) were other abnormal glucose (ICD-9 code: 790.29).

The Charlson Comorbidity Index (CCI) [23] was used to calculate baseline comorbidities using medical records prior to the date of endometrial cancer diagnosis. For the general population cohort, the CCI prior to the date of diagnosis of the case they were matched with, was taken as the baseline CCI. To avoid double adjustment, malignancy and metastatic solid tumor comorbidities were excluded in the CCI calculation.

Endometrial cancer patients were excluded if the cancer stage (n=165) or cancer grade (n=348) was missing, if they were diagnosed with diabetes before cancer diagnosis (n=71), or if they were diagnosed with diabetes both before and after cancer diagnosis (n=552). A total of 2,314 endometrial cancer survivors and 8,583 women from the general population were included in the final analysis (Figure 1). If women were diagnosed with diabetes, the follow-up period was calculated from the cancer diagnosis date (date of cancer diagnosis of the cancer patients they were matched to) to the date of diabetes diagnosis. If they were not diagnosed with diabetes, their follow-up period was calculated from the cancer diagnosis date to the date of death or last date of residence in Utah. The last residence date in Utah was determined by UPDB through the individual’s last contact with various data sources, including Utah birth/death certificate, driver’s license division, and voter registration.

We previously compared self-reported diabetes from a subset of the endometrial cancer patients (n=221) and EMR/statewide data that was used in this study to investigate concordance for various diseases including diabetes. Patients’ self-report was considered as the gold standard and the sensitivity and specificity for diabetes were 88.6% and 90.9%, respectively [4].

Statistical Analysis

Chi-square tests were used to compare demographic characteristics between the endometrial cancer survivors and the general population cohort. Cox proportional hazard models [24] were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of diabetes among endometrial cancer survivors in comparison with the general population

cohort. The follow up period was stratified into 0–1 year, >1–5 years, >5 years from endometrial cancer diagnosis. We adjusted for race, baseline body mass index (BMI), baseline CCI, birth state, and birth year. Hazard ratios for diabetes (all diabetes and type II diabetes) stratified by baseline BMI were also estimated using Cox proportional hazard models adjusted for matching factors (birth state, birth year), baseline CCI, race, and age at diagnosis. Proportional hazards assumptions were tested for all Cox proportional hazards models. If the proportional hazard assumption was violated, Cox proportional hazards regression models with cubic spline functions were used and we reported the estimate from the cubic spline function.

Cox proportional hazard models were also used to examine risk factors for type II diabetes only among endometrial cancer survivors. Potential risk factors investigated included age at cancer diagnosis, year of cancer diagnosis, race, baseline BMI, family history of diabetes, stage, grade, cancer treatment and baseline CCI. Family history of any cancer, endometrial cancer, and diabetes included first, second and third degree relatives. Adjustment variables for each potential risk factor were selected based on an assessment of the three properties of confounders based on prior knowledge. The stratified analyses and risk factors analyses were not conducted in type I diabetes due to the small number of type I diabetes cases ($n = 23$).

Weight and height were identified for the closest date 1 year before endometrial cancer diagnosis from the driver's license division. For women from the general population, the most recent BMI results at least 1 year before the endometrial cancer diagnosis date of the matched cancer patient was included. We chose the cutoff date to assess height and weight to minimize the possibility of the cancer diagnosis impacting the weight. The median years and interquartile range between the date of baseline BMI and cancer diagnosis/matched date were 3.76 (3.7) among endometrial cancer survivors and 4.1 (4.8) among women in the general population cohort. Approximately 27% of all participants were missing baseline BMI values. Thus, baseline BMI were imputed for individuals missing BMI with a linear regression model including the following covariates: cancer diagnosis, baseline CCI, race, and age at endometrial cancer diagnosis. We compared the HRs with and without imputation to assure that the inferences did not change due to the imputed BMI.

All P values were two-sided, and p -values <0.05 were considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

A total 2,314 endometrial cancer patients and 8,583 women from the general population were included in the final cohorts (Table 1). Endometrial cancer patients had a higher proportion of obesity than the general population cohort (41.4% vs. 16.0%, $p < 0.0001$). Women in the general population cohort were more likely to have normal weight than endometrial cancer survivors (49.9% vs. 28.7%, $p < 0.0001$). Family history of endometrial cancer was more common among endometrial cancer patients. (17.5% vs. 12.1%, $p < 0.0001$). Although we matched on birth year, the distribution was slightly different between the two cohorts after excluding the women in the general population cohort who had cancer

($p = 0.0247$). The proportion of individuals with diabetes was higher in the endometrial cancer cohort than the general population cohort (29.5% vs. 15.8%, $p < 0.0001$).

Approximately 58% of the endometrial cancer survivors were diagnosed with cancer from 50 years to 69 years of age (mean 60.5) (Table 2). The majority of endometrial cancer patients were diagnosed at local stage (77.5%), endometrioid adenocarcinoma histology (66.6%) and Type I endometrial cancer (84.6%). Nearly 95% of the endometrial cancer patients received surgical treatment and 8% received chemotherapy.

In the first year since cancer diagnosis, endometrial cancer survivors had a 5-fold increase in risk of any type of diabetes (overall, type I, type II, and other) compared to the general population (Table 3). The number of individuals diagnosed with diabetes in each period is summarized in Supplementary Table 3A. Endometrial cancer survivors had a significantly higher risk of diabetes when compared to the general population >1 –5 years since cancer diagnosis (HR=1.52, 95% CI=1.26, 1.84), and >5 years since cancer diagnosis (HR=1.46, 95% CI=1.22, 1.75) when adjusted for matching factors, race, baseline BMI and baseline CCI. Risks for type II diabetes and other diabetes were significantly higher for endometrial cancer survivors across all follow up periods, while risk for type I diabetes was significant for the overall period and only in the first year after cancer diagnosis.

Higher BMI at baseline was a significant risk factor for type II diabetes among endometrial cancer survivors, with a dose-response relation across all follow up periods (p trend <0.0001) (Table 4). Distant cancer stage at diagnosis (HR=2.32, 95% CI=1.05, 5.17) and higher CCI score (>2) (HR=2.06, 95% CI=1.18, 3.62, p trend = 0.026) were significant risk factors for type II diabetes after 1–5 years since cancer diagnosis, but not in the other follow up periods. Individuals with grade IV endometrial cancer were at higher risk for type II diabetes compared to those with grade I endometrial cancer in the first year since cancer diagnosis (HR=2.33, 95% CI=1.07, 5.07). Endometrial cancer survivors of other races (mostly American Indian [37%] and Pacific Islander [40%]) were more likely to be diagnosed with diabetes than white endometrial cancer survivors overall (HR=1.55, 95% CI=1.23, 1.94) and in the first year since cancer diagnosis (HR=2.16, 95% CI=1.45, 3.21). Age at cancer diagnosis, year of cancer diagnosis, family history of diabetes and cancer treatment were not associated with diabetes risk among endometrial cancer survivors.

When stratified by BMI, endometrial cancer survivors at normal BMI had higher risks for diabetes and type 2 diabetes compared to the general population across all four time periods (Table 5). Within the normal BMI group, the average baseline BMI before imputation were significantly different between endometrial cancer survivors (median=22.8, mean=22.5, standard deviation [SD] =1.75) and women (median=22.3, mean=22.2, SD=1.71) in the general population (t (3679) =−4.46, $p < 0.0001$). Overweight women in the endometrial cancer survivor cohort also had higher risks for all diabetes and type II diabetes overall, in the 0–1 year and 1–5 years follow up time periods. Overall, the highest HRs for all diabetes and type II diabetes were observed in the first year after cancer diagnosis, with 4 to 5-fold higher risks for diabetes among endometrial cancer survivors compared to the general population.

Stratified analyses for the risk of diabetes among endometrial cancer patients for Hispanic and non-Hispanic white women are shown in supplementary Table 3B and Table 3C. Although the sample size was small, among Hispanic individuals, endometrial cancer survivors had a high risk of diabetes overall (HR=4.97, 95%CI=1.16, 21.30) compared to the general population (Supplementary Table 3A). Among Non-Hispanic White individuals, endometrial cancer survivors had higher risks for overall diabetes and type II diabetes across all four time periods and other diabetes overall and in the 0–1 year periods compared to the general population (Supplementary Table 3B). There was not a statistically significant difference in these risk among Hispanic endometrial cancer survivors compared to non-Hispanic white endometrial cancer survivors.

Discussion

We observed that endometrial cancer survivors had increased risks of developing both type I and II diabetes after cancer diagnosis compared to women in the general population. The highest diabetes risks were observed within the first year after cancer diagnosis, and risks persisted throughout the follow up period. The highest risk of diabetes within the first year may be associated with medical surveillance before and after cancer treatment. Hwang *et al.* [19] also reported that the strongest risk of diabetes was among cancer patients in the first 2 years after cancer diagnosis, but the association was not significant (HR=1.17, 95%CI=0.77, 1.76) among endometrial cancer survivors. However, our study supports the hypothesis that endometrial cancer diagnosis is associated with a higher risk of developing diabetes. Prior studies reported on the association between diabetes history and the subsequent risk of endometrial cancer [13–18], but very few studies evaluated risk of diabetes after cancer diagnosis.

Among endometrial cancer survivors, overweight/obesity was a strong risk factor for type II diabetes as expected, with a dose-response relation across all follow up periods. Our results support previous findings that overweight/obesity is an important risk factor for diabetes in the general population [25, 26]. Later cancer stage, higher CCI score, and higher cancer grade were also suggested as risk factors for type II diabetes in our study, but only in select follow up periods. The increased risk of diabetes among higher stage/grade cancer patients may be associated with cancer treatment.

Paclitaxel/carboplatin, one of the most common chemotherapy combinations for endometrial cancer [27] may induce hyperglycemia [28]. In addition, medications to manage side effects resulting from chemotherapy may also induce hyperglycemia [29]. However, our results suggest that there is no association between cancer treatment and the risk of type II diabetes among endometrial cancer survivors. Age at diagnosis of endometrial cancer and family history of diabetes were not significant risk factors for type II diabetes. Although family history of diabetes has been associated with diabetes risk in general populations [30], it was not associated with diabetes risk among endometrial cancer survivors in our study.

In stratified analysis by BMI, higher risk for diabetes was observed among cancer survivors compared to the general population cohort in all BMI groups throughout the follow up periods. The highest risk for diabetes were observed immediately after cancer diagnosis

within the first year in all BMI groups but surveillance after a cancer diagnosis. The association persisting in the later follow up years suggests that the diagnosis of endometrial cancer is associated with diabetes risk regardless of BMI groups. Thus, even if endometrial cancer patients were at normal BMI at diagnosis, they had a higher risk of diabetes than women from the general population who are of similar age. Perhaps this observation is due to residual confounding within the normal BMI subgroup since the BMI was slightly higher among endometrial cancer patients within the normal BMI subgroup. Our results suggest that monitoring endometrial cancer patients for diabetes is important over the long-term. Further, it is crucial that healthcare providers are aware of the increased diabetes risk even if the endometrial cancer patient's body weight is within normal range.

The potential biological mechanisms between diabetes and cancers have been discussed in previous studies. The insulin-cancer hypothesis postulates that endometrial cancer cell proliferation is activated by chronic insulin resistance (i.e. reduced sensitivity of insulin-responsive tissues to insulin) [31] and its risk factors such as inflammatory mediators, adipokines, and excessive androgens. Even though endometrial cancer is not directly correlated with insulin, the increased level of insulin may result in adverse effects including cancer cell proliferation [32]. Another potential mechanism is that obesity and diabetes alter the regulation of sex hormones including estrogen which activates IGF-1 receptor on endometrial cancer cells and enhances cellular proliferation [31]. Diabetes could also advance tumorigenesis by increases in pro-inflammatory cytokines (e.g. interleukin (IL)-6 and tumor necrosis factor (TNF)- α), which mediate the increase in dysregulation of metabolic pathways resulting in insulin resistance and inflammatory response [33].

To our knowledge, this study is the first study that examined risk of subsequent diabetes after endometrial cancer diagnosis in comparison with a general population. Our study has many strengths, including the population-based study design with a very large cohort of approximately 2,300 endometrial cancer survivors and 8,500 women from the general population. Another strength of this study is the long follow-up period, which was >5 years for the majority of our study sample. Diabetes diagnoses were ascertained via medical records from the two largest healthcare providers in Utah, statewide inpatient hospital and ambulatory surgery records, which reduces recall errors due to self report and survival bias which is often an issue in cancer survivor cohorts. In addition, Utah has a small percentage of residents who seek health care out of state and a low out migration rate [20, 21]. Although the number of women diagnosed with type I diabetes was small, this is reflective of the general population which is expected to have very low type I diabetes prevalence (0.6%, 95%CI=0.5, 0.8) among individuals $\geq$ 45 years. Specifically, they reported that the weighted prevalence (% , 95%CI) for type I diabetes were 0.5 (0.3, 0.6), 0.6 (0.4, 0.7), and 0.6 (0.5, 0.8) in 20–44 aged, 45–64 aged, and $\geq$ 65 aged adults in the United States [34].

This study had several limitations such as possible errors in ICD coding and missing less severe cases of diabetes. The sensitivity (88.6%) and specificity (90.9%) using EMR and statewide healthcare databases to identify diabetes diagnoses among endometrial cancer patients in the study was fairly high [4]. Because we used ICD-9 codes and medical records as the source for diabetes diagnosis, we cannot eliminate the possibility of coding errors, although we would not expect such errors to be differential in cancer patients and the general

population. We did not have details on pre-diabetic diagnoses because we used medical record ICD codes as the source for diabetes diagnosis. Additionally, the women in the study may have been diagnosed with diabetes in hospitals not covered by our data sources. However, approximately 99.6% of the endometrial cancer patients and 98.5% of the general population cohort did have records in these data sources, particularly since we have statewide coverage for inpatient stays and ambulatory surgery [4]. Another limitation was the missing baseline BMI for some of our study subjects. Approximately 27% of all participants had missing baseline BMI, which were imputed. However, we assured that the inferences did not change due to the BMI imputation. Similarly, we had limited information about cancer treatment, thus we could not investigate associations between specific treatment agents and diabetes among endometrial cancer survivors. Potential confounders such as physical activity, diet, and levels of stress were not assessed, although BMI may act as a proxy for physical activity. Lastly, endometrial cancer survivors may be more likely to be diagnosed with diabetes during cancer treatment and follow up period due to surveillance bias. However, the association between endometrial cancer and diabetes risk persisted in the later follow up years (>5 years) at a time point where medical surveillance is recommended to return to that of the general population.

While few studies examined the risk of subsequent diabetes after endometrial cancer and their mechanism, the importance of preventing and managing diabetes among cancer survivors has been suggested in previous studies. Diabetes is not only associated with an increased mortality rate among endometrial cancer survivors [8, 9, 35], but it may also affect the efficacy of chemotherapy among cancer patients [36]. Diabetes diagnosis may also increase the risk of infections [37], which in turn may affect the cancer treatment plan. In particular, cancer patients with diabetes were less likely to self-manage their diabetes through exercise, diet, monitoring blood sugar when receiving chemotherapy [38].

Even though the prognostic impact of higher BMI on endometrial cancer survival has been conflicting, a meta-analysis including 665,694 endometrial cancer patients from 18 studies reported an elevated all-cause mortality rate in obese women with a dose-response relationship [39]. Physical activity was also associated with lower all-cause 5-year mortality [35]. Physical activity and better adherence to lifestyle recommendations (i.e. physical activity, diet, smoking) played a significant role in improving the health-related quality of life measured by the RAND 36 health status inventory ($p < 0.001$) among endometrial cancer survivors [40].

In conclusion, endometrial cancer survivors had a higher long-term risk of type I and II diabetes compared to women in the general population. Obesity was the strongest risk factor for diabetes among endometrial cancer survivors. Although endometrial cancer patients diagnosed at distant stage had a higher risk of diabetes, cancer treatment did not appear to contribute to any diabetes risks. These findings emphasize the importance of obesity intervention and diabetes prevention and long-term monitoring strategies among endometrial cancer survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- [1]. American Cancer Society. Cancer Facts and Figures, 2018. Atlanta, GA: American Cancer Society; 2018.
- [2]. Noone AM, Howlander N, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Review, 1975–2015, National Cancer Institute. Bethesda, MD, based on November 2017 SEER data submission, posted to the SEER web site, 4 2018.
- [3]. American Cancer Society. Cancer treatment and survivorship facts and figures, 2016–2017. Atlanta, GA: American Cancer Society; 2016.
- [4]. Soisson S, Ganz PA, Gaffney D, Rowe K, Snyder J, Wan Y, et al. Long-term cardiovascular outcomes among endometrial cancer survivors in a large, population-based cohort study. *J Natl Cancer Inst*, 2018; 110(12).
- [5]. Soisson S, Ganz PA, Gaffney D, Rowe K, Snyder J, Wan Y, et al. Long-term, adverse genitourinary outcomes among endometrial cancer survivors in a large, population-based cohort study. *Gynecol Oncol*, 2018; 148(3), 499–506. [PubMed: 29289418]
- [6]. Centers for Disease Control and Prevention. National diabetes statistics report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2017.
- [7]. Murphy SL, Xu JQ, Kochanek KD, Arias E. Mortality in the United States, 2017. *NCHS Data Brief*, no 328 Hyattsville, MD: National Center for Health Statistics 2018.
- [8]. Folsom AR, Anderson KE, Sweeney C, Jacobs DR Jr. Diabetes as a risk factor for death following endometrial cancer. *Gynecologic Oncology*, 2004; 94(3), 740–745. [PubMed: 15350367]
- [9]. Nagle CM, Crosbie EJ, Brand A, Obermair A, Oehler MK, Quinn M, et al. The association between diabetes, comorbidities, body mass index and all-cause and cause-specific mortality among women with endometrial cancer. *Gynecologic Oncology*, 2018; 150(1), 99–105. [PubMed: 29706522]
- [10]. American Diabetes Association. Economic Costs of Diabetes in the U.S. in 2017. *Diabetes Care*, 2018; 41(5), 917–928. [PubMed: 29567642]
- [11]. Joung KH, Jeong JW, Ku BJ The association between type 2 diabetes mellitus and women cancer: the epidemiological evidences and putative mechanisms. *Biomed Res Int*, 2015; 920618.
- [12]. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. *Diabetes Care*, 2010; 33(7), 1674–1685. [PubMed: 20587728]
- [13]. Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia*, 2007; 50(7), 1365–1374. [PubMed: 17476474]
- [14]. Saltzman BS, Doherty JA, Hill DA, Beresford SA, Voigt LF, Chen C, et al. Diabetes and endometrial cancer: an evaluation of the modifying effects of other known risk factors. *American Journal of Epidemiology*, 2008; 167(5), 607–614. [PubMed: 18071194]

- [15]. Lindemann K, Vatten LJ, Ellstrom-Eng M, Eskiild A. Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. *British Journal of Cancer*, 2008; 98(9), 1582–1585. [PubMed: 18362938]
- [16]. Oberaigner W, Ebenbichler C, Oberaigner K, Juchum M, Schonherr HR, Lechleitner M. Increased cancer incidence risk in type 2 diabetes mellitus: results from a cohort study in Tyrol/ Austria. *BMC Public Health*, 2014; 14, 1058. [PubMed: 25300498]
- [17]. Liao C, Zhang D, Mungo C, Tompkins DA, Zeidan AM Is diabetes mellitus associated with increased incidence and disease-specific mortality in endometrial cancer? A systematic review and meta-analysis of cohort studies. *Gynecologic Oncology*, 2014; 135(1), 163–171. [PubMed: 25072931]
- [18]. Garg SK, Maurer H, Reed K, Selagamsetty R. Diabetes and cancer: two diseases with obesity as a common risk factor. *Diabetes Obes Metab*, 2014; 16(2), 97–110. [PubMed: 23668396]
- [19]. Hwangbo Y, Kang D, Kang M, Kim S, Lee EK, Kim YA, et al. Incidence of diabetes after cancer development: a Korean national cohort study. *JAMA Oncol*, 2018; 4(8), 1099–1105. [PubMed: 29879271]
- [20]. The National Association of Health Data Organizations. Next Steps for the Inter State Exchange of Nonresident Data Between State Health Data Organizations. Salt Lake City, Utah: The National Association of Health Data Organizations; 2009 Retrieved from <https://www.nahdo.org/sites/nahdo.org/files/Resources/Publications/nex%20steps%20in%20x%20border.pdf>
- [21]. US Census Bureau. State-to-state migration flows. 2016 Retrieved from <https://www.census.gov/data/tables/time-series/demo/geographic-mobility/state-to-state-migration.html> Accessed November 2018.
- [22]. Felix AS, Weissfeld JL, Stone RA, Bowser R, Chivukula M, Edwards RP, et al. Factors associated with Type I and Type II endometrial cancer. *Cancer Causes & Control*, 2010; 21(11), 1851–1856. [PubMed: 20628804]
- [23]. Charlson ME, Pompei P, Ales KL, MacKenzie CR A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*, 1987; 40(5), 373–383. [PubMed: 3558716]
- [24]. Prentice RL, Breslow NE Retrospective studies and failure time models, *Biometrika*, 1978; 65(1), 153–158.
- [25]. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care*, 1994; 17(9), 961–969. [PubMed: 7988316]
- [26]. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *The New England Journal of Medicine*, 2001; 345(11), 790–797. [PubMed: 11556298]
- [27]. Bestvina CM, Fleming GF Chemotherapy for Endometrial Cancer in Adjuvant and Advanced Disease Settings. *Oncologist*, 2016; 21(10):1250–1259. [PubMed: 27412393]
- [28]. Pennell NA Selection of chemotherapy for patients with advanced non-small cell lung cancer. *Cleve Clin J Med*, 2012; 79 Electronic Suppl 1, eS46–50. [PubMed: 22614966]
- [29]. Leak A, Davis E, Houchin L, Mabrey M. Diabetes management and self-care education for hospitalized patients with cancer. *Clinical Journal of Oncology Nursing*, 2009; 13(2), 205–210. [PubMed: 19349267]
- [30]. Harrison TA, Hindorff LA, Kim H, Wines RC, Bowen DJ, McGrath BB, et al. Family history of diabetes as a potential public health tool. *American Journal of Preventive Medicine*, 2003; 24(2), 152–159. [PubMed: 12568821]
- [31]. Bruchim I, Sarfstein R, Werner H. The IGF hormonal network in endometrial cancer: functions, regulation, and targeting approaches. *Front Endocrinol (Lausanne)*, 2014; 5, 76. [PubMed: 24904527]
- [32]. Mu N, Zhu Y, Wang Y, Zhang H, Xue F. Insulin resistance: a significant risk factor of endometrial cancer. *Gynecol Oncol*, 2012; 125(3), 751–757. [PubMed: 22449736]
- [33]. Shoelson SE, Lee J, Goldfine AB Inflammation and insulin resistance. *J Clin Invest*, 2006; 116(7), 1793–1801. [PubMed: 16823477]

- [34]. Xu G, Liu B, Sun Y, Du Y, Snetselaar LG, Hu FB, et al. Prevalence of diagnosed type 1 and type 2 diabetes among US adults in 2016 and 2017: population based study. *BMJ*, 2018; 362, k1497.
- [35]. Arem H, Park Y, Peller C, Ballard-Barbash R, Irwin ML, Hollenbeck A, et al. Prediagnosis body mass index, physical activity, and mortality in endometrial cancer patients. *J Natl Cancer Inst* 2013, 105(5), 342–349. [PubMed: 23297041]
- [36]. Ariaans G, de Jong S, Gietema JA, Lefrandt JD, de Vries EG, Jalving M. Cancer-drug induced insulin resistance: innocent bystander or unusual suspect. *Cancer Treat Rev*, 2015; 41(4), 376–384. [PubMed: 25724262]
- [37]. Latham R, Lancaster AD, Covington JF, Pirolo JS, Thomas CS Jr. The association of diabetes and glucose control with surgical-site infections among cardiothoracic surgery patients. *Infect Control Hosp Epidemiol*, 2001; 22(10), 607–612. [PubMed: 11776345]
- [38]. Hershey DS, Tipton J, Given B, Davis E. Perceived impact of cancer treatment on diabetes self-management. *Diabetes Educ*, 2012; 38(6), 779–790. [PubMed: 22983823]
- [39]. Secord AA, Hasselblad V, Von Gruenigen VE, Gehrig PA, Modesitt SC, Bae-Jump V, et al. Body mass index and mortality in endometrial cancer: A systematic review and meta-analysis. *Gynecol Oncol*, 2016; 140(1), 184–190. [PubMed: 26524722]
- [40]. Blanchard CM, Courneya KS, Stein K. Cancer survivors' adherence to lifestyle behavior recommendations and associations with health-related quality of life: results from the American Cancer Society's SCS-II. *J Clin Oncol*, 2008; 26(13), 2198–2204. [PubMed: 18445845]

Highlights

- Endometrial cancer survivors in all BMI groups had an increased risk of diabetes.
- 29.5% of endometrial cancer patients were diagnosed with diabetes after diagnosis of endometrial cancer.
- Obesity was the most important risk factor for type II diabetes among endometrial cancer survivors.
- Overall, endometrial cancer survivors had a twofold higher risk of type II diabetes compared to the general population.

Figure 1.
Study Inclusion/Exclusion Criteria.

Table 1.

Demographic characteristics of endometrial cancer patient and general population cohorts in Utah

	Endometrial Cancer (n=2,314)	General population (n=8,583)	P-value ^a
Birth year			
<1920	113 (4.9)	439 (5.1)	0.0247
1920–1929	281 (12.1)	924 (10.8)	
1930–1939	462 (20.0)	1560 (18.2)	
1940–1949	660 (28.5)	2407 (28.0)	
1950–1959	514 (22.2)	2049 (23.9)	
>1960	284 (12.3)	1204 (14.0)	
Race			
White	2207 (95.4)	7805 (90.9)	<0.0001
Other	96 (4.2)	401 (4.7)	
Unknown	11 (0.5)	377 (4.4)	
Hispanic			
No	2142 (92.6)	5555 (64.7)	<0.0001
Yes	154 (6.7)	487 (5.7)	
Unknown	18 (0.8)	2541 (29.6)	
Vital status			
Alive	1624 (70.2)	7309 (85.2)	<0.0001
Dead	690 (29.8)	1274 (14.8)	
Baseline body mass index, kg/m ²			
<18.5	30 (1.3)	241 (2.8)	<0.0001
18.5–24.9	663 (28.7)	4282 (49.9)	
25 – 29.9	662 (28.6)	2685 (31.3)	
30	959 (41.4)	1375 (16.0)	
Follow-up period, year			
0–1	172 (7.4)	10 (0.1)	<0.0001
>1–5	536 (23.2)	1859 (21.7)	
>5–10	780 (33.7)	3233 (37.7)	
>10–15	532 (23.0)	2277 (26.5)	
15+	294 (12.7)	1204 (14.0)	
Baseline Charlson Comorbidity Index			
1	559 (24.2)	2002 (23.3)	0.4021
0	1755 (75.8)	6581 (76.7)	
Family history of any cancer ^b			
No	1048 (45.3)	3958 (46.1)	0.4798
Yes	1266 (54.7)	4625 (53.9)	
Family history of endometrial cancer ^b			
No	1909 (82.5)	7547 (87.9)	<0.0001
Yes	405 (17.5)	1036 (12.1)	

	Endometrial Cancer (n=2,314)	General population (n=8,583)	P-value ^a
Family history of diabetes ^b			
No	1104 (47.7)	4073 (47.5)	0.8272
Yes	1210 (52.3)	4510 (52.6)	
Diagnosis of diabetes after diagnosis of endometrial cancer			
No	1632 (70.5)	7225 (84.2)	<0.0001
Yes	682 (29.5)	1358 (15.8)	
Diabetes type			
Type I	7 (0.3)	16 (0.2)	<0.0001
Type II	474 (20.5)	843 (9.8)	
Other	201 (8.7)	499 (5.8)	
Follow up time, years			
0–1	221 (9.6)	139 (1.6)	<0.0001
>1–5	222 (11.4)	515 (6.1)	
>5–10	239 (18.4)	704 (11.4)	

^aTwo-sided chi-square test

^bIncludes first, second and third degree relatives.

^cIncludes secondary diabetes mellitus, abnormal glucose, impaired fasting glucose, impaired glucose tolerance test (oral), other abnormal glucose, glycosuria, and acetonuria.

Table 2.

Clinical Characteristics among endometrial cancer patients in a population-based cohort in Utah

	n	%
Year of cancer diagnosis		
1997–2000	567	24.5
2001–2003	433	18.7
2004–2006	409	17.7
2007–2009	464	20.1
2010–2012	441	19.1
Age at cancer diagnosis		
<40	131	5.7
40–49	293	12.7
50–59	696	30.1
60–69	636	27.5
70–79	370	16.0
>80	188	8.1
Age at cancer diagnosis, mean (SD)	60.5 (12.8)	
Grade		
Grade I (Well differentiated)	1093	47.2
Grade II (moderately differentiated)	740	32.0
Grade III (poorly differentiated)	403	17.4
Grade IV (undifferentiated)	78	3.4
Cancer stage		
Local	1793	77.5
Regional	394	17.0
Advanced	127	5.5
Histology		
Endometrioid adenocarcinoma	1541	66.6
Adenocarcinoma, NOS	328	14.2
Adenocarcinoma with squamous metaplasia	58	2.5
Serous adenocarcinoma	85	3.7
Clear cell adenocarcinoma	17	0.7
Mixed cell adenocarcinoma	38	1.6
Mucinous adenocarcinoma	36	1.6
Carcinosarcoma	27	1.2
Stromal sarcoma	43	1.9
Leiomyosarcoma	44	1.9
Other	97	4.2
Endometrial cancer type		
Type I	1957	84.6
Type II	84	3.6
Other	273	11.8

	n	%
Treatment		
Surgery only	1531	66.2
Surgery and radiation	487	21.1
Surgery, radiation and chemotherapy	98	4.2
Surgery and chemotherapy	75	3.2
Other (Radiation only / Chemo only/ radiation & Chemo)	25	1.1
No available information	98	4.2
Surgery		
Yes	2191	94.7
No	25	1.1
Unknown	98	4.2
Chemotherapy		
Yes	187	8.1
No	2029	87.7
Unknown	98	4.2

Table 3.

The risk of diabetes among endometrial cancer survivors compared to the general population cohort in Utah, by years since cancer diagnosis

Endometrial cancer Survivors N = 2,314		General Population N = 8,583		Overall		0–1 year		>1–5 years		>5 years	
N	%	N	%	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Diabetes mellitus	29.5	1358	15.8	1.91	(1.73, 2.10) ^a	5.02	(4.01, 6.28) ^a	1.52	(1.26, 1.84)	1.46	(1.22, 1.75)
Type I	0.3	16	0.2	3.93	(1.03, 14.94)	11.33	(1.16, 110.7)	0.38	(0.02, 8.08)	-	-
Type II	20.5	843	9.8	2.05	(1.82, 2.31) ^a	5.22	(4.05, 6.71) ^a	1.67	(1.31, 2.12)	1.65	(1.29, 2.11)
Other ^b	8.7	499	5.8	1.69	(1.42, 2.01) ^a	4.55	(2.51, 8.22)	1.69	(1.26, 2.27) ^a	1.4	(1.10, 1.78) ^a

Note: All analyses adjusted for race, baseline BMI, baseline CCI score, birth state and birth year.

^aProportional hazard assumption was violated; HRs are from Cox models with cubic splines.

^bIncludes secondary diabetes mellitus, abnormal glucose, impaired fasting glucose, impaired glucose tolerance test (oral), other abnormal glucose, glycosuria, and acetoneuria.

Table 4.

Risk factors for type II diabetes among endometrial cancer survivors in a population-based cohort in Utah, by years since cancer diagnosis

	Diabetes mellitus					
	Overall		0–1 year		> 1–5 years	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Age at diagnosis ^a						
< 40 years		Reference		Reference		Reference
40–50 years	1.05	(0.69, 1.59)	1.20	(0.55, 2.61)	0.91	(0.46, 1.83)
50–60 years	0.91	(0.61, 1.34)	0.98	(0.47, 2.04)	0.79	(0.42, 1.50)
60–70 years	0.96	(0.65, 1.43)	1.67	(0.82, 3.41)	0.61	(0.31, 1.19)
70–80 years	0.97	(0.63, 1.48)	1.50	(0.70, 3.18)	0.78	(0.39, 1.57)
80+ years	1.04	(0.62, 1.72)	1.69	(0.74, 3.89)	0.88	(0.38, 2.02)
Year of diagnosis ^b						
1997–2000		Reference		Reference		Reference
2001–2003	1.09	(0.85, 1.41)	1.09	(0.69, 1.72)	1.25	(0.77, 2.03)
2004–2006	1.01	(0.76, 1.34)	0.91	(0.56, 1.49)	1.38	(0.86, 2.22)
2007–2009	0.82	(0.60, 1.11)	1.01	(0.64, 1.59)	0.79	(0.46, 1.35)
2010–2012	0.71	(0.50, 1.02)	0.93	(0.57, 1.51)	0.56	(0.30, 1.06)
Race						
White		Reference		Reference		Reference
Other	1.55	(1.23, 1.94)	2.16	(1.45, 3.21)	1.34	(0.91, 1.97)
Baseline BMI ^c						
<18.5 kg/m ²	1.31	(0.86, 2.00)	2.39	(1.02, 5.56)	1.38	(0.67, 2.83)
18.5–24.9 kg/m ²		Reference		Reference		Reference
25–29.9 kg/m ²	1.80	(1.56, 2.08)	2.26	(1.61, 3.19)	1.87	(1.47, 2.39)
30+ kg/m ²	2.99	(2.59, 3.45)	3.46	(2.48, 4.82)	3.52	(2.77, 4.46)
P trend	<0.001		<0.001		<0.001	<0.001
Family history of diabetes ^d						
No		Reference		Reference		Reference

	Diabetes mellitus					
	Overall		0–1 year		> 1–5 years	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Yes	1.13	(0.93, 1.37)	1.24	(0.90, 1.72)	1.19	(0.84, 1.69)
Cancer stage at diagnosis ^e						
Localized	Reference		Reference		Reference	
Regional	1.11	(0.86, 1.43)	1.32	(0.91, 1.90)	1.09	(0.70, 1.72)
Distant	1.62	(1.00, 2.63)	1.45	(0.74, 2.85)	2.32	(1.05, 5.17)
Grade ^e						
I	Reference		Reference		Reference	
II	0.83	(0.68, 1.02)	1.05	(0.75, 1.47)	0.78	(0.54, 1.13)
III	0.80	(0.58, 1.10)	1.04	(0.63, 1.70)	0.57	(0.30, 1.09)
IV	1.46	(0.78, 2.71)	2.33	(1.07, 5.07)	1.04	(0.29, 3.74)
Treatment ^f						
Surgery only	Reference		Reference		Reference	
Surgery and radiation	1.14	(0.91, 1.43)	1.29	(0.91, 1.85)	1.05	(0.69, 1.58)
Surgery, radiation and chemotherapy	0.86	(0.49, 1.51)	0.85	(0.37, 1.95)	1.37	(0.60, 3.15)
Surgery and chemotherapy	1.50	(0.88, 2.58)	1.90	(0.96, 3.76)	1.67	(0.61, 4.55)
Other [*]	1.54	(0.56, 4.19)	1.11	(0.27, 4.56)	3.65	(0.84, 15.87)
Surgery ^f						
Yes	0.67	(0.25, 1.83)	0.98	(0.24, 4.00)	0.28	(0.06, 1.22)
No	Reference		Reference		Reference	
Chemotherapy ^f						
Yes	1.14	(0.78, 1.66)	1.27	(0.77, 2.11)	1.56	(0.84, 2.91)
No	Reference		Reference		Reference	
Baseline CCI ^g						
0	Reference		Reference		Reference	
1	0.91	(0.70, 1.18)	0.72	(0.47, 1.12)	1.14	(0.74, 1.76)
2+	1.20	(0.82, 1.76)	0.73	(0.39, 1.37)	2.06	(1.18, 3.62)
P trend	0.773		0.126		0.026	0.986

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- ^a Adjusted for BMI, CCI, race, cancer stage, and year of diagnosis
- ^b Adjusted for BMI, CCI, race, and endometrial cancer type
- ^c Adjusted for CCI, race, age at diagnosis
- ^d Adjusted for BMI, CCI, race, age at diagnosis, endometrial cancer type, year of diagnosis, and age at diagnosis
- ^e Adjusted for BMI, CCI, race, age at diagnosis, year of diagnosis, and histology
- ^f Adjusted for BMI, CCI, race, age at diagnosis, and year of diagnosis
- ^g Adjusted for race, age at diagnosis, and year of diagnosis
- ^{*} Includes radiation only and radiation & chemotherapy

Table 5.

Diabetes risk stratified by baseline BMI among endometrial cancer survivors compared to the general population, by years since cancer diagnosis

	Normal		Overweight		Obese	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Overall						
Diabetes mellitus	1.75	(1.43, 2.14)	1.82	(1.53, 2.17) ^a	1.98	(1.70, 2.31) ^a
Type II	1.97	(1.53, 2.55)	1.94	(1.56, 2.41) ^a	2.06	(1.72, 2.46) ^a
0–1 year						
Diabetes mellitus	4.03	(2.44, 6.64) ^a	4.81	(3.30, 7.00) ^a	5.64	(3.90, 8.15) ^a
Type II	3.91	(2.21, 6.92) ^a	5.32	(3.49, 8.10) ^a	5.60	(3.72, 8.43) ^a
>1–5 years						
Diabetes mellitus	1.45	(1.00, 2.09)	1.67	(1.23, 2.26)	1.56	(1.23, 1.99)
Type II	1.73	(1.10, 2.72)	1.64	(1.13, 2.39)	1.44	(1.08, 1.91)
>5 years						
Diabetes mellitus	1.58	(1.19, 2.09)	1.24	(0.94, 1.64)	1.41	(1.10, 1.81)
Type II	1.70	(1.16, 2.48)	1.12	(0.76, 1.66)	1.57	(1.16, 2.14)

Adjusted for CCI, race, age at diagnosis, birth state, birth year

^aProportional hazard assumption was violated; HRs are from Cox models with cubic splines