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Cardiovascular disease mortality among women with endometrial cancer in the Iowa Women's Health Study

Ashley S. Felix¹, Cindy K. Blair^{2,3}, Amy Lehman⁴, Julie K. Bower¹, Subha V. Raman⁵, DeAnn Lazovich^{6,7}, David E. Cohn⁸, Anna E. Prizment^{6,7}

¹Division of Epidemiology, College of Public Health, The Ohio State University, Columbus, OH

²Department of Internal Medicine, University of New Mexico, Albuquerque, NM

³University of New Mexico Comprehensive Cancer Center, Albuquerque, NM

⁴Center for Biostatistics, The Ohio State University, Columbus, OH

⁵Division of Cardiology, College of Medicine, The Ohio State University, Columbus, OH

⁶Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN

⁷Masonic Cancer Center, University of Minnesota, Minneapolis, MN

⁸Division of Gynecologic Oncology, College of Medicine, The Ohio State University, Columbus, OH

Abstract

Purpose: Obesity is associated with endometrial cancer (EC) development and cardiovascular disease (CVD) mortality. As the number of obese EC survivors continues to increase, an examination of CVD mortality in this vulnerable population is warranted.

Methods: In the Iowa Women's Health Study (1986–2011), we examined CVD mortality among 552 women with EC compared with 2,352 age- and body mass index (BMI)-matched women without EC (controls). Hazard ratios (HRs) and 95% confidence intervals (CIs) for CVD mortality were estimated using multivariable-adjusted Cox proportional hazards regression models stratified by an indicator for match set.

Results: Compared to controls, women with EC more often reported a history of diabetes, hypertension, and never smoking. Compared with controls, women with EC had lower CVD mortality (HR=0.75, 95% CI=0.56–0.99), and higher all-cause mortality (HR=1.50, 95% CI=1.30–1.74).

Conclusions: Although some CVD risk factors were more common in women with versus without EC, CVD mortality was lower among the former group. Additional well-adjusted analyses with larger study populations are needed to understand interactions between CVD risk factors with

Corresponding author: Ashley S. Felix, PhD, 1841 Neil Avenue, 346 Cunz Hall, Columbus, OH 43210, Phone: 614-688-1477, Fax: 614-688-3533, Felix.20@osu.edu.

Conflict of Interest

The authors have no conflict of interests to disclose.

CVD mortality among EC survivors. The CVD risk factor profile of EC survivors warrants emphasis on cardiovascular health.

Keywords

Uterus Neoplasm; Cardiovascular disease; Mortality; Survivor; Comparison group

Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in the United States (U.S.), with an estimated 61,380 new cases and 10,920 deaths expected in 2017 [1]. Mean age at EC diagnosis is 61 years and obesity is the strongest modifiable risk factor for development of this malignancy, conferring a two- to ten-fold greater risk when compared with normal-weight [2]. Moreover, obesity influences the profile of tumor characteristics. Obese EC patients are more likely to have well-differentiated and localized tumors [3–6] of endometrioid morphology [7] – prognostic features associated with high five-year disease-specific survival rates of 90% [8]. As the number of obese EC survivors entering post-treatment surveillance grows each year, investigations of the long-term health of this population are needed. In particular, women with EC are vulnerable to chronic conditions associated with their underlying obesity, namely cardiovascular disease (CVD).

We recently described cause-specific and all-cause mortality among women with EC using data from the Surveillance, Epidemiology and End Results (SEER) Program [9]. Among women diagnosed with well-differentiated endometrioid or localized tumors, 60% and 65% of the cohort, respectively, CVD was the most frequent cause of death. Overall, CVD deaths accounted for 20% of all deaths; however, the proportion of CVD deaths increased from 13% within five years of the EC diagnosis to 31% and 37% in the intervals 5–10 years and greater than 10 years since diagnosis. We further demonstrated that age-specific CVD mortality rates were 8 times higher among women with EC compared with women in the general U.S. population. Important limitations of this prior work include the lack of information on body mass index (BMI), diabetes, or other factors implicated in the etiology of EC and CVD mortality, as well as the absence of an internal comparison group. Therefore, within the large prospective Iowa Women's Health Study (IWHS) cohort, we examined CVD and all-cause mortality among women diagnosed with EC during follow-up compared with an age- and BMI-matched group of women who did not develop EC. Given our prior work showing an increase in CVD mortality five years after diagnosis, we also explored whether CVD mortality varied by time after the EC diagnosis. We also examined determinants of CVD death among women with and without EC.

Methods

Participants and study design

Full details regarding the IWHS design have been published elsewhere [10]. Briefly, the IWHS is a prospective cohort study designed to examine the effect of host, dietary, lifestyle factors, reproductive factors, and medical history on cancer incidence among postmenopausal women. Approximately 99% of women in this cohort are white. In 1986,

41,836 women, ages 55–69 years, were enrolled and asked to complete a self-administered questionnaire. Five follow-up questionnaires were sent to women in 1987, 1989, 1992, 1997, and 2004. The IWHS was approved by the University of Minnesota Institutional Review Board and this secondary analysis was approved by the Ohio State University Institutional Review Board.

From the overall IWHS cohort, we excluded 3,830 women who reported a cancer diagnosis (excluding non-melanoma skin cancer) at baseline, leaving 38,006 women prospectively followed for EC occurrence. Incident EC cases were ascertained through linkage to the State Health Registry of Iowa, which is a member of the SEER program. A total of 705 incident ECs [International Classification of Diseases (ICD)-10 codes C54–C55] were identified from cohort baseline through December 31, 2010, and morphology codes were used to classify cancers as endometrioid (morphology codes: 8140, 8210, 8260–8263, 8380–8382, 8480, 8560, and 8570) or non-endometrioid (morphology codes: 8310, 8323, 8441, 8460–8461, 8950, 8951, and 8980). We applied the following exclusions to cases: developed cancer at another site before the EC diagnosis (n=56), development of endometrial sarcoma or other rare histologic subtypes (n=21), or *in situ* behavior (n=25), leaving 603 EC cases. Information on each incident cancer including date of diagnosis, morphology, stage, and grade at cancer diagnosis, as well as first-course of treatment (surgery, chemotherapy, and radiation) was collected.

We matched women in the IWHS cohort who did not develop EC during follow-up until December 31, 2010 (i.e. non-cancer controls, n=37,301) to the EC cases for comparison purposes using a two-step process. First, for each cancer case, we constructed a pool of controls (cancer-free women) who were alive at the time of the case's diagnosis and did not report a hysterectomy. Controls who died or reported a hysterectomy on the baseline (1986) or follow-up questionnaires (1992 and 2004, n=8,376) were excluded. For controls that could be associated with more than one case (i.e. women who were alive at the time of more than one case's diagnosis date), assignment to a case pool was performed randomly to ensure that each control appeared in only one case's pool. Once all eligible controls were allocated into pools, they were assigned a reference date equivalent to the diagnosis date of their associated EC case. In the second step, we randomly selected women for each EC case among the pool of associated controls generated in the first step. Selected women were required to have BMI within 5 kg/m² of the case and age within 5 years of the case, based on control information closest to the calculated reference date. Our goal was to randomly select 5 controls for each case; however, for some cases (n=121), there were fewer than 5 eligible controls in their pool. For these cases, we then selected available controls that met eligibility criteria. In addition, we excluded 51 EC cases without any appropriate matches. We observed no differences in baseline characteristics between these 51 cases and the cases who were included. Controls were sampled without replacement and could experience a cancer diagnosis (other than EC) after the reference date.

Outcome assessment

Deaths through December 31, 2011, were identified through the State Health Registry of Iowa or the National Death Index for women who did not respond to the last follow-up

questionnaire (2004) or who emigrated from Iowa. International Classification of Diseases (ICD), 9th and 10th Edition codes (ICD-9, ICD-10), were used to determine the underlying cause of death. ICD-9 codes 390–459 or ICD-10 codes I00–I99 were used to identify CVD deaths as the underlying cause. Deaths from EC were identified with ICD-9 codes (179 and 182) and ICD-10 codes (C54–C55). Person-years of follow-up were accumulated from EC diagnosis or the reference date for controls until death or administrative censoring at the end of follow-up (December 31, 2011) whichever occurred first.

Covariates

The baseline and follow-up questionnaires included questions concerning potential confounders, including demographic factors (age, education at baseline), lifestyle factors (physical activity, smoking, and alcohol use at baseline), medical history (high blood pressure, diabetes, and heart disease at baseline and each follow-up), anthropometrics (height at baseline and weight at baseline and each follow-up) and medication use (hormone replacement therapy at baseline and each follow-up). We used information collected closest to the reference date (i.e. diagnosis date for cases and match date for controls) in all analyses. Missing data were treated as separate categories in all mortality analyses.

Statistical analysis

Participant characteristics were summarized for women diagnosed with EC and controls. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between EC status with CVD and all-cause mortality. Days since the reference/diagnosis date were used as the underlying time metric in all analyses, and the baseline hazards were stratified by an indicator for match set. In the CVD mortality models, deaths from other causes were treated as censoring events. In the final multivariable model we adjusted for elapsed time from completion of the most recent questionnaire to the reference/diagnosis date (continuous), as well as variables significantly associated with CVD mortality among the control population (education, history of oral contraceptive use, alcohol use, diabetes, hypertension, CVD, and smoking status). We additionally included age and BMI to control for potential residual confounding; however, no differences between models with and without these predictors were observed (data not shown). To compare results from this analysis to our previous study in SEER [9], we examined the association between EC status and CVD mortality in a model adjusted for age without matching for BMI.

We conducted several sensitivity analyses. We first restricted the case definition to women with low-grade (i.e. grades 1 or 2) endometrioid tumors or women with localized disease, groups for whom we hypothesized that CVD mortality would be high. We also conducted analyses restricting the study population to women without self-reported CVD, women who self-reported never smoking, and women with questionnaire data within five years of the reference/diagnosis date. The latter analysis was conducted to account for possible misclassification of CVD risk factor data associated with questionnaires more distal to the reference/diagnosis date, respectively.

The proportional hazards assumption was evaluated using a Wald test for the multiplicative interaction term between follow-up time (natural log scale) and EC status. Based on the borderline statistically significant interaction ($P=0.07$) and our prior observation of higher CVD mortality five years after the EC diagnosis [9], we evaluated the association between EC status and CVD mortality in two time periods: less than five years following the reference/diagnosis date and greater than five years after the reference/diagnosis date by fitting separate models for each time period. For the first time period, we included all women and censored CVD events occurring five years after the reference/diagnosis date, and in the second time period, follow-up time started five years after the reference/diagnosis date and ended at the date of CVD death or end of follow-up. In a full model, we evaluated a multiplicative interaction term between EC status and time period to determine whether the estimates were significantly different.

We also examined determinants of CVD mortality according to case status using Cox proportional hazards regression models. We employed the same multivariable model as previously mentioned to directly compare results between EC cases and controls. For the EC cases, we evaluated a second model which also included tumor characteristics and treatment information. Analyses were conducted using SAS/STAT software (version 9.3, SAS Institute, Cary, NC, USA).

Results

Our final study population included 552 women diagnosed with EC and 2,352 age- and BMI-matched controls, *i.e.* women who did not develop cancer by the time of the case cancer diagnosis. Our matching strategy produced similar distributions of age [median age of EC cases and controls was 72 (range: 56–90) and 72 (range: 55–92), respectively] and BMI closest to the reference/diagnosis date [median BMI among EC cases and controls was 28.4 (range=14.8–46.7) and 27.3 (range=16.5–44.0) kg/m², respectively]. Additional characteristics of the study population are shown in Table 1. Compared with controls, women with EC were more commonly nulliparous, former hormone users, never users of oral contraceptives, never smokers, diabetic, and hypertensive. Median time from completion of the most recent questionnaire and the reference/diagnosis date was 2.3 years (range: 0.04–20.9) for cases and 2.4 years (range 0.01–22.8) for controls.

CVD mortality: Women with EC versus control women

During follow-up (median=12.3 years, range=0.01–25.8), 12.9% of women with EC and 17.6% of controls died from CVD. Contrary to our hypothesis and despite having a higher prevalence of certain CVD risk factors, women with EC had lower CVD mortality (HR=0.74, 95% CI=0.56–0.99), compared to controls. We observed similar associations in analyses restricting the case definition to low-grade endometrioid EC (HR=0.76, 95% CI=0.55–1.05) or localized tumors (HR=0.75, 95% CI=0.54–1.02) (Table 2). Among women without CVD, never smokers, or women with questionnaire data within five years of the reference/diagnosis date, the association between EC status and CVD mortality was only slightly attenuated. We also examined the association between EC status and CVD mortality

in models adjusted for age (but not matched on BMI) and we observed no association (HR=0.97, 95% CI=0.77–1.21).

To assess whether EC status showed different associations with CVD mortality over the follow-up period, we assessed the association within the first five years after the reference/diagnosis date and in the interval five years or more after the reference/diagnosis date. No significant differences were observed (<5 years of reference/diagnosis date HR= 0.90, 95% CI=0.52 –1.54 versus (vs.) 5 years after reference/diagnosis date HR=0.70, 95% CI=0.49–1.00, p-interaction=0.41) (data not shown).

All-cause mortality: Women with EC vs. control women

Deaths due to any cause were more frequent among women with EC compared with controls (53.1% vs. 41.8%). The leading causes of death among women with EC were cancer (25.2%), coronary heart disease (6.9%), stroke (2.9%), and respiratory disease (2.5%). Among controls, the leading causes of death were coronary heart disease (8.5%), cancer (7.6%), respiratory disease (4.5%), and stroke (3.8%). Cancer and CVD-related illnesses are the top causes of death among women older than 65 years in the general population [11]. We observed 50% higher all-cause mortality among women with EC compared with controls in a Cox proportional hazards model with adjustment for the covariates described previously in the CVD model (HR=1.50, 95% CI=1.30–1.74, data not shown).

Predictors of CVD mortality among women with EC and controls

Table 3 shows multivariable-adjusted associations between patient characteristics and CVD mortality in two groups: among women with EC and among controls. Older age at diagnosis (≥ 75 vs. < 70 HR=3.93, 95% CI=1.85–8.36), history of oral contraceptive use (HR=2.00, 95% CI=1.09–3.65), history of diabetes (HR=4.31, 95% CI=2.21, 8.06), and hypertension (HR=1.65, 95% CI=0.99–2.71) were significantly associated with increased CVD mortality among women with EC. Among the controls, older age (≥ 75 vs. < 70 HR=5.27, 95% CI=3.92–7.09), more education (some college vs. less than high school HR=0.59, 95% CI=0.45–0.78), ever smoking (HR= 1.53, 95% CI=1.24–1.90), diabetes (HR=1.82, 95% CI=1.35–2.46), hypertension (HR=1.82, 95% CI=1.47–2.24), and CVD (HR=1.68, 95% CI=1.32–2.15) were related to CVD mortality. BMI was not associated with CVD mortality among EC cases or controls. In the case-only model, we additionally included tumor characteristics (stage and histology) and treatment (surgery, chemotherapy, radiation) information to the model and observed no significant associations (data not shown).

Discussion

Contrary to our hypothesis and despite having a higher prevalence of certain CVD risk factors, we observed that older women diagnosed with EC had lower CVD mortality when compared with age- and BMI-matched women without an EC diagnosis. Our results may speak to the importance of engaging with the health care system following a cancer diagnosis or the utility of a cancer diagnosis in initiating behavior change.

EC and CVD share many risk factors, including obesity and diabetes [9]. Of all obesity-related cancers occurring among women, EC is the malignancy most strongly related to

excess adiposity [2]. Further, obesity is more strongly related to development of indolent EC subtypes associated with relatively favorable survival as compared to aggressive subtypes [7]. As such, we hypothesized that women with EC were particularly vulnerable to CVD mortality after their cancer diagnosis. In a previous analysis using data from the SEER registries, we demonstrated that women with indolent forms of EC had a higher absolute risk of dying from CVD than their underlying malignancy, a risk that manifested five years after their cancer diagnosis [9]. Moreover, we observed an eight-fold higher risk of CVD mortality among EC cases compared with women in the general population [9]. The major limitations of the prior study included an inability to adjust for important confounders, namely BMI and diabetes, as well as the lack of an internal comparison group. The current analysis was undertaken to address these limitations. Unexpectedly, in the age- and BMI-matched analysis, we observed that women with EC had a 25% lower risk of CVD mortality than non-cancer controls. When we repeated the analysis without matching by BMI or adjustment for any factors (to make this study more comparable to our previous SEER study), we found no association. The shift of HR towards the null and closer to the estimates observed in the SEER study implies that the SEER findings could be partially attributed to confounding by BMI and other factors. In the study in the IWHS, the confounding could be smaller due to the internal control group that was not drastically different in terms of BMI or other characteristics. Beyond availability of confounder data, the IWHS and SEER cohorts differ in several ways. First, the percentage of all-cause deaths and CVD deaths was lower in the SEER population of EC cases (31.5% and 6.5%, respectively) compared to IWHS EC cases (53.1% and 12.8%). Moreover, EC cases in the SEER cohort were younger at diagnosis (median age: 62 vs. 72 years) and experienced shorter follow-up time (median follow-up: 5 vs. 12 years) compared with cases in the IWHS population. Finally, localized tumors were more common in the IWHS than the SEER population (76.1% vs. 64.9%). However, these differences would be expected to favor higher CVD mortality among EC cases in the IWHS population rather than the SEER population and would not explain the observed differences between the IWHS and SEER findings. We did note that a higher percentage of controls had a history of CVD than EC cases in the IWHS study population, and in a sensitivity analysis excluding women with prevalent CVD, no difference in CVD mortality was observed. In the IWHS population, all-cause mortality was higher among EC cases compared with controls, similar to our findings in SEER.

Several mechanisms could explain our findings of lower CVD mortality among EC patients compared with non-cancer controls. It is possible that EC patients had more contact with the health care system following their diagnosis as compared with women of similar age and BMI without EC. More frequent health care assessments may have led to the early detection of CVD events and subsequent treatment, preventing CVD deaths. However, the extent to which surveillance accounts for lower CVD mortality in our study cannot be directly addressed. It is also plausible that women in the IWHS made positive behavior changes following their EC diagnosis. The timing of cancer diagnoses and follow-up questionnaires precluded our ability to examine post-diagnosis BMI, diabetes, hypertension, and physical activity; however, the role of these behaviors on mortality after an EC diagnosis is unclear. Further, although women with EC had a higher prevalence of diabetes, hypertension, and

CVD, it is possible that control women had more severe disease, resulting in higher CVD mortality.

In the Kaiser Permanente Southern California (KPSC) managed care organization, Armenian and colleagues [12] examined CVD risk among 2-year survivors of adult-onset cancers compared with non-cancer controls matched by age, sex, and residential ZIP code. No association between uterine cancer status and risk of clinical CVD events was observed. However, it is important to point out several differences between our current analysis and the KPSC study. First and foremost, we were only able to identify CVD deaths through the State Health Registry of Iowa or the National Death Index as opposed to Armenian et al., [12] where incident CVD events were captured using electronic health records. In addition, we included women with a self-reported history of CVD, a group that was explicitly excluded from the KPSC study. Moreover, the KPSC analysis excluded individuals with a CVD diagnosis within two year of their cancer diagnosis in order to examine new onset CVD after the post-treatment period. In our sensitivity analysis excluding individuals with a history of CVD, we did not observe a significant association between cancer status and CVD mortality; however, the direction of the association remained.

In our examination of CVD determinants among women with EC and controls, we observed that some of the classical CVD risk factors, including older age, diabetes, and hypertension, were associated with CVD mortality among both groups. In particular, diabetes conferred a 4-fold higher risk of CVD death among EC cases, compared to a 2-fold higher risk of CVD death among the controls. We lacked information on management of diabetes in the IWHS population; however, future studies should explore diabetes, its severity and management, and CVD mortality among EC cases. We did not observe associations between smoking status or a history of CVD with CVD death among women with EC; however, these factors were significant predictors among controls. Our study may have been underpowered to detect these associations among the cases or the factors predictive of CVD mortality among women with EC differ from the general population. Notably, BMI was unrelated to CVD mortality among EC cases or controls, a finding in contrast to previous analyses among EC cases [13] and the general population [14].

Strengths of our study include the presence of a non-cancer comparison group, the ability to match EC cases with non-cancer controls on age and BMI, and adjustment for other potential confounders. Limitations of our study include the inability to directly assess potential lifestyle changes or interactions with the health care system following the cancer diagnosis as explanations for reduced CVD mortality among EC cases. In addition, the women in the IWHS are predominately white, limiting generalizability to other racial and ethnic groups. We also relied on self-reported exposure information; however, any misclassification bias would likely be non-differential between EC cases and control women. With respect to CVD mortality, there is likely some misclassification present in our study, as underlying cause of death in NDI is ascertained through death certificates. Given the small number of CVD deaths among women with EC in the current analysis, which may contribute to differences between the SEER and IWHS analyses, additional studies, with larger sample sizes, are required to confirm our surprising finding.

In this study of women with and without EC, CVD mortality was significantly lower among women with EC compared with controls. The long-term health outcomes of EC survivors require attention, as this subgroup is increasing in magnitude and unlikely to die from their cancer diagnosis. Despite the comparatively lower CVD mortality risk observed in this study, it is important for health care providers to counsel these women on the wide range of poor health outcomes associated with obesity and other CVD risk factors. This may represent a pivotal opportunity for clinicians to encourage behavior change that might ultimately reduce obesity-related morbidity.

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References:

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA: a cancer journal for clinicians. 2017;67(1):7–30. [PubMed: 28055103]
2. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. Lancet. 2014;384(9945):755–65. [PubMed: 25129328]
3. Munstedt K, Wagner M, Kullmer U, Hackethal A, Franke FE. Influence of body mass index on prognosis in gynecological malignancies. Cancer causes & control : CCC. 2008;19(9):909–16. [PubMed: 18392944]
4. Everett E, Tamimi H, Greer B, Swisher E, Paley P, Mandel L, et al. The effect of body mass index on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer. Gynecol Oncol. 2003;90(1):150–7. [PubMed: 12821356]
5. Pavelka JC, Ben-Shachar I, Fowler JM, Ramirez NC, Copeland LJ, Eaton LA, et al. Morbid obesity and endometrial cancer: surgical, clinical, and pathologic outcomes in surgically managed patients. Gynecol Oncol. 2004;95(3):588–92. [PubMed: 15581968]
6. Anderson B, Connor JP, Andrews JI, Davis CS, Buller RE, Sorosky JI, et al. Obesity and prognosis in endometrial cancer. Am J Obstet Gynecol. 1996;174(4):1171–8; discussion 8–9. [PubMed: 8623844]
7. Setiawan VW, Yang HP, Pike MC, McCann SE, Yu H, Xiang YB, et al. Type I and II endometrial cancers: have they different risk factors? J Clin Oncol. 2013;31(20):2607–18. [PubMed: 23733771]
8. Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, et al. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2006;95 Suppl 1:S105–43.
9. Felix AS, Bower JK, Pfeiffer RM, Raman SV, Cohn DE, Sherman ME. High cardiovascular disease mortality after endometrial cancer diagnosis: Results from the Surveillance, Epidemiology, and End Results (SEER) Database. Int J Cancer. 2017;140(3):555–64. [PubMed: 27741565]
10. Folsom AR, Kaye SA, Prineas RJ, Potter JD, Gapstur SM, Wallace RB. Increased incidence of carcinoma of the breast associated with abdominal adiposity in postmenopausal women. Am J Epidemiol. 1990;131(5):794–803. [PubMed: 2138863]
11. Leading Causes of Death (LCOD) by Age Group, All Females-United States, 2014 [Available from: <https://www.cdc.gov/women/lcod/2014/all-females/index.htm>.
12. Armenian SH, Xu L, Ky B, Sun C, Farol LT, Pal SK, et al. Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study. J Clin Oncol. 2016;34(10):1122–30. [PubMed: 26834065]
13. Arem H, Park Y, Pelsner 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):342–9. [PubMed: 23297041]

14. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med*. 2010;363(23):2211–9. [PubMed: 21121834]

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Table 1.

Characteristics of 552 endometrial cancer cases and 2,352 controls in the Iowa Women's Health Study, 1986–2011

Characteristic	Women with endometrial cancer		Controls		p
	n ^a	%	n ^a	%	
Education^d					0.52
Less than high school	90	16.3	431	18.3	
High school graduate	291	52.7	1,215	51.7	
Some college	171	31.0	702	29.8	
Smoking status^b					0.05
Never	403	73.0	1,584	67.3	
Former	103	18.7	523	22.2	
Current	36	6.5	208	8.8	
Alcohol intake					0.08
No	331	60.0	1,313	55.8	
Yes	221	40.0	1,039	44.2	
Physical activity					0.83
Inactive	263	47.6	1,073	45.6	
Moderately active	146	26.4	652	27.7	
Very active	133	24.1	588	25.0	
Number of live births					<0.001
Nulliparous	69	12.5	217	9.2	
1	70	14.6	163	7.7	
2	131	27.3	534	25.3	
3–4	209	43.5	912	43.1	
5	70	14.6	505	23.9	
Menopausal hormone use^b					<0.001
Never	315	57.1	1,619	68.8	
Former	93	16.8	166	7.1	
Current	142	25.7	558	23.7	
History of oral contraceptive use					0.006
Never	480	87.0	1,915	81.4	
Ever	72	13.0	432	18.4	
Diabetes^b					<0.001
No	476	86.2	2,154	91.6	
Yes	76	13.8	198	8.4	
Hypertension^b					0.007
No	270	48.9	1,299	55.2	

Characteristic	Women with endometrial cancer		Controls		p
	n ^a	%	n ^a	%	
Yes	282	51.1	1,053	44.8	
CVD^b					0.26
No	464	84.1	2,021	85.9	
Yes	88	15.9	331	14.1	
Histology^c					
Low-grade endometrioid adenocarcinoma	389	70.5	---	---	
High-grade endometrioid adenocarcinoma	79	14.3	---	---	
Non-endometrioid adenocarcinoma	63	11.4	---	---	
Tumor summary stage					
Localized	420	76.1	---	---	
Regional	89	16.1	---	---	
Distant	30	5.4	---	---	
Surgery					
No	16	2.9	---	---	
Yes	524	94.9	---	---	
Radiation					
No	356	64.5	---	---	
Yes	194	35.1	---	---	

^aFrequencies may not add up to the total because of missing values

^bUpdated based on risk factor questionnaires closest to the reference date

^cTwenty-one endometrioid cases with missing grade could not be further categorized

^dAt baseline

Hazard ratios (HR) and 95% confidence intervals (CIs) for the association between endometrial cancer status and CVD mortality in the Iowa Women's Health Study

Table 2.

Characteristic	CVD Mortality	
Overall model	Deaths, n (%) ^a	HR (95% CI) ^b
Endometrial cancer status		
No (n=2,352)	413 (17.6)	1.0
Yes (n=552)	71 (12.9)	0.75 (0.56, 0.99)
Sensitivity analyses		
<i>Cases restricted to low-grade endometrioid endometrial cancer</i>		
Endometrial cancer status		
No (n=2,352)	413 (17.6)	1.0
Yes (n=389)	56 (14.4)	0.76 (0.55, 1.05)
<i>Cases restricted to localized stage cancer</i>		
Endometrial cancer status		
No (n=2,352)	413 (17.6)	1.0
Yes (n=420)	59 (14.0)	0.75 (0.54, 1.02)
<i>Restricted to women without prevalent CVD</i>		
Endometrial cancer status		
No (n=2,021)	317 (15.7)	1.0
Yes (n=464)	56 (12.1)	0.78 (0.56, 1.09)
<i>Restricted to never smokers</i>		
Endometrial cancer status		
No (n=1,584)	266 (16.8)	1.0
Yes (n=403)	52 (12.9)	0.79 (0.55, 1.13)
<i>Restricted to women with questionnaire data 5 years before the reference/diagnosis date</i>		
Endometrial cancer status		
No (n=1,865)	342 (18.3)	1.0
Yes (n=447)	62 (13.9)	0.88 (0.59, 1.34)

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row percentage

Adjusted for time between questionnaire completion and reference/diagnosis date, history of oral contraceptive use (never, ever), alcohol use (no, yes), diabetes (no, yes), hypertension (no, yes), prevalent CVD (no, yes), education (< high school, high school graduate, > high school), smoking status (never, former, current), and stratified by match set ID

Hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between patient characteristics and CVD mortality stratified by case status in the Iowa Women's Health Study (1986–2011)

Table 3.

Characteristic	CVD Mortality					
	Women with endometrial cancer (deaths=71, N=552)			Controls (deaths=413, N=2,352)		
	deaths, n (%) ^a	HR (95% CI) ^b	P	deaths, n (%) ^a	HR (95% CI) ^b	P
Age at diagnosis			<0.001			<0.001
<70	25 (11.6)	1.00		157 (16.6)	1.00	
70–74	26 (18.6)	3.24 (1.73, 6.09)		107 (19.4)	2.31 (1.77, 3.01)	
75	20 (10.2)	3.93 (1.85, 8.36)		149 (17.4)	5.27 (3.92, 7.09)	
Body mass index (BMI)			0.09			0.31
<25 kg/m ²	21 (14.1)	1.00		118 (16.5)	1.00	
25–30 kg/m ²	27 (15.3)	1.21 (0.68, 2.18)		171 (16.9)	1.06 (0.84, 1.35)	
30–35 kg/m ²	17 (11.0)	0.68 (0.35, 1.33)		93 (18.2)	0.90 (0.68, 1.19)	
≥35 kg/m ²	6 (8.3)	0.42 (0.16, 1.11)		31 (27.0)	1.31 (0.87, 1.98)	
Education			0.35			<0.001
Less than high school	15 (16.7)	1.00		116 (26.9)	1.00	
High school graduate	36 (12.4)	0.69 (0.37, 1.27)		191 (15.7)	0.65 (0.52, 0.83)	
Some college	20 (11.7)	0.61 (0.31, 1.21)		105 (15.0)	0.59 (0.45, 0.78)	
Smoking status			0.66			<0.001
Never	52 (12.9)	1.00		266 (16.8)	1.00	
Ever	18 (13.0)	0.77 (0.44, 1.36)		139 (19.0)	1.53 (1.24, 1.90)	
Alcohol intake			0.98			0.06
No	45 (13.6)	1.00		263 (20.0)	1.00	
Yes	26 (11.8)	0.99 (0.60, 1.65)		150 (14.4)	0.82 (0.66, 1.01)	
History of oral contraceptive use			0.02			0.56
No	57 (11.9)	1.00		359 (18.7)	1.00	
Yes	14 (19.4)	2.00 (1.09, 3.65)		53 (12.3)	1.01 (0.98, 1.03)	
Diabetes			<0.001			<0.001

Characteristic	CVD Mortality					
	Women with endometrial cancer (deaths=71, N=552)			Controls (deaths=413, N=2,352)		
	deaths, n (%) ^a	HR (95% CI) ^b	P	deaths, n (%) ^a	HR (95% CI) ^b	P
No	53 (11.1)	1.00		359 (16.7)	1.00	
Yes	18 (23.7)	4.31 (2.21, 8.06)		54 (27.3)	1.82 (1.35, 2.46)	
Hypertension			0.06			<0.001
No	30 (11.1)	1.00		173 (13.3)	1.00	
Yes	41 (14.5)	1.64 (0.99, 2.71)		240 (22.8)	1.82 (1.47, 2.24)	
CVD			0.99			<0.001
No	56 (12.1)	1.00		317 (15.7)	1.00	
Yes	15 (17.0)	1.00 (0.53, 1.89)		96 (29.0)	1.68 (1.32, 2.15)	

^a row percentage

^b HRs and 95% CIs adjusted for time between questionnaire completion and diagnosis), age at diagnosis, history of oral contraceptive use, prevalent diabetes, prevalent hypertension, prevalent cardiovascular disease, and surgery. All variables categorized as shown in table.

^c Twenty-one endometrioid cases with missing grade could not be further classified