HHS Public Access

Author manuscript

Cancer Epidemiol. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

Cancer Epidemiol. 2017 December ; 51: 62–67. doi:10.1016/j.canep.2017.10.009.

Risk of cardiovascular disease among women with endometrial cancer compared to cancer-free women in the Women's Health Initiative

Ashley S. Felix[1], **Amy Lehman**[2], **Randi E. Foraker**[1], **Michelle J. Naughton**[3], **Julie K. Bower**[1], **Lewis Kuller**[4], **Gloria E. Sarto**[5], **Marcia L. Stefanick**[6], **Linda Van Horn**[7], **Rebecca D. Jackson**[8], and **Electra D. Paskett**[1,3]

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

[2]Center for Biostatistics, The Ohio State University, Columbus, OH

[3]Division of Cancer Prevention and Control, The Ohio State University, Columbus, OH

[4]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA

[5]Department of Obstetrics and Gynecology, School of Medicine & Public Health, University of Wisconsin, Madison, WI

[6]Division of Cardiovascular Medicine, Department of Medicine, Stanford, University School of Medicine, Stanford, CA

[7]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL

[8]Division of Endocrinology, Diabetes, and Metabolism, College of Medicine, The Ohio State University, Columbus, OH

Abstract

Background—The majority of women diagnosed with endometrial cancer (EC) have low cancer-specific mortality; however, a high prevalence of cardiovascular disease (CVD) risk factors places EC patients at high risk of developing CVD. In the Women's Health Initiative (WHI), we assessed the hypothesis that CVD risk was higher among women who developed EC compared with women who did not develop EC.

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.

Potential Conflicts of Interest: None declared

Authorship contribution

ASF drafted and directed this manuscript. AL conducted all statistical analyses. LK, GES, MLS, LVH, RDJ, and EDP were each involved in the acquisition of data for this project. ASF, AL, REF, MJN, JKB, LK, GES, MLS, LVH, RDJ, and EDP contributed to the data analysis and interpretation. ASF, AL, REF, MJN, JKB, LK, GES, MLS, LVH, RDJ, and EDP provided feedback on the draft of this manuscript and approved the final version to be published.

Methods—We compared the incidence of fatal and non-fatal CVD events among 1,179 women who developed Type I EC, 211 women who developed Type II EC, and 92,217 women who did not develop EC. We first estimated univariable cause-specific hazard ratios (CHRs) and 95% confidence intervals (CIs) for the association between an EC diagnosis (overall and by EC type) with CVD risk using Cox proportional hazards regression. Potential confounders were examined using a risk factor modeling approach; final multivariable-adjusted models included covariates that changed univariable CHRs for EC diagnosis by ≥ 5%.

Results—In multivariable-adjusted models, CVD risk did not significantly differ between women who developed EC compared to women who did not develop EC (CHR=1.01, 95% CI=0.87–1.16), particularly for the subgroup of women who developed Type I EC (CHR=0.98, 95% CI=0.84–1.14); however, there was a positive but statistically nonsignificant association for Type II EC (CHR=1.32, 95% CI=0.88–1.97).

Conclusion—Despite our null findings, women with EC should still receive counseling and support to make lifestyle changes aimed at reducing weight as appropriate, given the high prevalence of CVD risk factors at diagnosis.

Keywords

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

1. Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in the United States (U.S.) [1]. Since 2000, incidence rates have been increasing, likely due to changes in the distribution of several risk factors, most notably increases in the prevalence of obesity [2]. Currently, over 30% of U.S. women are classified as obese [2] which is associated with a two- to tenfold greater risk of developing EC compared with normal weight [3]. Moreover, obesity is most strongly related to development of endometrioid ECs (also referred to as Type I) [4, 5], which are characterized by high five-year disease-specific survival rates of 90% [6]. Consequently, women with obesity-driven EC subtypes, while unlikely to die from their malignancy, are at risk of developing and dying from other obesity-related chronic conditions, such as cardiovascular disease (CVD). Other EC risk factors, including diabetes [7] and hypertension [8], are also implicated in CVD, further emphasizing the shared etiology of these chronic diseases. At the time of EC diagnosis, more than half of women have hypertension and one-quarter are diabetic, which is substantially higher than population estimates for women in similar age categories [9]. Moreover, Kurnit and colleagues [9] reported higher odds of congestive heart failure and pulmonary circulation disorders among women undergoing hysterectomy for EC compared to women undergoing non-EC hysterectomies.

Findings are mixed with respect to CVD incidence and mortality following an EC diagnosis. Three studies have compared CVD mortality between women with and without EC, one reporting significantly higher CVD mortality among women with EC [10], one reporting significantly lower CVD mortality among women with EC [11], and one showing no difference [12]. To further examine CVD outcomes post-EC diagnosis, we used the large,

prospective Women's Health Initiative (WHI) study to examine the incidence of fatal and non-fatal CVD events among women who developed EC after study enrollment, compared with women who did not develop this cancer.

2. Materials and Methods

2.1 Study population

Full details of the WHI have been described previously [13–15]. Briefly, between 1993 and 1998, postmenopausal women between the ages of 50–79 years were recruited from 40 clinical sites across the U.S. into one or more randomized clinical trials (WHI-CT n=68,132) or an observational study (WHI-OS n=93,676). Women in the WHI-OS were either unwilling or ineligible to be included in a CT [16]. The WHI-CT and WHI-OS were closed in 2004–2005, and participants were invited to continue follow-up in the WHI Extension Study 1 (2005–2010), Extension Study 2 (2010–2015), and Extension Study 3 (2015–2020). Written informed consent was obtained from all study participants. Institutional review board (IRB) approval was obtained at all participating institutions. A standardized written protocol, centralized training of staff, and quality assurance visits by the Clinical Coordinating Center were used to ensure uniform data collection [16].

Our study sample was drawn from the 161,808 women participating in either the WHI-CT or WHI-OS. Of these, we excluded women in the estrogen-alone trial (or who self-reported a hysterectomy) and women with a self-reported history of EC (n=67,574), women who had a CVD event on the date of enrollment (n=8), and women who were missing dates of follow-up (n=619), leaving 93,607 women in our analytic sample.

2.2 Baseline characteristics

At enrollment, participants completed self-administered questionnaires detailing demographic characteristics, medical and reproductive history, previous use of postmenopausal hormone therapy, family history of cancer, diabetes status, physical activity, smoking history, alcohol use, diet, and other risk factors. Details of diet assessment and estimation of diet quality index score have been previously described [17]. A baseline food frequency questionnaire, calibrated against 24-hour dietary recalls and 4-day food records [18], was modified from the Health Habits and Lifestyle Questionnaire [19] for the WHI cohort. As described by McTiernan and colleagues [20], physical activity was quantified with questions on frequency, duration, and intensity of participation in different forms of physical activity. Weekly recreational physical activity was calculated by multiplying an assigned energy expenditure level for each category of activity by the hours exercised per week to calculate total metabolic equivalents per week (METs per week). Participants also underwent a clinic visit where trained staff measured each participant's height, weight, and blood pressure using a standardized protocol. Body mass index (BMI) was calculated based on these height and weight measurements, and was updated annually until study closeout for WHI-CT participants and at Year 3 for WHI-OS participants. Hypertension was defined as either a blood pressure of at least 140/90 mm Hg or hypertension medication use and categorized as not hypertensive, untreated hypertensive, or treated hypertensive.

2.3 Ascertainment of Cancer and CVD

Information regarding cancer occurrence was collected semi-annually in the WHI-CT during the main WHI trial and annually thereafter and annually in the WHI-OS. Reported invasive cancers were initially verified by medical record and pathology report review at the local Clinical Centers by trained physician adjudicators [21] with final adjudication and coding for stage and tumor characteristics at the WHI Clinical Coordinating Center using Surveillance, Epidemiology, and End Results (SEER) criteria.

We used International Classification of Diseases for Oncology (ICD-O) morphology codes to classify EC as Type I vs. Type II. Type I histologies included endometrioid adenocarcinomas (8380–8383), adenocarcinoma with squamous metaplasia (8570), adenosquamous carcinomas (8560), mucinous adenocarcinoma (8480, 8481), and adenocarcinoma, not otherwise specified (8140). Type II histologies included serous (8440–8441, 8460–8461), clear cell (8310), mixed cell (8323), and carcinosarcoma (8950–8951, 8980).

The primary outcome of our analysis was time to any CVD event (non-fatal or fatal), including angina, coronary artery bypass graft, carotid artery disease, coronary heart disease, myocardial infarction, coronary revascularization, congestive heart failure, stroke, peripheral artery disease, transient ischemic attack, percutaneous transluminal coronary angioplasty, carotid revascularization, or CVD-related death. These events were initially ascertained by self-report and subsequent medical record review. Potential cases were then centrally adjudicated using standardized case definitions and clinical criteria and updated annually through December 31, 2015 (end of Extension Study 2). Death certificate and medical record reviews were used to determine cause of death. A 94% rate of agreement between local and central clinical adjudicators for cause of death in WHI has been previously reported [22].

2.4 Statistical Analysis

Baseline characteristics among women who developed Type I, Type II EC or did not develop EC were summarized separately. We estimated cause-specific hazard ratios (CHRs, deaths from other causes were censored) and 95% confidence intervals (CIs) for the association between EC status and CVD risk using the Cox proportional hazards regression model with the baseline hazard stratified by WHI trial membership [WHI-OS, Estrogen + Progestin (E+P) clinical trial, Dietary Modification (DM) trial, E+P and DM]. EC status was modeled as a time varying covariate as the time from baseline to diagnosis of EC varied widely among women in our study (mean=7.8 years, range: 0 to 21 years). Participant age was used as the underlying time scale. All women who developed other cancers during follow-up (n=17,443) were censored at the time of their incident cancer. Because the number of events among women with EC was small, we did not examine individual CVD diagnoses (*e.g.* coronary heart disease).

We first examined the association between EC status and CVD risk in univariable (unadjusted) Cox regression models. Next, we checked for the presence of confounding by adding covariates to the univariable model separately and quantifying the percent change in

the univariable CHR for EC status. Sixteen potential confounders of interest were identified from Table 1 and included ethnicity, education, smoking status, BMI, age at menarche, parity, hormone use, type of hormones used, oral contraceptive use, diabetes status, use of anti-diabetic drugs, energy expenditure, Healthy Eating Index (HEI)-2005 score (measure of diet quality) [23], hypertension history, history of CVD, and history of (non-endometrial) cancer. Detailed information about the categorizations of each variable is listed in Table 1. All variables that changed the CHR for EC from the univariable model by ≥5% were then included in a multivariable-adjusted model. The remaining variables that were not included in this initial step were then added to the adjusted model to ensure that no additional confounding among the candidate variables remained. Finally, we tested for effect modification by assessing the significance of all two-way interactions between EC status and variables in our multivariable model.

We conducted a sensitivity analysis where we examined incidence of non-fatal CVD events separate from CVD mortality by excluding 745 CVD-related deaths from the outcome. We also examined effect modification by history of CVD. All analyses were performed using SAS/STAT software (version 9.4 of the SAS System for Windows, SAS Institute, Cary, NC, USA). All *P* values were two-sided with the probability of a Type I error set at <5%.

3. Results

3.1 Study population

The average follow-up time for the 93,607 women in our study was 12.9 years (range: 0 – 22.5 years). Over the course of follow-up, 1,179 (1.3%) women developed Type I and 211 (0.2%) developed Type II EC. Mean age at EC diagnosis was 71.1 years (range: 51.4–93.2) and mean time from enrollment to EC cancer diagnosis was 7.8 years. Baseline characteristics of the study population by EC cancer status are shown in Table 1. Most characteristics were similar between women who did and did not develop EC; however, women who developed EC were more commonly obese, more likely to have a college degree, and current, long-term users (i.e. greater than 10 years) of hormone therapy when compared with women who did not develop EC.

3.2 CVD risk: Women with EC vs. cancer-free women

During follow-up, 15,952 women (17%) developed a CVD event, a small proportion of which were due to CVD-related deaths (n=745; 5%). Angina was the most common CVD event (n=6,214; 39%), followed by stroke (n=2,849; 18%) and coronary heart disease (n=2,568; 16%). Among the women with EC, 16% (186/1,179) of women with Type I and 12% (26/211) of women with Type II EC experienced a CVD event compared to 17% of women who did not develop EC. Median age at first CVD event was highest among women with Type I EC, followed by Type II EC, and women without EC (78.5 vs. 77.9 vs. 76.2 years) and an average of 6.6 years elapsed between EC diagnosis and the CVD event (Type I EC: 6.9 years, Type II EC: 3.8).

Table 2 presents univariable modeling results. We observed a non-statistically significant association between an EC diagnosis (either Type I or II) and subsequent CVD risk

(CHR=1.12, 95% CI=0.98–1.28; p=0.10). When considering EC type, CVD risk did not significantly differ when comparing women who did not develop EC to women who developed Type I (HR=1.09, 95% CI=0.94–1.26; p=0.24) or Type II EC (HR=1.36, 95% CI=0.93–2.00; p=0.11).

Next, we considered potential confounders of the relationship between EC status and subsequent CVD by adding covariates to the univariable models separately (Supplemental Table 1). For all models (overall EC, Type I, Type II), both history of hypertension and BMI changed the univariable CHR by at least 5%; history of (non-endometrial) cancer was an additional confounder in the Type II EC model (Supplemental Table 1). Adjustment for these confounders attenuated the association between EC and CVD risk as shown in Table 3. CVD risk associated with any EC diagnosis was 1.01 (95% CI=0.87–1.16) while for women with Type I EC the CHR was 0.98 (95% CI=0.84–1.14) and for women with Type II EC the CHR was 1.32 (95% CI=0.88–1.97).

Furthermore, the addition of all remaining variables listed in Supplemental Table 1 did not significantly change the overall association between EC and CVD risk [adjusted CHR for all EC = 1.07 (95% CI: 0.93 – 1.24); adjusted CHR for Type I = 1.03 (95% CI: 0.89, 1.21); adjusted CHR for Type II = 1.38 (95% CI: 0.91, 2.07)], and therefore no additional confounders were added to the final multivariable models. We also did not observe any strong evidence of effect modification among the covariates in our multivariable models (all interaction p-values >0.06; results not shown).

Based on the final multivariable models (Table 3), overweight and obese women had a higher risk of CVD than normal weight women regardless of EC classification (all EC cases, Type I EC, or Type II EC). Similarly, a history of hypertension, either treated or untreated, was associated with higher CVD risk compared to no history of hypertension regardless of EC classification.

3.3 Sensitivity analyses

We conducted two sensitivity analyses. First, we examined incidence of non-fatal CVD events by excluding 745 CVD-related deaths from our outcome and noted minimal changes in the association between an EC diagnosis and CVD risk (data not shown). Second, we examined whether history of CVD modified the association between EC status and CVD risk and noted no interactions when examining all EC cases combined or according to type (all interaction p-values >0.20).

4. Discussion

In this large, prospective study of postmenopausal women, we observed no significant difference in CVD risk between women who developed EC compared to women who did not develop EC. We initially hypothesized that, as a consequence of having a higher frequency of CVD risk factors, women with EC would have a higher risk of developing CVD compared to women without EC. Moreover, we postulated that women who developed Type I EC would have the highest risk of CVD, based on the strong association between obesity and Type I cancer and favorable cancer-specific survival associated with this subtype. The

latter characteristic could provide an opportunity for the development of other chronic conditions. In our study, women with Type I EC that experienced a CVD event, did so an average of 7 years after the diagnosis. It is possible that with additional follow-up, an increase in CVD events may be observed. Contrary to our hypothesis, we observed an increased but not statistically significant CVD risk among women who developed Type II EC.

The association between CVD risk after an EC diagnosis has been examined in a retrospective analysis of the Surveillance, Epidemiology, End Results (SEER) program [10] and in two cohort studies including EC cases and matched, cancer-free women [11, 12]. In our SEER analysis, we demonstrated an eight-fold higher risk of CVD mortality among 157,496 women with EC compared with women in the general population [10]. The major limitations of the SEER analysis included the use of an external comparison group that may have differed in key ways from the cancer cases and the inability to adjust for potential confounders. Within the Kaiser Permanente Southern California (KPSC) managed care health maintenance organization, Armenian and colleagues [12] examined CVD risk among 1,761 uterine cancer cases compared with approximately 3,500 matched controls, and no difference in CVD risk was observed (incidence rate ratio=0.98, 95% CI=0.81–1.17) [12]. Conversely, in the population-based Iowa Women's Health Study (IWHS), we observed lower CVD mortality among women with EC compared with cancer-free women (HR=0.74, 95% CI=0.56–0.99) [11].

In comparison to the two prior cohort studies, our WHI findings agree with those from the KPSC study, where no increased risk of CVD was observed [12]. In both studies, ascertainment of cancer and CVD diagnoses was likely highly accurate, based on physician adjudicated reports in WHI or electronic health records in KPSC, compared with the IWHS study, which employed linkage to the State Health Registry of Iowa or the National Death Index (NDI). A recent reliability study reported modest sensitivity (73.4%) of detecting CVD-related deaths comparing the NDI with expert adjudication [24]. Additionally, unlike the KPSC and IWHS analyses, we were unable to individually or frequency match cancer-free women with EC cases in the WHI study; however, our statistical analyses controlled for potential confounders such as age. Furthermore, the age distribution of WHI EC cases is similar to that reported in the IWHS study population (71 years in WHI vs. 72 years in IWHS) but likely older than the KPSC population. Mean age at diagnosis of individual cancer sites was not reported in the KPSC study; however, it is likely that women were closer to the national average of 61 years at EC diagnosis. In addition, the KPSC study excluded women with a history of CVD, whereas in both the WHI and IWHS analyses we included these women and conducted stratified analyses. In the subgroup of women with no history of CVD, all three studies were similar in reporting no increased risk of CVD after EC. In addition, none of the three studies captured information on post-EC diagnosis lifestyle behaviors or surveillance patterns, which likely play a role in subsequent CVD risk. Taken together, these three cohort studies suggest no significant increased CVD risk after an EC diagnosis; however, with longer follow-up and additional CVD events, meaningful patterns could emerge.

It is possible that we observed no difference in CVD risk between women with and without EC in WHI because all women were closely monitored. WHI participants underwent screening (annual in CT and at year three in the OS), which included collection of additional risk factor information and blood draws. This follow-up provides an opportunity for WHI women to receive treatment for CVD risk factors, ultimately lowering their risk of developing CVD. Future studies that incorporate information on follow-up care, possibly with the use of electronic health record data, will be instrumental in clarifying the relationship between CVD management following an EC diagnosis and CVD risk.

Our finding of a potentially increased risk of CVD among women with Type II EC may be due to treatment effects. Potentially cardiotoxic chemotherapies, while rarely used among women with endometrioid and mucinous EC, are indicated for women who develop the aggressive Type II histologies [25]. Among breast cancer survivors, chemotherapy treatment is associated with increased CVD mortality [26]. Because power was limited in this analysis, a real increase in CVD risk cannot be ruled out by our data. Therefore, the association between treatment and CVD risk among women with Type II ECs should be explored in future studies.

Limitations of our study include small numbers of cases and subsequent events, limiting our ability to simultaneously consider multiple CVD risk factors in our models. As mentioned, we lacked information on cancer treatment; however, we stratified our analysis according to the type of EC women developed in an effort to examine CVD risk among groups of women who likely had similar treatment. We also lacked information on all components used to define metabolic syndrome, which could be a more relevant predictor of CVD risk than considering CVD risk factors individually. In addition, we did not account for the possibility that CVD competes with the risk of being exposed, i.e. developing EC. Strengths of the study include the centralized adjudicated outcomes, an internal non-cancer comparison group, and the multiple time points at which BMI data were collected, allowing us to consider the role of changing BMI.

In conclusion, our results do not suggest increased risk of CVD following an EC diagnosis compared to a group of women without EC; however, this association should be further examined among women with Type II EC. Although our findings do not suggest increased CVD risk among women with EC compared with cancer-free women, women with EC should still receive counseling and support to make lifestyle changes aimed at reducing weight and increasing physical activity as appropriate, given the high prevalence of obesity at the time of diagnosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like acknowledge the following WHI Principal Investigators and academic medical centers. Program office: Jacques Rossouw, Shari Ludlam, Dale Burwen, Joan McGowan, Leslie Ford, and Nancy Geller (National Heart, Lung, and Blood Institute, Bethesda, Maryland); Clinical Coordinating Center: Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg (Fred Hutchinson Cancer Research Center, Seattle, WA);

Investigators and Academic Centers: JoAnn E. Manson (Brigham and Women's Hospital, Harvard Medical School, Boston, MA); Barbara V. Howard (MedStar Health Research Institute/Howard University, Washington, DC); Marcia L. Stefanick (Stanford Prevention Research Center, Stanford, CA); Rebecca Jackson (The Ohio State University, Columbus, OH); Cynthia A. Thomson (University of Arizona, Tucson/Phoenix, AZ); Jean Wactawski-Wende (University at Buffalo, Buffalo, NY); Marian Limacher (University of Florida, Gainesville/Jacksonville, FL); Robert Wallace (University of Iowa, Iowa City/Davenport, IA); Lewis Kuller (University of Pittsburgh, Pittsburgh, PA); Sally Shumaker (Wake Forest University School of Medicine, Winston-Salem, NC).

Funding

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017; 67(1):7–30. [PubMed: 28055103]
2. Flegal KM, et al. Trends in Obesity Among Adults in the United States, 2005 to 2014. JAMA. 2016; 315(21):2284–91. [PubMed: 27272580]
3. Bhaskaran K, et al. 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]
4. Setiawan VW, et al. Type I and II endometrial cancers: have they different risk factors? J Clin Oncol. 2013; 31(20):2607–18. [PubMed: 23733771]
5. Brinton LA, et al. Etiologic heterogeneity in endometrial cancer: Evidence from a Gynecologic Oncology Group trial. Gynecol Oncol. 2013; 129(2):277–84. [PubMed: 23485770]
6. Creasman WT, et al. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet. 2006; 95(Suppl 1):S105–43. [PubMed: 17161155]
7. Friberg E, et al. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia. 2007; 50(7):1365–74. [PubMed: 17476474]
8. Aune D, Sen A, Vatten LJ. Hypertension and the risk of endometrial cancer: a systematic review and meta-analysis of case-control and cohort studies. Sci Rep. 2017; 7:44808. [PubMed: 28387226]
9. Kurnit KC, et al. Increased prevalence of comorbid conditions in women with uterine cancer. Gynecol Oncol. 2015; 138(3):731–4. [PubMed: 26160712]
10. Felix AS, et al. High cardiovascular disease mortality after endometrial cancer diagnosis: Results from the Surveillance, Epidemiology, and End Results (SEER) Database. Int J Cancer. 2017; 140(3):555–564. [PubMed: 27741565]
11. Felix AS, et al. Cardiovascular disease mortality among women with endometrial cancer in the Iowa Women's Health Study. Cancer Causes Control. 2017
12. Armenian SH, 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. Anderson GL, et al. Implementation of the Women's Health Initiative study design. Ann Epidemiol. 2003; 13(9 Suppl):S5–17. [PubMed: 14575938]
14. Hays J, et al. The Women's Health Initiative recruitment methods and results. Ann Epidemiol. 2003; 13(9 Suppl):S18–77. [PubMed: 14575939]
15. Stefanick ML, et al. The Women's Health Initiative postmenopausal hormone trials: overview and baseline characteristics of participants. Ann Epidemiol. 2003; 13(9 Suppl):S78–86. [PubMed: 14575940]
16. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Control Clin Trials. 1998; 19(1):61–109. [PubMed: 9492970]
17. Vargas AJ, et al. Diet Quality and Colorectal Cancer Risk in the Women's Health Initiative Observational Study. Am J Epidemiol. 2016; 184(1):23–32. [PubMed: 27267948]
18. Patterson RE, et al. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. Ann Epidemiol. 1999; 9(3):178–87. [PubMed: 10192650]

19. Block G, et al. A data-based approach to diet questionnaire design and testing. Am J Epidemiol. 1986; 124(3):453–69. [PubMed: 3740045]

20. McTiernan A, et al. Recreational physical activity and the risk of breast cancer in postmenopausal women: the Women's Health Initiative Cohort Study. Jama. 2003; 290(10):1331–6. [PubMed: 12966124]

21. Curb JD, et al. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. Ann Epidemiol. 2003; 13(9 Suppl):S122–8. [PubMed: 14575944]

22. Heckbert SR, et al. Comparison of self-report, hospital discharge codes, and adjudication of cardiovascular events in the Women's Health Initiative. Am J Epidemiol. 2004; 160(12):1152–8. [PubMed: 15583367]

23. Guenther PM, Reedy J, Krebs-Smith SM. Development of the Healthy Eating Index-2005. J Am Diet Assoc. 2008; 108(11):1896–901. [PubMed: 18954580]

24. Olubowale OT, et al. Comparison of Expert Adjudicated Coronary Heart Disease and Cardiovascular Disease Mortality With the National Death Index: Results From the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study. J Am Heart Assoc. 2017; 6(5)

25. National Comprehensive Cancer Network. NCCN Guidelines for Treatment of Cancer by Site (Uterine Neoplasms Version 2.2016) November 30, 2015]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf

26. Bradshaw PT, et al. Cardiovascular Disease Mortality Among Breast Cancer Survivors. Epidemiology. 2016; 27(1):6–13. [PubMed: 26414938]

Highlights

- Endometrial cancer (EC) incidence is increasing in the United States.
- Women with EC have a high prevalence of cardiovascular disease (CVD) risk factors.
- CVD risk did not differ between women with EC and those who did not develop EC.

Table 1

Descriptive characteristics at study enrollment among women with EC and cancer-free women in the Women's Health Initiative, n=93,607

Characteristic	No Type I,II EC (n=92,217)	Incident Type I EC (n=1,179)	Incident Type II EC (n=211)
Age at screening			
<50 years	31,748 (34%)	424 (36%)	74 (35%)
60–69 years	40,909 (44%)	533 (45%)	96 (45%)
≥70 years	19,560 (21%)	222 (19%)	41 (19%)
Age at screening, mean (SD)	63.1 (10.7)	62.8 (7.0)	63.0 (11.3)
Ethnicity			
White (not of Hispanic origin)	78,079 (85%)	1074 (91%)	179 (85%)
Black or African-American	6360 (7%)	51 (4%)	23 (11%)
Hispanic/Latino	3474 (4%)	17 (1%)	6 (3%)
Asian or Pacific Islander	2694 (3%)	14 (1%)	3 (1%)
American Indian or Alaskan Native	329 (<1%)	2 (<1%)	0 (0%)
Other	1027 (1%)	18 (2%)	0 (0%)
Education			
Less than High school diploma or GED	4,162 (5%)	31 (3%)	7 (3%)
High school diploma or GED	14,590 (16%)	169 (14%)	30 (14%)
Some college	32,617 (35%)	384 (33%)	72 (34%)
College graduate or higher	40,182 (44%)	591 (50%)	101 (48%)
Smoking status			
Never smoked	45,870 (50%)	631 (54%)	105 (50%)
Past smoker	38,785 (42%)	484 (41%)	90 (43%)
Current smoker	6,367 (7%)	53 (4%)	12 (6%)
BMI			
<25 kg/m^2	34,877 (38%)	373 (32%)	69 (33%)
25–29 kg/m^2	31,327 (34%)	317 (27%)	63 (30%)
≥30 kg/m^2	25,161 (27%)	479 (41%)	77 (36%)
BMI, mean (SD)	27.5 (5.8)	29.5 (7.2)	29.1 (6.5)
Age at menarche			
≤11 years	19,101 (21%)	285 (24%)	42 (20%)
12–13 years	50,835 (55%)	687 (58%)	133 (63%)
≥14 years	21,914 (24%)	204 (17%)	36 (17%)
Parity			
Nulliparous	11,961 (13%)	187 (16%)	20 (9%)
1–2	31909 (35%)	422 (36%)	75 (36%)
≥3	47756 (52%)	566 (48%)	114 (54%)
Hormone use			

Characteristic	No Type I,II EC (n=92,217)	Incident Type I EC (n=1,179)	Incident Type II EC (n=211)
Never	50708 (55%)	533 (45%)	111 (53%)
Past user	13064 (14%)	163 (14%)	28 (13%)
Current user <5 years	11483 (12%)	130 (11%)	22 (10%)
Current user 5 to <10 years	8449 (9%)	135 (11%)	22 (10%)
Current user ≥10 years	8454 (9%)	216 (18%)	28 (13%)
Type of hormone use			
Never used E alone or E+P	50708 (55%)	533 (45%)	111 (53%)
Past user of either E alone or E+P	13064 (14%)	163 (14%)	28 (13%)
E alone	1994 (2%)	58 (5%)	6 (3%)
E+P	26392 (29%)	423 (36%)	66 (31%)
Oral contraceptive use			
No	53132 (58%)	705 (60%)	121 (57%)
Yes	39085 (42%)	474 (40%)	90 (43%)
Diabetes status			
No	87524 (95%)	1119 (95%)	197 (93%)
Yes	4632 (5%)	60 (5%)	14 (7%)
Use of anti-diabetic drugs			
No	88732 (96%)	1134 (96%)	201 (95%)
Yes	3410 (4%)	45 (4%)	10 (5%)
Energy expenditure			
None	12866 (14%)	157 (13%)	26 (12%)
>0 – 3.75 MET-hours/week	12240 (13%)	152 (13%)	28 (13%)
3.75–8.75 MET-hours/week	17863 (19%)	220 (19%)	40 (19%)
8.75–17.5 MET-hours/week	20336 (22%)	275 (23%)	48 (23%)
≥17.5 MET-hours/week	24694 (27%)	318 (27%)	58 (27%)
HEI-2005 Score, quartiles			
20.7 – 60.3	2521 (3%)	13 (1%)	6 (3%)
60.3 – 68.9	22400 (24%)	313 (27%)	53 (25%)
58.9 – 75.8	22444 (24%)	283 (24%)	40 (19%)
86.9 – 93. 4	22417 (24%)	295 (25%)	55 (26%)
Hypertension history			
Never hypertensive	61219 (66%)	755 (64%)	138 (65%)
Currently untreated hypertensive	6664 (7%)	83 (7%)	14 (7%)
Currently treated hypertensive	19512 (21%)	272 (23%)	48 (23%)
WHI trial membership			
WHI-OS	53373 (58%)	677 (57%)	125 (59%)
E+P	11811 (13%)	92 (8%)	16 (8%)
DM	22456 (24%)	360 (31%)	60 (28%)
E+P and DM	4577 (5%)	50 (4%)	10 (5%)

Characteristic	No Type I,II EC (n=92,217)	Incident Type I EC (n=1,179)	Incident Type II EC (n=211)
History of CVD			
No	73346 (80%)	949 (80%)	177 (84%)
Yes	13695 (15%)	165 (14%)	24 (11%)
History of cancer (non-endometrial)			
No	85448 (93%)	2159 (92%)	392 (93%)
Yes	6022 (7%)	182 (8%)	26 (6%)

WHI-OS: WHI Observational study; E+P: Estrogen plus progestin; DM: Dietary modification; GED: General Educational Development; HEI: Healthy Eating Index; MET: metabolic equivalent of task

Table 2

Univariable association between EC (overall and according to EC type) with CVD in the Women's Health Initiative, n=93,607

	CV events/N	CHR (95% CI)[1]	p-value
EC status			
No EC	15,740/92,217 (17%)	1.00	
Both Type I and II	212/1,390 (15%)	1.12 (0.98, 1.28)	0.10
Type I	186/1,179 (16%)	1.09 (0.94, 1.26)	0.24
Type II	26/211 (12%)	1.36 (0.93, 2.00)	0.11

p-value comparing women with EC to non-EC women

Table 3

Multivariable-adjusted CVD risk among women with EC compared with cancer-free women in the Women's Health Initiative, overall and stratified by Type I vs. II, n=93,607

Variable	CV events/N	CHR (95% CI)[1]	p
Overall (Type I and II)			
EC status[2]			0.92
No	15,740/92,217 (17%)	1.00	
Yes	212/1,390 (15%)	1.01 (0.87, 1.16)	
BMI			<0.001
Normal weight (<25 kg/m^2)	5,139/35,319 (15%)	1.00	
Overweight (25–29 kg/m^2)	5,387/31,707 (17%)	1.13 (1.09, 1.18)	
Obese (≥30 kg/m^2)	5,277/25,717 (21%)	1.45 (1.39, 1.51)	
Hypertension history			<0.001
Never hypertensive	8,449/62,112 (14%)	1.00	
Untreated hypertensive	1,460/6,761 (22%)	1.58 (1.50, 1.68)	
Treated hypertensive	5,140/19,832 (26%)	1.86 (1.80, 1.93)	
Type I			
EC status[2]			<0.001
No	15,740/92,217 (17%)	1.00	
Yes	186/1,179 (16%)	0.98 (0.84, 1.14)	
BMI			<0.001
Normal weight (<25 kg/m^2)	5,129/35,250 (15%)	1.00	
Overweight (25–29 kg/m^2)	5,377/31,644 (17%)	1.13 (1.09, 1.18)	
Obese (≥30 kg/m^2)	5,271/25,640 (21%)	1.46 (1.40, 1.52)	
Hypertension history			<0.001
Never hypertensive	8,432/6,1974 (14%)	1.00	
Untreated hypertensive	1,460/6,747 (22%)	1.59 (1.50, 1.68)	
Treated hypertensive	5,133/19,784 (26%)	1.87 (1.80, 1.93)	
Type II			
EC status[2]			
No	15,740/92,217 (17%)	1.00	0.17
Yes	26/211 (12%)	1.32 (0.88, 1.97)	
BMI			<0.001
Normal weight (<25 kg/m^2)	5,096/34,946 (15%)	1.00	
Overweight (25–29 kg/m^2)	5,344/31,390 (17%)	1.13 (1.09, 1.18)	
Obese (≥30 kg/m^2)	5,180/25,238 (21%)	1.46 (1.40, 1.52)	
Hypertension history			<0.001
Never hypertensive	8,355/61,357 (14%)	1.00	

Variable	CV events/N	CHR (95% CI)[1]	p
Untreated hypertensive	14,49/6,678 (22%)	1.59 (1.50, 1.68)	
Treated hypertensive	5,075/19,560 (26%)	1.87 (1.80, 1.94)	
History of cancer (non-endometrial)			0.31
No	14,562/85,644 (17%)	1.00	
Yes	1,051/6,035 (17%)	1.03 (0.97, 1.10)	

[1] Cox proportional hazards regression models with baseline hazards stratified by trial membership (OS, E+P, DM, E+P and DM) and age as the underlying time scale with adjustment for variables shown

[2] EC status was treated as a time-varying covariate

CHR: Cause-specific hazard ratio