Cardiovascular disease diagnoses among older women with endometrial cancer

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Abstract

Background: Endometrial cancer (EC) shares risk factors (e.g. obesity) with cardiovascular disease (CVD), yet little research has investigated CVD diagnoses among EC survivors. We aimed to describe the burden of CVD diagnoses among older women with EC compared to women without a cancer history.

Methods: Women aged 66+ years with an EC diagnosis during 2004-2017 (N=44,386) and matched women without cancer (N=221,219) were identified in the SEER-Medicare linked data. An index date was defined as the cancer diagnosis date of the EC case in that matched set. ICD-9/10 diagnosis codes were used to define CVD outcomes in the Medicare claims. Prevalent CVD was identified using diagnosis codes in the year before the index date. Hazard ratios (HRs) for incident CVD diagnoses after the index date were estimated using multivariable Cox proportional hazards regression. Women with a prevalent CVD were excluded from incidence analyses for that outcome.

Results: Compared to women without cancer, women with EC had a higher prevalence of CVD diagnoses at the index date. In analyses beginning follow-up at 1 year post-index date, EC survivors had an increased risk of incident CVD diagnoses including ischemic heart diseases (HR=1.73; 95% CI: 1.69-1.78), pulmonary heart disease (HR=1.95; 95% CI: 1.88-2.02), and diseases of the veins and lymphatics (HR=2.71; 95% CI: 95% CI: 2.64-2.78). Risk of CVD diagnoses among women with EC was also elevated within the first year post-index date.

Conclusions: Management of pre-existing CVD and monitoring for incident CVD may be critical during EC treatment and throughout long-term survivorship.

Introduction

Endometrial cancer is the fourth most commonly diagnosed cancer among U.S. women, accounting for an estimated 65,950 new cases in the year 2022.[1] With five-year survival currently exceeding 80% overall,[2] endometrial cancer is also the second most common cancer, after breast cancer, among female cancer survivors. Between 2019 and 2030, the number of U.S. women with an endometrial cancer history is predicted to increase by approximately 27%, from about 800,000 to just over 1 million.[3] With continued growth in the survivor population, and the potential for unique health concerns following cancer diagnosis and treatment, there is a critical need for survivorship research to address the long-term health concerns of women with an endometrial cancer history.

Obesity is one of the strongest known risk factors for developing endometrial cancer,[4] and is also one of the most prevalent and well-known risk factors for cardiovascular disease (CVD).[5] The shared nature of this key risk factor suggests that women with endometrial cancer may have an elevated risk of adverse cardiovascular outcomes, making prevention and management of CVD an important component of post-treatment survivorship care. This may be especially true for older women with endometrial cancer, given the increase in risk of CVD with age. To date, however, few studies have examined the prevalence of CVD-related conditions at endometrial cancer diagnosis, and the incidence of new CVD diagnoses after endometrial cancer remains largely undescribed.[6, 7] Understanding patterns of CVD outcomes among older women with endometrial cancer, and how these compare to those among demographically similar women without cancer, may inform surveillance recommendations and help reduce the burden of CVD in this population.

In this study, our objective was to describe the burden of CVD diagnoses among older women (age 65+) with endometrial cancer. Specifically, we aimed to examine 1) the prevalence of CVD-related conditions in the year prior to endometrial cancer diagnosis and 2) the incidence of CVD diagnoses after endometrial cancer diagnosis. We included a matched comparison group of women without a cancer diagnosis to address the potential for an elevated risk of CVD among older endometrial cancer survivors relative to the general population.

Methods

Data source and study cohort

Women with and without endometrial cancer were identified using data from the Surveillance, Epidemiology, and End Results (SEER) program linked to Medicare enrollment records and claims. The SEER program collects and reports cancer incidence and survival data from population-based cancer registries and currently covers approximately 48% of the total U.S. population.[8] Information routinely collected by SEER includes patient demographics, primary tumor site and morphology, stage at diagnosis, first course of treatment, vital status, and cause of death. Medicare is the U.S. federal government health insurance program for individuals aged 65 years and older and those younger than 65 with qualifying conditions. Part A of Medicare covers inpatient hospital and skilled nursing facility care, while Part B covers outpatient care and physician services.[9, 10] This study was considered exempt by the University of North Carolina Institutional Review Board.

For these analyses, we used SEER data from 2004-2017 linked to Medicare claims from 2003-2018. We identified women with a first malignant primary endometrial cancer (sites C54.0-C54.9, C55.9) at ages 66 years and older. Eligible women were required to have a least one year

of continuous enrollment in Parts A and B of Medicare prior to their endometrial cancer diagnosis for identification of pre-existing cardiovascular conditions and other comorbidities. We excluded women diagnosed with endometrial cancer by death certificate or autopsy and those enrolled in a managed care plan in the month of or year before cancer diagnosis. Endometrial cancer cases were then matched with replacement on year of birth, state of residence, and race/ethnicity to up to 5 women from the random 5% sample of Medicare beneficiaries without a cancer history.[9] In total, 44,386 women with endometrial cancer and 221,219 women without a cancer history were included in our analyses. An index date for each matched set was defined as the cancer diagnosis date of the endometrial cancer case included in that set.

Outcomes

CVD outcomes were identified using ICD-9 and ICD-10 diagnosis codes in any position in the Medicare inpatient, outpatient, and physician/supplier claims. For each outcome, we required one inpatient claim and/or two or more outpatient/physician claims >30 days apart. Primary outcomes (level 1) included ischemic heart disease; pulmonary heart disease; other forms of heart disease; cerebrovascular disease; diseases of the arteries, arterioles, and capillaries; and diseases of the veins and lymphatics. Within these broad outcome categories, we also defined selected, more specific secondary outcomes (level 2; e.g. acute myocardial infarction, cardiomyopathy, etc.). Codes used to define study outcomes are provided in Supplemental Table 1. Women diagnosed with a particular CVD outcome within the year prior to the index date were considered to have prevalent disease for that condition. Follow-up for incident CVD-related diagnoses began at the index date and continued until the outcome of

interest, disenrollment from Medicare parts A or B, death, or end of the study period in Dec. 2018, whichever occurred first.

Covariates

Information on age at the index date, race/ethnicity, state of residence, and date of death was extracted from the Medicare enrollment files. We used state of residence to define four geographic regions (Midwest, Northeast, South, West). The Klabunde adaptation of the Charlson comorbidity index was used to define comorbidity status in the year before the index date.[11, 12] We defined hypertension in the year prior to the index date using ICD-9 codes 401-405 and ICD-10 codes I10-I16 in the inpatient, outpatient, and physician/supplier claims. Hyperlipidemia was defined similarly using ICD-9 codes 272.0-272.4 and ICD-10 codes E78.0-E78.5.

Cancer characteristics abstracted from the SEER data included summary stage, histology, and grade. Both the Medicare claims and the SEER data were used to identify receipt of endometrial cancer treatments. We considered women to have received a particular treatment type (hysterectomy, radiation, chemotherapy) if they had at least one claim with a relevant code (code list provided in Supplemental Table 2) within the 12 months after cancer diagnosis or if the SEER data indicated that they received that treatment type during their first course of treatment.

Statistical analysis

We tabulated the proportion of women with prevalent CVD-related conditions in the year prior to the index date. Chi-squared tests were used to compare prevalence between women with and with endometrial cancer. The cumulative incidence of CVD diagnoses was estimated using models that accounted for death as a competing risk, with follow-up beginning at the index date. We used multivariable Cox proportional hazards models to estimate hazards ratios (HRs) for

CVD diagnoses, comparing women with and without endometrial cancer. Because we expected an increase in CVD diagnoses among women with endometrial cancer around the time of cancer diagnosis and treatment, due to increased engagement with the healthcare system, we estimated HRs within three separate time intervals: index date-<3 months, 3 months-<1 year, and ≥1 year. To examine CVD risk among long-term endometrial cancer survivors, we also estimated HRs with follow-up beginning at 5 years after the index date. Women diagnosed with a particular CVD outcome prior to the start of each interval were excluded from that specific analysis. Base models were adjusted for demographic characteristics (age at the index date, geographic region, and race/ethnicity). Fully adjusted models were additionally adjusted for Charlson score, hypertension, and hyperlipidemia. In separate analyses, we used Cox proportional hazards models to examine associations between demographic and cancer-related characteristics and CVD diagnoses among women with endometrial cancer, with follow-up beginning at one year after the index date.

Results

Descriptive characteristics of women with endometrial cancer and matched women without cancer are shown in Table 1. At the index date, those in the endometrial cancer group were more likely to have prevalent hypertension (75% vs 51%), hyperlipidemia (66% vs 45%) and a Charlson comorbidity index of ≥1 (62% vs 43%) than the matched comparison group. Cancer characteristics of women with endometrial cancer are included in Table 2. Most had localized stage disease (65%), grade 1 or 2 disease (62%), and endometrioid histology (69%). Treatment most commonly included hysterectomy only (43%), followed by hysterectomy and radiation (21%). Among all women with endometrial cancer who died during the study period and had cause of death information available from SEER (N=13,045), 46% died from

endometrial cancer, and 17% died from CVD. For those with localized stage cancer, proportions were similar for deaths from endometrial cancer (26%) and cardiovascular diseases (26%).

In the year prior to the index date, the prevalence of all CVD-related conditions among women in the endometrial cancer group exceeded that in the matched comparison group (Table 3). Level 1 outcomes with the highest prevalence among women with endometrial cancer included other forms of heart disease (33%), ischemic heart disease (20%), and diseases of the arteries, arterioles, and capillaries (17%). The most common level 2 outcomes examined included cardiac dysrhythmias (19%), heart failure (11%), and atherosclerosis (9%).

Figure 1 shows the cumulative incidence of level 1 outcomes among women with and without endometrial cancer, with follow-up beginning at the index date. For all study outcomes, the cumulative incidence among endometrial cancer survivors exceeded that among the matched comparison group. For example, approximately 18% of endometrial cancer survivors were diagnosed with ischemic heart disease within the year after the index date, with the cumulative incidence rising to 33% and 43% by 5 and 10 years, respectively. Among matched women without cancer, cumulative incidence of ischemic heart disease at 1, 5, and 10 years was 6%, 19%, and 29%, respectively.

Within the first 3 months after the index date, women with endometrial cancer had a significantly higher risk of all CVD diagnoses examined compared to matched women without cancer (Table 4). In models adjusted only for demographic characteristics, HRs for level 1 outcomes ranged from 2.88 (95% CI: 2.73, 3.05) for cerebrovascular disease to 11.46 (95% CI: 11.07, 11.87) for other forms of heart disease. In analyses of 3 months- <1 year post-index date, HRs were of smaller magnitude than those estimated within the first 3 months of the index date and, for level 1 outcomes, ranged from 1.45 (95% CI: 1.38, 1.52) for cerebrovascular disease to

4.53 (95% CI: 4.33, 4.73) for diseases of the veins and lymphatics. Within both time intervals, HRs across level 2 outcomes tended to be highest for conditions involving the veins and lymphatics, particularly phlebitis and thrombophlebitis and other venous embolism and thrombosis. Magnitudes of HRs were consistently attenuated in fully adjusted models that additionally accounted for Charlson comorbidity index, hypertension, and hyperlipidemia, though most estimates still indicated significantly elevated risks among endometrial cancer survivors.

In analyses of ≥1 year after the index date, risk of all level 1 CVD outcomes was increased among women with endometrial cancer. HRs in demographics-adjusted models ranged from 1.73 (95% CI: 1.68, 1.77) for cerebrovascular disease and 1.73 (95% CI: 1.69, 1.78) for ischemic heart disease to 2.71 (95% CI: 2.64, 2.78) for diseases of the veins and lymphatics (Table 5). HRs in fully adjusted models were attenuated, but most remained statistically significant. As in earlier follow-up intervals, magnitudes of HRs across level 2 outcomes were highest for phlebitis and thrombophlebitis and other venous embolism and thrombosis. Patterns were generally similar in analyses of ≥5 years after the index date (Supplemental Table 3).

Associations between demographic and cancer-related characteristics and level 1 CVD outcomes among women with endometrial cancer, with follow-up beginning at 1 year after the index date, are shown in Supplemental Table 4. Risk of CVD diagnoses tended to increase with increasing age at cancer diagnosis and Charlson comorbidity index. Compared to White women, Black women had a higher risk of CVD diagnoses. Few other significant associations with race/ethnicity were observed. Hypertension was consistently associated with a higher risk of CVD outcomes; associations were less consistent for hyperlipidemia. Across cancer-related characteristics, women with regional or distant stage disease tended to have a higher risk of CVD

diagnoses than women with localized stage disease. Patterns according to histology were inconsistent across outcomes. Risk of pulmonary heart disease and diseases of the veins and lymphatics, but not other level 1 outcomes, appeared to increase consistently with disease grade. Compared to women who were treated with hysterectomy only, those who received chemotherapy and/or radiation without hysterectomy had a significantly increased risk of all level outcomes. Patterns were less consistent across other treatment categories.

Discussion

In this study, we used population-based cancer registry data and linked Medicare enrollment records and claims to describe the burden of CVD among older women with an endometrial cancer diagnosis. We found that women with endometrial cancer had a higher prevalence of CVD-related conditions at the time of their cancer diagnosis than demographically similar women without a cancer history. They also had a higher incidence of CVD diagnoses after endometrial cancer, particularly within the first three months, but also at 1+ and 5+ years after their cancer diagnosis date. These findings have implications for the care of women with endometrial cancer, both during the initial cancer treatment period and during long-term survivorship care.

We defined prevalent CVD-related conditions using the one-year time window prior to endometrial cancer diagnosis, the minimum length of continuous Medicare enrollment required for inclusion in our cohort. Consequently, the true prevalence of ever having been diagnosed with these conditions, at the time of endometrial cancer diagnosis, is probably somewhat larger than we observed. Nevertheless, our findings suggest that older women undergoing endometrial cancer diagnosis and treatment may be more likely than their cancer-free peers to have a history of serious heart conditions and other adverse cardiovascular outcomes. Because these pre-

existing conditions may impact cancer treatment decisions and necessitate additional medical intervention from non-cancer specialists, careful assessment of CVD history and management of prevalent CVD-related conditions may be an especially critical component of oncology care for older women newly diagnosed with endometrial cancer.

Several studies have investigated CVD-specific mortality among endometrial cancer survivors compared to cancer-free women, with conflicting results,[13-16] but ours is among the first to examine incident CVD diagnoses in this population. We found a striking increase in the risk of most CVD-related conditions within the first three months after endometrial cancer diagnosis, which is likely due, in large part, to an increase in general medical surveillance and interactions with the health care system that accompany cancer diagnosis and initial cancer treatment. The elevation in risk was less pronounced, though still apparent, in later intervals, when many women would have completed (or would soon complete) their endometrial cancer treatment. The persistent increase in risk during this period may be largely explained by shared risk factors for endometrial cancer and many CVD-related conditions, namely obesity and its attendant medical comorbidities (e.g. diabetes, hypertension, etc.). While we were unable to adjust for body mass index, since this information is not routinely captured in either cancer registry data or Medicare claims, we were able to account for Charlson comorbidity index (which includes diabetes) and prevalent hypertension and hyperlipidemia using Medicare claims for the year prior to endometrial cancer diagnosis. Adjustment for these factors attenuated, but did not erase, the significant increase in risk of most CVD-related conditions after endometrial cancer.

Our findings are largely similar to those of a prior study which used cancer registry data and electronic medical records to examine CVD diagnoses among endometrial cancer survivors

(N=2648) in Utah.[7] In their report, women with an endometrial cancer diagnosis at age 18 years or older had an increased risk of diseases of the heart (HR=1.47; 95% CI: 1.31, 1.64), diseases of the arteries, arterioles, and capillaries (HR=1.47; 95% CI: 1.26, 1.72), and diseases of the veins and lymphatics (HR=1.87; 95% CI: 1.63, 2.15) compared to age-matched women from the general population, even with adjustment for body mass index, during 1-5 years after cancer diagnosis. These elevated risks persisted, with only slight attenuation, in analyses of 5-10 years post-cancer diagnosis. New CVD diagnoses within the first year after endometrial cancer diagnosis were not evaluated in their analysis. Taken together, our results and those of the Utah study suggest that endometrial cancer survivors may face a higher burden of adverse cardiovascular outcomes than demographically similar women in the general population which persists long after their initial cancer diagnosis. For clinicians treating this population, surveillance for new-onset CVD and its risk factors, and appropriate referral to primary or specialty care for CVD management, may form an important part of long-term survivorship care after endometrial cancer.

Use of the SEER-Medicare data resource allowed us sufficient sample size and diversity to investigate predictors of CVD diagnoses among older endometrial cancer survivors. In addition to associations with older age at diagnosis and comorbidities, we found that Black women were at higher risk of most CVD diagnoses than White women. Though differences in CVD outcomes according to race have also been documented among individuals in the general U.S. population,[17] it is possible that a cancer diagnosis could exacerbate these existing disparities. Black women may therefore be a priority group to target for interventions aimed at reducing the burden of adverse CVD outcomes after endometrial cancer.

Although our study is one of the first to examine CVD diagnoses among endometrial cancer survivors compared to cancer-free women, our analyses have some limitations. Obesity is a shared risk factor for endometrial cancer and many adverse cardiovascular outcomes, but we were unable to directly assess its impact on our findings due to the very low sensitivity of ICD codes for obesity in Medicare claims data.[18, 19] However, we were able to account for hypertension and other obesity-related conditions (e.g. diabetes) included in the Charlson comorbidity index. It is possible that some CVD diagnoses that we classified as incident were actually prevalent conditions that did not appear in the claims in the year prior to the index date. Code lists used to define our study outcomes have not been previously validated, and mapping between ICD-9 and ICD-10 codes may not be exact. Additionally, relevant cardiovascular conditions that were undiagnosed would not be captured by the data sources used for our analyses.

Results of the current study suggest that older women with endometrial cancer have a higher prevalence of CVD-related conditions at the time of their cancer diagnosis, and a higher risk of these conditions after cancer diagnosis, than demographically similar women without a cancer history. Management of pre-existing CVD and monitoring for new conditions may be critical during endometrial cancer treatment and throughout long-term survivorship.

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Table 1. Demographic and comorbidity characteristics of women with endometrial cancer and matched women without cancer

	Endometrial cancer (N=44,386)		No cancer (N=221,219)	
	N	**%**	**N**	**%**
Age at diagnosis/index date				
66-69	12034	27%	60271	27%
70-74	12410	28%	61918	28%
75-79	8910	20%	44278	20%
80-84	6028	14%	29945	14%
85+	5004	11%	24807	11%
Race/ethnicity				
White	37756	85%	188723	85%
Black	4182	9%	20762	9%
Other	781	2%	3795	2%
Asian	797	2%	3899	2%
Hispanic	564	1%	2671	1%
North American Native	108	0%	450	0%
Unknown	198	0%	919	0%
Region				
Midwest	4198	9%	20894	9%
Northeast	20810	47%	103820	47%
South	6620	15%	32932	15%
West	12758	29%	63573	29%
Charlson score				
0	17031	38%	126293	57%
1	11530	26%	40060	18%
2+	15825	36%	54866	25%
Hypertension[a]				
No	11027	25%	109290	49%
Yes	33359	75%	111929	51%
Hyperlipidemia [a]				
No	14922	34%	120572	55%
Yes	29464	66%	100647	45%

[a] Defined by at least one claim with a code for that condition in the year prior to the index date

Table 2. Cancer characteristics among women with endometrial cancer (N=44,386)

	N	%

Stage		
Localized	27434	65%
Regional	9899	24%
Distant	4559	11%
Unknown/unstaged	2494	
Histology		
Endometrioid	30625	69%
Serous	4142	9%
Carcinosarcoma	3021	7%
Clear Cell	881	2%
Mixed	2841	6%
Other	2876	6%
Grade		
1	11596	33%
2	10001	29%
3	9420	27%
Undifferentiated	3723	11%
Unknown	9646	
Hysterectomy		
No	6264	14%
Yes	38122	86%
Chemotherapy		
No	33265	75%
Yes	11121	25%
Radiation		
No	27549	62%
Yes	16837	38%
Treatment		
Hysterectomy only	19081	43%
Hysterectomy + radiation	9138	21%
Hysterectomy + chemotherapy	4088	9%
Hysterectomy + radiation + chemotherapy	5815	13%
Chemo and/or radiation	3647	8%
No chemo, radiation, or hysterectomy	2617	6%

Table 3. Prevalent cardiovascular diseases at index date among women with endometrial cancer and matched women without cancer [a]

	Endometrial cancer (N=44,386)		**No cancer group (N=221,219)**		
	N	**%**	**N**	**%**	p
Cardiovascular diseases [b]					

Ischemic heart disease	9013	20%	33112	15%	<0.001
Acute myocardial infarction	728	2%	2610	1%	<0.001
Angina pectoris	1473	3%	5677	3%	<0.001
Pulmonary heart disease	1487	3%	4897	2%	<0.001
Other forms of heart disease	14914	34%	49791	23%	<0.001
Peri-, endo- and myocarditis	116	0%	415	0%	0.002
Cardiomyopathy	1216	3%	4114	2%	<0.001
Conduction disorders	1869	4%	5844	3%	<0.001
Cardiac dysrhythmias	8644	19%	28537	13%	<0.001
Cardiac arrest	54	0%	193	0%	0.030
Heart failure	4897	11%	16505	7%	<0.001
Cerebrovascular disease	5626	13%	22465	10%	<0.001
Diseases of arteries, arterioles, capillaries	7495	17%	27873	13%	<0.001
Atherosclerosis	4201	9%	15650	7%	<0.001
Diseases of the veins and lymphatics	3318	7%	9777	4%	<0.001
Phlebitis and thrombophlebitis	868	2%	2445	1%	<0.001
Other venous embolism and thrombosis	1225	3%	3315	1%	<0.001
Other diseases of veins and lymphatics	1889	4%	5542	3%	<0.001

[a] Endometrial cancer survivors and women without cancer were matched on age, race/ethnicity and state of residence at the index date

[b] Defined by at least one claim with a code for that condition in the year prior to the index date

Table 4. Cardiovascular disease diagnoses among older women with endometrial cancer and matched women without cancer within the first year after the index date

	Index date - <3 months				3 months - <1 year			
	Endometrial cancer cases	**Noncancer group**	**HR (95% CI)[a]**	**HR (95% CI)[b]**	**Endometrial cancer cases**	**Noncancer group**	**HR (95% CI)[a]**	**HR (95% CI)[b]**
	N events	**N events**			**N events**	**N events**		
Cardiovascular diseases								
Ischemic heart disease	4167	3329	7.15 (6.84, 7.49)	5.45 (5.20, 5.72)	2093	7304	1.73 (1.65, 1.82)	1.20 (1.14, 1.26)
Acute myocardial infarction	791	627	6.40 (5.76, 7.10)	5.14 (4.61, 5.72)	635	1761	1.83 (1.67, 2.00)	1.36 (1.24, 1.49)
Angina pectoris	713	1019	3.56 (3.23, 3.92)	2.63 (2.38, 2.89)	580	2183	1.35 (1.23, 1.48)	0.93 (0.85, 1.02)
Pulmonary heart disease	1889	949	10.30 (9.53, 11.13)	8.75 (8.08, 9.48)	1340	2399	2.94 (2.75, 3.14)	2.16 (2.02, 2.31)
Other forms of heart disease	8542	5173	11.46 (11.07, 11.87)	9.41 (9.08, 9.76)	3051	11460	2.19 (2.10, 2.28)	1.50 (1.44, 1.56)
Peri-, endo- and myocarditis	124	101	6.16 (4.73, 8.00)	5.16 (3.94, 6.76)	153	300	2.54 (2.09, 3.09)	1.87 (1.53, 2.28)
Cardiomyopathy	681	637	5.45 (4.89, 6.07)	4.32 (3.87, 4.83)	523	1581	1.68 (1.53, 1.86)	1.24 (1.12, 1.37)
Conduction disorders	2067	1052	10.26 (9.53, 11.05)	8.67 (8.03, 9.36)	899	2761	1.74 (1.61, 1.87)	1.28 (1.19, 1.38)
Cardiac dysrhythmias	5239	3224	9.51 (9.10, 9.94)	8.01 (7.65, 8.38)	2535	7776	2.06 (1.97, 2.15)	1.50 (1.43, 1.57)
Cardiac arrest	301	238	6.35 (5.35, 7.52)	5.25 (4.42, 6.25)	342	573	2.97 (2.60, 3.40)	2.20 (1.92, 2.52)
Heart failure	2718	2235	6.57 (6.21, 6.95)	5.25 (4.96, 5.56)	1878	5341	1.95 (1.85, 2.05)	1.41 (1.34, 1.49)
Cerebrovascular disease	1866	3403	2.88 (2.73, 3.05)	2.19 (2.07, 2.32)	2143	7846	1.45 (1.38, 1.52)	1.00 (0.96, 1.05)
Diseases of arteries, arterioles, capillaries	3149	3610	4.79 (4.57, 5.03)	3.62 (3.45, 3.80)	2996	8669	1.99 (1.91, 2.08)	1.37 (1.31, 1.43)
Atherosclerosis	2024	2156	4.95 (4.66, 5.26)	3.78 (3.55, 4.02)	2016	5312	2.06 (1.96, 2.17)	1.44 (1.37, 1.52)
Diseases of the veins and lymphatics	2825	1722	8.74 (8.23, 9.28)	7.60 (7.15, 8.09)	3517	4381	4.53 (4.33, 4.73)	3.44 (3.29, 3.60)
Phlebitis and thrombophlebitis	995	466	10.93 (9.79, 12.20)	9.43 (8.42, 10.56)	1135	1232	4.78 (4.41, 5.18)	3.53 (3.25, 3.84)
Other venous embolism and thrombosis	1809	675	13.86 (12.69, 15.14)	12.62 (11.52, 13.83)	1904	1676	6.02 (5.64, 6.43)	4.67 (4.36, 4.99)
Other diseases of veins and lymphatics	964	992	5.00 (4.58, 5.46)	4.22 (3.85, 4.62)	1886	2667	3.72 (3.51, 3.95)	2.87 (2.70, 3.05)

[a] Adjusted for age at start of follow-up, race/ethnicity, region (coded from state)

[b] Adjusted for age at start of follow-up, race/ethnicity, region (coded from state), Charlson score, hypertension, hyperlipidemia

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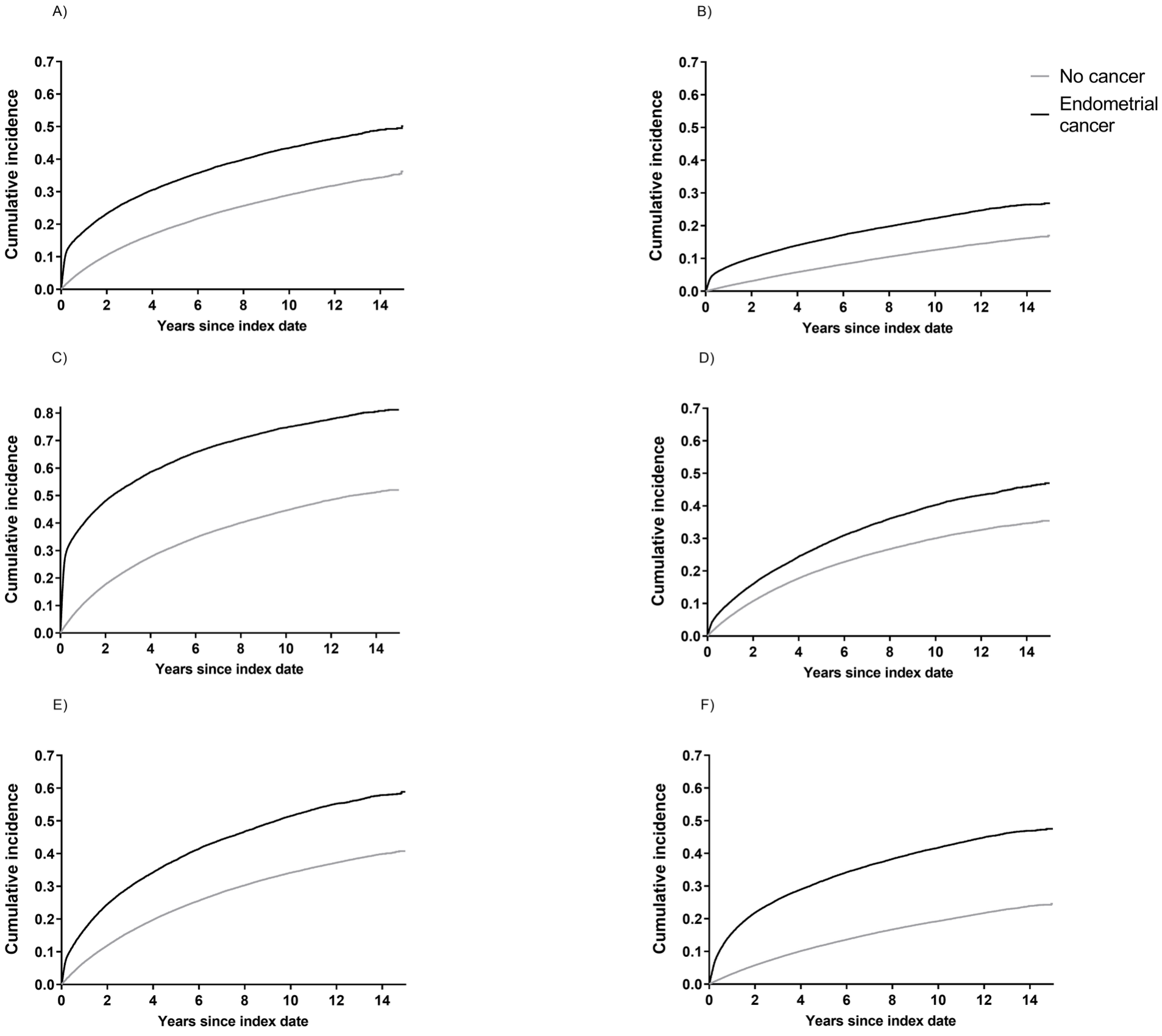
Table 5. Cardiovascular disease diagnoses among older women with endometrial cancer and matched women without cancer, with follow-up starting at 1 year after the index date

	Endometrial cancer cases N events	Noncancer group N events	HR (95% CI)[a]	HR (95% CI)[b]
Cardiovascular diseases				
Ischemic heart disease	6095	21123	1.73 (1.69, 1.78)	1.18 (1.14, 1.21)
Acute myocardial infarction	2602	7916	1.52 (1.46, 1.59)	1.13 (1.08, 1.18)
Angina pectoris	2118	7007	1.46 (1.39, 1.54)	0.99 (0.94, 1.04)
Pulmonary heart disease	4284	10746	1.95 (1.88, 2.02)	1.41 (1.36, 1.46)
Other forms of heart disease	7132	29679	2.15 (2.09, 2.21)	1.39 (1.35, 1.43)
Peri-, endo- and myocarditis	724	1607	2.05 (1.88, 2.24)	1.47 (1.35, 1.61)
Cardiomyopathy	2151	5942	1.71 (1.63, 1.80)	1.23 (1.17, 1.29)
Conduction disorders	3751	11156	1.67 (1.61, 1.73)	1.21 (1.17, 1.26)
Cardiac dysrhythmias	7187	24621	1.87 (1.82, 1.92)	1.31 (1.27, 1.34)
Cardiac arrest	1249	3141	1.80 (1.68, 1.92)	1.35 (1.26, 1.44)
Heart failure	6256	18919	1.73 (1.68, 1.78)	1.22 (1.18, 1.26)
Cerebrovascular disease	7685	23437	1.73 (1.68, 1.77)	1.15 (1.12, 1.18)
Diseases of arteries, arterioles, capillaries	8921	26177	2.09 (2.04, 2.14)	1.35 (1.32, 1.39)
Atherosclerosis	6831	18838	1.95 (1.90, 2.01)	1.31 (1.28, 1.35)
Diseases of the veins and lymphatics	7675	16424	2.71 (2.64, 2.78)	1.95 (1.90, 2.01)
Phlebitis and thrombophlebitis	2243	4186	2.67 (2.54, 2.81)	1.94 (1.84, 2.04)
Other venous embolism and thrombosis	4212	7088	3.00 (2.89, 3.12)	2.23 (2.15, 2.32)
Other diseases of veins and lymphatics	5546	11395	2.56 (2.48, 2.65)	1.87 (1.81, 1.93)

[a] Adjusted for age at start of follow-up, race/ethnicity, region (coded from state)

[b] Adjusted for age at start of follow-up, race/ethnicity, region (coded from state), Charlson score, hypertension, hyperlipidemia

Figure 1. Cumulative incidence of a) ischemic heart disease, b) pulmonary heart disease, c) other heart disease, d) cerebrovascular disease, e) diseases of the arteries, arterioles, and capillaries, f) diseases of the veins and lymphatics


A)
B)
C)
D)
E)
F)
Cumulative incidence
Years since index date
No cancer
Endometrial cancer