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Article

Patterns and trends in the cause of death for patients with endometrial cancer

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Abstract

Background: Racial disparities in endometrial cancer have been reported in the United States, but trends and the underlying causes are not well understood. We aimed to examine the trends and contributing factors in racial disparities for causes of death among endometrial cancer patients.

Method: In this population-based cohort study, we identified 139 473 women diagnosed with first, primary endometrial cancer between 1992 to 2018 from the Surveillance, Epidemiology, and End Results Program. We used the "Fine and Gray" method to calculate the cumulative incidence of all-cause and specific-cause death. We used proportional subdistribution hazard (PSH) and cause-specific hazard (CSH) models to quantify the relative risk of Black–White disparities. We performed a mediation analysis to assess the contribution of potential factors to disparities.

Results: The cumulative incidence of all-cause death decreased in endometrial cancer patients, with estimates at 5 years of 26.72% in 1992-1996 and 22.59% in 2007-2011. Compared with White patients, Black patients persistently had an increased risk of death due to endometrial cancer (PSH hazard ratio [HR] = 2.05, 95% confidence interval [CI] = 1.90 to 2.22; CSH HR = 2.19, 95% CI = 2.00 to 2.40) and causes other than endometrial cancer (PSH HR = 1.23, 95% CI = 1.10 to 1.37; CSH HR = 1.46, 95% CI = 1.31 to 1.63). Grade, histological subtype, surgery utilization, and stage at diagnosis explained 24.4%, 20.1%, 18.4%, and 16.6% of the Black-White disparity in all-cause death, respectively.

Conclusions: Although the cumulative incidence of all-cause death decreased, the Black–White gaps persisted in patients with endometrial cancer. Grade and histological subtype had the greatest influence. More efforts are needed to address the disparities.

Endometrial cancer is the fourth-most common cancer among women in the United States, with an estimated 66 570 newly diagnosed cases in 2021 (1). With a high incidence and survival rate, endometrial cancer has become the second-most prevalent cancer among females in the United States (2). Endometrial cancer is generally associated with a good prognosis, and nearly 70% of patients were diagnosed at an early stage (2). However, this good prognosis has not equitably benefitted all population groups. Disparities in cancer-specific and noncancer death have been reported among patients with endometrial cancer (3,4). How to improve health equity and equality in patients with endometrial cancer has become a challenge for individuals and the health system in the country.

The risk of death from endometrial cancer has decreased over the past 40 years (5), whereas the proportion of noncancer death increased (5). For some of these patients, the risk of dying from noncancer death has surpassed the risk of death from endometrial cancer (6). Considering that Black and White patients with endometrial cancer present with different diagnostic and treatment characteristics, the changing trends of patterns in cause-specific death may differ between races. However, temporal trends in racial differences for cause-specific death among endometrial cancer patients in the United States have not been well described. Furthermore, how much of the disparity is related to the impact of underlying disease characteristics and treatment is not adequately addressed. To fill the data gap, the primary aim of

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our study was to characterize the distribution and time trends of causes of death among patients with endometrial cancer overall and according to race. The second aim was to quantify the contribution of disease characteristics and treatment to Black–White disparities in cause of death. Such results may provide valuable clues for the explanation of disparities in endometrial cancer outcomes and may further guide precise preventive measures to reduce disparities.

Methods

Study design and data sources

We followed the Guidelines for the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) to report our observational study (Supplementary Methods, available online). In this retrospective observational cohort study, we obtained population-based endometrial cancer data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program in the United States. The SEER program is a network of population-based cancer registries covering various geographic and demographic population groups in the United States (7). To ensure the length of follow-up time and race coverage, we used the SEER database from 13 registries (San Francisco-Oakland SMSA, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, Alaska Natives, San Jose-Monterey, Los Angeles, Rural Georgia) (November 2020 submission), covering approximately 11.2% of the Black population and 11.0% of the White population in the United States since 1992 (8). We identified all patients diagnosed with first, primary endometrial cancer (International Classification of Diseases for Oncology, 3rd Edition ICD-O-3: C54.0-C55.9) using SEER*Stat software version 8.3.9 (9). Uterine sarcomas and carcinosarcomas were excluded.

We generated a case listing including the following variables: race, age at diagnosis, year of diagnosis, primary tumor site, histological subtype, stage at diagnosis, grade, and use of surgery. The SEER program assigns race based on data from various data sources, including hospital records, medical records, pathology reports, hospital discharge data, and death certificates (10). We categorized race using the SEER coding of Black, White, or Other (including American Indian or Alaska Native, Asian or Pacific Islander, other unspecified, and unknown). For between-race comparison, we restricted to the 2 racial categories, which were discretely specified (Black and White). By histological subtype, we classified endometrial adenocarcinoma, endometroid, mucinous adenocarcinoma, and adenocarcinoma with squamous differentiation histological subtypes into type I (ICD-O-3 morphology codes 8140, 8260, 8380, 8382, 8480, 8482, 8560, and 8570). Clear cell carcinomas and papillary serous carcinomas were classified as type II (ICD-O-3 morphology codes 8310, 8441, and 8460) (11). We categorized disease stage at diagnosis into localized, regional, distant, and unknown using the SEER summary stage standard. We defined regional and distant stage cancer as nonlocalized cancer (12). The grade was categorized as well-differentiated, moderately differentiated, poorly differentiated or undifferentiated, and unknown. We identified a person with surgery based on whether they had cancer-directed surgery.

Outcomes measures

We followed up with the patients from the date of cancer diagnosis until death or censored them on December 31, 2018, whichever came first. Cause of death was classified by ICD-Ninth Revision (ICD-9) edition for individuals who died from 1992 through 1998 and by ICD-10 for individuals who died thereafter (13). Patients who died of unknown causes were excluded from the analysis. We structured the causes of death into 6 clusters, with each grouping being comprehensive and mutually exclusive (Supplementary Table 1, available online): endometrial cancer, cardiovascular disease (CVD), other cancers, chronic obstructive pulmonary disease, diabetes, and other specific causes. We obtained ethical approval for this study from the institutional review board of the Cancer Hospital, Chinese Academy of Medical Sciences.

Statistical analysis

Using time to death, we calculated the cumulative incidence of death from all causes and specific causes overall by diagnostic period and according to race. We calculated the cumulative incidence of death from each specific cause using the Fine and Gray method, treating other causes of death as competing risks (14). Time trends were analyzed according to year of diagnosis grouped into five 5-year periods: 1992-1996, 1997-2001, 2002-2006, 2007-2011, and 2012-2016. We reported cumulative incidence of death at 5- and 10-year points. The absolute changes for the cumulative incidence of death were calculated between the periods 1992-1996 and 2007-2011. We used Gray's test to evaluate whether the cumulative incidence of death changed over diagnostic periods, treating the diagnostic period as a categorical variable (15). To further examine the patterns and trends of the disparities, we performed stratified analyses according to stage at diagnosis and histological subtype.

Two regression approaches have been widely used to study mortality risk in the presence of competing risks: proportional subdistribution hazard (PSH) and cause-specific hazard (CSH) (14). The PSH approach provides measures of both associations of race with a single cause of death and the contribution of another competing event. The CSH approach provides a direct measure of the association of race with a single cause of death, treating any competing events as censored at the time they occurred. Considering that PSH and CSH yield different interpretations, we used both models to assess Black–White disparities in all-cause and cause-specific death among patients with endometrial cancer (15). We reported unadjusted hazard ratios (HRs) and 95% confidence intervals (CIs).

We performed a mediation analysis to examine factors that mediated observed Black–White disparities in all-cause and cause-specific death. We selected potential contributors based on prior knowledge and data availability, including grade, histological subtype, stage at diagnosis, and surgery performance (3,4). We added each potential mediating variable to the multivariable cause-specific hazard model and calculated the mediation proportion and its 95% confidence interval (16). The mediation proportion was the proportion of excess risk of death of Black patients relative to White patients that could be attributed to the mediator. We further presented the distribution of these factors for each diagnostic period and used linear regression to test for the significance of trends over diagnostic periods. We conducted mediation analysis using SAS software with a SAS macro (version 9.4) (17). We conducted all other analyses using R software (version 4.0.2) (18,19). Two-sided P less than .05 was considered statistically significant.

Results

We included 139 473 women with endometrial cancer diagnosed during 1992-2018. Table 1 shows the characteristics of the study

Table 1. Characteristics of included patients according to race

Characteristics	Overall (N = 139 473)	Black (n = 11 191)	White (n = 112 566)	Others (n = 15 716)
Follow-up years				
Median (IQR)	6.17 (2.08, 12.58)	3.50 (1.08, 8.67)	6.58 (2.33, 13.08)	5.58 (1.83, 11.50)
Diagnosis years, no. (%)				
1992-1996	20 317 (14.57)	1189 (10.62)	17 747 (15.7)	1381 (8.79)
1997-2001	22 083 (15.83)	1422 (12.71)	18 778 (16.68)	1883 (11.98)
2002-2006	23 170 (16.61)	1742 (15.57)	18 996 (16.88)	2432 (15.47)
2007-2011	27 677 (19.84)	2398 (21.43)	21 853 (19.41)	3426 (21.80)
2012-2016	32 232 (23.11)	3049 (27.25)	24 774 (22.01)	4409 (28.05)
2017-2018	13 994 (10.03)	1391 (12.43)	10 418 (9.26)	2185 (13.90)
Vital status, no. (%)				
Alive	86 056 (61.70)	5797 (51.80)	68 598 (60.94)	11 661 (74.20)
Dead from endometrial cancer	23 607 (16.93)	3264 (29.17)	18 178 (16.15)	2165 (13.78)
Dead from causes other than endometrial cancer	29 064 (20.84)	2070 (18.50)	25 255 (22.44)	1739 (11.07)
Dead from CVD	11 244 (8.06)	856 (7.65)	9774 (8.68)	614 (3.91)
Dead from other cancers	5636 (4.04)	408 (3.65)	4834 (4.29)	394 (2.51)
Dead from COPD	1217 (0.87)	104 (0.93)	1007 (0.89)	106 (0.67)
Dead from diabetes	1150 (0.82)	49 (0.44)	1061 (0.94)	40 (0.25)
Other specific causes	9817 (7.04)	653 (5.84)	8579 (7.62)	585 (3.72)
Dead with unknown causes	746 (0.53)	60 (0.54)	535 (0.48)	151 (0.96)
Age at diagnosis, no. (%)				
Mean (SD)	62.96 (12.31)	63.22 (11.78)	63.64 (12.18)	57.91 (12.36)
<55 y	33 377 (23.93)	2208 (19.73)	24 989 (22.20)	6180 (39.32)
55-64 y	43 235 (31.00)	3748 (33.49)	34 534 (30.68)	4953 (31.52)
65-74 y	36 088 (25.87)	3365 (30.07)	29 729 (26.41)	2994 (19.05)
75+ y	26 773 (19.20)	1870 (16.71)	23 314 (20.71)	1589 (10.11)
Histological subtype[a], no. (%)				
Type I	112 942 (81.98)	6939 (62.01)	93 064 (82.68)	12 939 (82.31)
Type II	11 054 (7.93)	2117 (18.92)	7738 (6.87)	1199 (7.63)
Others[b]	15 477 (11.10)	2135 (19.08)	11 764 (10.45)	1578 (10.04)
Stage, no. (%)				
Local	97 773 (70.10)	6315 (56.43)	80 710 (71.70)	10 748 (68.38)
Regional	25 720 (18.44)	2674 (23.89)	19 958 (17.73)	3088 (19.65)
Distant	10 177 (7.30)	1516 (13.55)	7510 (6.67)	1151 (7.32)
Unknown	5803 (4.16)	686 (6.13)	4388 (3.90)	729 (4.64)
Grade, no. (%)				
Well	49 959 (35.82)	2294 (20.50)	41 648 (37.00)	6017 (38.28)
Moderate	32 781 (23.50)	2073 (18.52)	27 319 (24.27)	3389 (21.56)
Poorly	21 883 (15.69)	2715 (24.26)	16 669 (14.81)	2499 (15.90)
Undifferentiated	9227 (6.62)	1382 (12.35)	6676 (5.93)	1169 (7.44)
Unknown	25 623 (18.37)	2727 (24.37)	20 254 (17.99)	2642 (16.81)
Surgery, no. (%)				
Yes	126 496 (90.70)	9206 (82.26)	103 013 (91.51)	14 277 (90.83)
No	11 768 (8.44)	1845 (16.49)	8644 (7.70)	1279 (8.14)
Unknown	1209 (0.87)	140 (1.25)	909 (0.81)	160 (1.02)

[a] Type I: ICD-O-3 morphology codes: 8140, 8260, 8380, 8382, 8480, 8482, 8560, and 8570; type II: ICD-O-3 morphology codes: 8310, 8441, and 8460. COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; IQR = interquartile range.
[b] Others: All other invasive endometrial cancers.

population overall and according to race. The median follow-up time was 6.17 years (interquartile range = 2.08 to 12.58). Overall, 53 417 (38.30%) deaths were documented, including 23 607 from endometrial cancer, 29 064 from causes other than endometrial cancer, and 746 of unknown causes. The mean age at diagnosis was 62.96 years (SD = 12.31). Black patients had a lower proportion of type I, localized-stage, and well-differentiated cancer compared with White patients. The proportion of patients who received surgery was lower in Black patients than White patients (Table 1). The detailed characteristics of the study population were further shown by diagnostic period (Supplementary Table 2, available online).

Patients with endometrial cancer were most likely to die from endometrial cancer, followed by CVD, other cancers, and chronic obstructive pulmonary disease. The cumulative incidence of death from endometrial cancer rapidly increased within the first 5 years after diagnosis and then increased slowly, with estimates of 15.77% at 5 years and 18.41% at 10 years after an endometrial cancer diagnosis. In contrast, the cumulative incidence of CVD death was continuously rising, with estimates of 3.22% at 5 years and 6.54% at 10 years after endometrial cancer diagnosis (Figure 1, A and C; Supplementary Table 3, available online). By race, in the first 10 years after diagnosis, Black patients consistently had a higher cumulative incidence of death from all causes and specific causes except for diabetes compared with White patients. This Black–White gap was mostly driven by the disparity in death from endometrial cancer (Black vs White patients for 5-year cumulative incidence: 29.73% vs 14.70%; Black vs White patients for 10-year cumulative incidence: 33.08% vs 17.30%) (Figure 1, B and D; Supplementary Table 3, available online). In the stratified analyses, the Black–White gaps were consistent across all stages and histological subtypes (Supplementary Tables 4 and 5, available online). Similar patterns were observed when we further separately analyzed clear cell carcinomas and papillary serous carcinomas (Supplementary Table 6, available online).

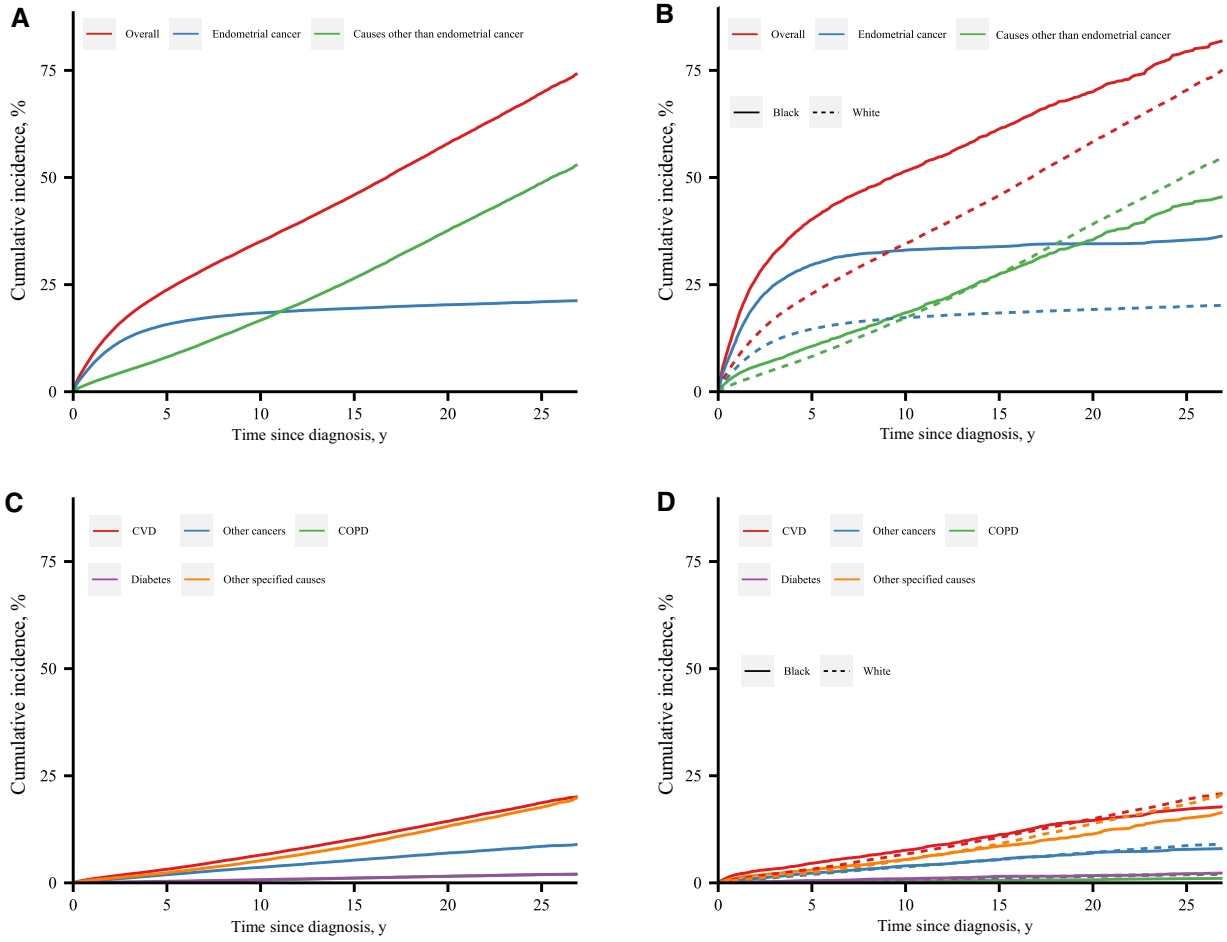

Figure 1. Cumulative incidence of all-cause and cause-specific death for patients with endometrial cancer by time since diagnosis. **A**) The cumulative incidence of death from all causes, endometrial cancer, and causes other than endometrial cancer of the overall study population. **B**) The cumulative incidence of death from all causes, endometrial cancer, and causes other than endometrial cancer by race. **C**) The cumulative incidence of death from non-endometrial cancer-specific death of the overall study population. **D**) The cumulative incidence of death from non-endometrial cancer-specific death by race. COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease.

We further presented the cumulative incidence of death from all causes and specific causes for patients with endometrial cancer by diagnostic period (Figure 2). Overall, the cumulative incidence of death from all causes decreased over diagnostic periods ($P < .001$), with a 5-year cumulative incidence of 26.72% for the 1992-1996 diagnostic period and 22.59% for the 2007-2011 diagnostic period. This downward trend was mostly driven by the decreasing rates of death from causes other than endometrial cancer. The absolute change in 5-year cumulative incidence of death from endometrial cancer and causes other than endometrial cancer was −0.49% and −3.64%, respectively. We found persistent Black–White gaps in death from all causes in each diagnostic period (Black vs White patients for 5-year cumulative incidence during 1992-1996: 49.06% vs 25.76%; Black vs White patients for 5-year cumulative incidence during 2007-2011: 38.64% vs 21.56%). The 10-year cumulative incidence of death showed similar patterns for Black–White disparities (Table 2). In stratified analyses by histological subtypes and stages, similar results were observed (Supplementary Tables 7 and 8, available online).

We then further quantified the Black–White disparities and calculated the relative risks of death from all causes and specific causes. Compared with White patients, Black patients persistently had an increased risk of death from all causes (2007-2011: PSH HR = 1.84, 95% CI = 1.72 to 1.96; CSH HR = 1.84, 95% CI = 1.71 to 1.98), endometrial cancer (PSH HR = 2.05, 95% CI = 1.90 to 2.22; CSH HR = 2.19, 95% CI = 2.00 to 2.40), and causes other than endometrial cancer (PSH HR = 1.23, 95% CI = 1.10 to 1.37; CSH HR = 1.46, 95% CI = 1.31 to1.63) (Table 3).

We explored factors that mediated Black–White disparities in death from all causes and specific causes. The most important factor explaining the Black–White disparity in all-cause death was grade (24.4%, 95% CI = 21.7% to 27.4%), followed by histological subtype (20.1%, 95% CI = 17.7% to 22.8%). Grade, histological subtype, stage at diagnosis, and surgery explained 44.5% (95% CI = 39.4% to 49.6%) of Black–White disparity in all-cause death, 63.2% (95% CI = 57.1% to 68.9%) of disparity in endometrial cancer death, and 20.5% (95% CI = 15.3% to 26.9%) disparity in death due to causes other than endometrial cancer (Table 4).

We further presented the distribution of these factors for Black and White patients by diagnostic period. Compared with White patients, Black patients had a persistently higher proportion of type II (1992-1996: 14.46% vs 5.25%; 2007-2011: 20.89% vs 7.42%), nonlocalized (1992-1996: 40.40% vs 21.53%; 2007-2011:

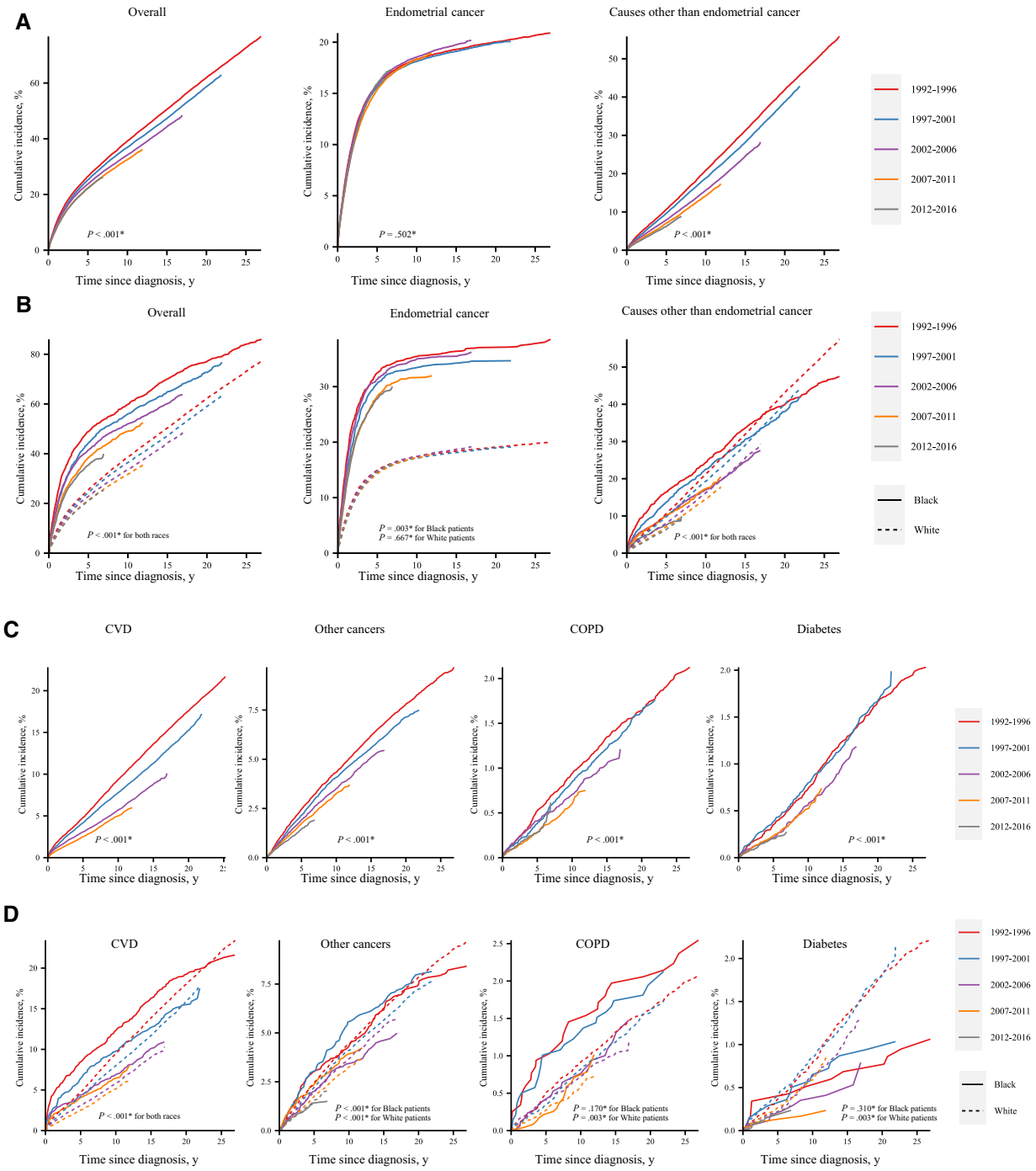

Figure 2. Cumulative incidence of all-cause and cause-specific death for patients with endometrial cancer by diagnostic period. **A**) The cumulative incidence of death from all causes, endometrial cancer, and causes other than endometrial cancer of the overall study population. **B**) The cumulative incidence of death from all causes, endometrial cancer, and causes other than endometrial cancer by race. **C**) The cumulative incidence of death from non-endometrial cancer-specific death of the overall study population. **D**) The cumulative incidence of death from non-endometrial cancer-specific death by race. COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease. *Gray's test for evaluating the differences in cumulative incidence function between diagnostic periods.

38.37% vs 27.06%), and poorly or undifferentiated cancer (1992-1996: 41.21% vs 21.95%; 2007-2011: 44.75% vs 24.00%). Moreover, the proportion of patients who underwent surgery was consistently lower in Black patients than in White patients (1992-1996: 92.54% vs 97.31%; 2007-2011: 92.09% vs 96.81%) (Supplementary Figure 1, available online). By histological subtype, we found a higher proportion of both clear cell carcinomas and papillary serous carcinomas in Black patients than in White patients (Supplementary Figure 2, available online).

Discussion

Our results showed that although the cumulative incidence of all-cause death had declined, the Black–White disparities

Table 2. Five-year and 10-year cumulative incidence of all-cause and cause-specific death for endometrial cancer patients overall and by race and diagnostic periods

		5-y Cumulative incidence of death (%)						10-y Cumulative incidence of death (%)					
Race	Cause of death	Overall	1992-1996	1997-2001	2002-2006	2007-2011	Absolute change (%)[a]	Overall	1992-1996	1997-2001	2002-2006	2007-2011	Absolute change (%)[a]
Overall													
	Overall	23.97	26.72	25.43	23.94	22.59	−4.13	35.22	39.39	37.07	34.35	32.65	−6.74
	Endometrial cancer	15.77	15.92	15.66	15.95	15.43	−0.49	18.41	18.37	18.13	18.57	18.32	−0.05
	Causes other than endometrial cancer	8.20	10.79	9.77	7.99	7.15	−3.64	16.81	21.02	18.94	15.77	14.33	−6.69
	CVD	3.22	4.85	4.24	3.11	2.53	−2.32	6.54	9.43	7.82	5.74	5.03	−4.40
	Other cancers	1.94	2.49	2.17	1.95	1.77	−0.72	3.65	4.37	4.09	3.53	3.28	−1.09
	COPD	0.37	0.53	0.39	0.41	0.29	−0.24	0.75	0.95	0.85	0.72	0.61	−0.34
	Diabetes	0.27	0.36	0.40	0.21	0.24	−0.12	0.64	0.75	0.81	0.58	0.52	−0.23
Black													
	Overall	40.45	49.06	44.63	41.60	38.64	−10.42	51.62	60.04	56.11	52.11	49.10	−10.94
	Endometrial cancer	29.73	32.56	30.81	31.44	28.39	−4.17	33.08	35.48	33.48	35.04	31.68	−3.80
	Causes other than endometrial cancer	10.72	16.50	13.82	10.16	10.25	−6.25	18.54	24.56	22.63	17.07	17.42	−7.14
	CVD	4.61	8.55	6.48	4.43	4.10	−4.45	7.66	12.49	9.80	6.98	6.57	−5.92
	Other cancers	2.27	3.08	3.10	2.04	2.43	−0.65	4.00	4.45	5.62	3.46	4.02	−0.43
	COPD	0.54	1.03	1.08	0.47	0.26	−0.77	0.99	1.54	1.37	0.82	0.79	−0.75
	Diabetes	0.25	0.43	0.36	0.23	0.17	−0.26	0.44	0.60	0.72	0.41	0.23	−0.37
White													
	Overall	23.06	25.76	24.59	23.04	21.56	−4.20	34.71	38.87	36.56	33.81	31.86	−7.01
	Endometrial cancer	14.70	15.02	14.66	14.89	14.39	−0.63	17.30	17.45	17.12	17.45	17.24	−0.21
	Causes other than endometrial cancer	8.37	10.74	9.93	8.15	7.17	−3.57	17.41	21.42	19.44	16.36	14.62	−6.80
	CVD	3.27	4.79	4.24	3.12	2.54	−2.25	6.78	9.55	8.04	5.88	5.17	−4.38
	Other cancers	2.00	2.48	2.23	2.04	1.78	−0.70	3.75	4.44	4.12	3.70	3.27	−1.17
	COPD	0.37	0.52	0.36	0.41	0.28	−0.24	0.76	0.92	0.83	0.74	0.60	−0.32
	Diabetes	0.30	0.37	0.43	0.22	0.28	−0.09	0.71	0.80	0.87	0.65	0.59	−0.21

[a] Absolute change is between the period 1992-1996 and the period 2007-2011. COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease.

persisted over time. We uncovered that grade and histological subtype had the greatest influence on the Black–White disparity in all-cause death. Some modifiable factors such as stage at diagnosis and surgery use may also drive the racial disparities. To our best knowledge, this is the most comprehensive study with the most updated population-based data to systematically examine the distribution and time trends of causes of death and racial disparities in endometrial cancer. Our results provide insight into understanding racial disparities in endometrial cancer, which may further guide precise preventive measures to reduce these disparities.

Consistent with existing findings (3), our results showed that the cumulative incidence of death from all causes declined. Of note, the greatest reduction was seen in death from CVD. This success probably reflects the declined CVD mortality in the US general population (20). However, we found the cumulative incidence of death from endometrial cancer did not change over the past 20 years. There are several possible reasons. First, it may partly be due to the increase in the proportion of patients diagnosed at a later stage (3,4). For those patients, effective and curable treatment options are still lacking (21,22). Second, it may partly be attributable to the increase in the proportion of patients with type II endometrial cancer (23). This subtype of cancer usually behaves more aggressively, having a higher risk of recurrence and a worse response to standard therapies compared with type I (22). Furthermore, due to the lack of more specific therapies for the subtype of endometrial cancer, type II endometrial cancer patients with advanced stage are still mainly treated in the same way as type I (24). Our results highlight a need for a better understanding of the disease's biology and more precise and effective treatment options.

Previous studies have shown racial disparities in cancer-specific and noncancer death for patients with endometrial cancer (3,4). In line with these findings, our study further identified Black–White disparities in death from all causes and all specific causes examined except for diabetes, with the largest gap in death from endometrial cancer. Trend analysis showed that Black–White disparities persisted over time. We further revealed that biological factors, including grade and histological subtype, were the most influential contributors. Meanwhile, Black patients persistently had a higher proportion of high-grade, more aggressive tumors (type II) compared with White patients (25). Especially, the increase of type II endometrial cancer is most prominent among Black patients, although it increased in all races from 2003 to 2015 (23). Notably, the effect of type II endometrial cancer on racial disparities was driven by both clear cell carcinomas and papillary serous carcinomas. Studies reported that Black women may be more likely to have molecular markers of aggressive disease (26). More studies are needed to fully understand the cause of the higher rate of increase of this subtype in Black women, including both biological and nonbiological factors, which is important for addressing the persistent racial disparities.

Similar to previous results (3,4,27), we found modifiable factors, including stage at diagnosis and receipt of surgery, were also important contributors to Black–White disparities in endometrial cancer outcomes. Of note, Black patients persistently had a higher proportion of advanced-stage cancer than White patients. It may partly be attributable to the lack of recognition and evaluation of postmenopausal bleeding (28), knowledge gaps and silence about menopause (29), and limited source of health care in Black women. Improving cancer awareness in Black women is

Table 3. Hazard ratios for all-cause overall and cause-specific death among Black patients compared with White patients estimated by PSH and CSH models[a]

	PSH HR (95% CI) for cause of death				CSH HR (95% CI) for cause of death			
Diagnostic period	Overall	Endometrial cancer	Causes other than endometrial cancer	CVD	Overall	Endometrial cancer	Causes other than endometrial cancer	CVD
1992-1996	1.66 (1.54 to 1.79)	2.22 (2.01 to 2.45)	0.88 (0.80 to 0.96)	1.00 (0.88 to 1.14)	1.57 (1.46 to 1.69)	2.40 (2.14 to 2.68)	1.30 (1.24 to 1.36)	1.35 (1.17 to 1.56)
1997-2001	1.64 (1.53 to 1.76)	2.08 (1.89 to 2.29)	0.99 (0.90 to 1.08)	1.02 (0.89 to 1.18)	1.64 (1.52 to 1.76)	2.25 (2.02 to 2.51)	1.33 (1.22 to 1.46)	1.39 (1.19 to 1.61)
2002-2006	1.73 (1.61 to 1.85)	2.19 (2.01 to 2.39)	0.99 (0.89 to 1.10)	1.13 (0.97 to 1.33)	1.64 (1.52 to 1.76)	2.18 (1.97 to 2.41)	1.27 (1.15 to 1.41)	1.35 (1.12 to 1.62)
2007-2011	1.84 (1.72 to 1.96)	2.05 (1.90 to 2.22)	1.23 (1.10 to 1.37)	1.30 (1.09 to 1.55)	1.84 (1.71 to 1.98)	2.19 (2.00 to 2.40)	1.46 (1.31 to 1.63)	1.55 (1.28 to 1.88)

[a] CI = confidence interval; CSH = cause-specific hazard regression; CVD = cardiovascular disease; HR = hazard ratio; PSH = proportional subdistribution hazard.

Table 4. Mediation analysis of the association between race and all-cause overall and cause-specific death[a]

	Overall		Endometrial cancer		Causes other than endometrial cancer	
Mediator	Mediated (95% CI) (%)	P	Mediated (95% CI) (%)	P	Mediated (95% CI) (%)	P
Grade	24.4 (21.7 to 27.4)	<.0001	43.3 (39.6 to 47.0)	<.0001	7.2 (5.4 to 9.5)	<.0001
Histological subtype	20.1 (17.7 to 22.8)	<.0001	34.4 (31.2 to 37.9)	<.0001	2.1 (0.9 to 4.6)	.006
Stage at diagnosis	16.6 (13.4 to 20.4)	<.0001	30.0 (25.7 to 34.6)	<.0001	4.4 (4.7 to 10.9)	<.0001
Surgery	18.4 (14.2 to 23.5)	<.0001	24.2 (17.8 to 31.9)	<.0001	14.6 (10.0 to 20.6)	<.0001
Mediators combined	44.5 (39.4 to 49.6)	<.0001	63.2 (57.1 to 68.9)	<.0001	20.5 (15.3 to 26.9)	<.0001

[a] CI = confidence interval.

important. Postmenopausal bleeding provides an opportunity for cancer early detection (30). More intensive health promotion on disease prevention may be an effective way to improve early diagnosis in Black women in the near future (31).

Access to appropriate care may also contribute to the persistent disparity between Black and White patients (32). Previous studies indicated that Black patients were less likely than White patients with endometrial cancer to receive evidence-based care (31-35). Similarly, we found a consistent Black–White gap in surgery performance, which may contribute to the persistently worse outcome in Black patients. It may reflect interventions to address persistent treatment inequity in endometrial cancer are still lacking (36). Increased efforts should be directed at providing surgical treatment for Black patients with endometrial cancer. Moreover, studies have shown a higher prevalence of comorbid conditions and less use of preventive services among Black patients compared with White patients with endometrial cancer, which might also contribute to the disparities (37,38). Therefore, management of chronic comorbid conditions and providing preventive services for Black patients may be effective strategies to close the disparities (39).

Our study has several limitations. First, we did not have access to information such as biological factors and comorbidities, which limited our ability to fully analyze the influence of these factors on racial disparities. Several studies have reported biological differences between Black and White patients with endometrial cancer such as *TP53* mutations and MicroRNAs expression (41,42). More robust genetic and molecular profile studies are needed to explain the racial disparities. Second, potential misclassification of cause of death from population-based cancer registries could not be ruled out (40). In our study, we excluded patients with unknown causes of death from the study to minimize this misclassification. Third, we used data from 13 SEER registries, which cannot fully represent the whole Black and White populations in the United States. Fourth, we did not include uterine carcinosarcomas in this study; therefore, the racial disparities of this disease are not characterized.

A strength of our study is the use of reliable and the most updated population-level data, enabling stratification by race and deaths into 6 cause groups. In addition, the lengthy follow-up allowed us to describe time trends in specific causes of death by race, which to our knowledge previously has not been investigated in detail. This is the first study to our knowledge to quantify the contribution of multilevel factors to racial disparities in cause of death among patients with endometrial cancer and to disentangle the importance of biological and modifiable factors.

In summary, this study describes the decrease in the cumulative incidence of all-cause death among patients with endometrial cancer over the past 20 years. However, Black–White gaps in death from both endometrial cancer and other than endometrial cancer death are persistent. Grade and histological subtype were the most influential contributors. Our findings highlight a need for more effort to address racial disparities in endometrial cancer outcomes. Coupled with a continued effort to address diagnosis and treatment inequity, ongoing research on biologic mechanisms underlying histopathologic differences may help narrow disparities.

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Data availability

The data underlying this article were all obtained from SEER database and are publicly available.

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