Racial/ethnic disparities in the cause of death among patients with prostate cancer in the United States from 1995 to 2019: a population-based retrospective cohort study

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Summary

Background Racial/ethnic disparities in prostate cancer are reported in the United States (US). However, long-term trends and contributors of racial/ethnic disparities in all-cause and cause-specific death among patients with prostate cancer remain unclear. We analysed the trends and contributors of racial/ethnic disparities in prostate cancer survivors according to the cause of death in the US over 25 years.

Methods In this retrospective, population-based longitudinal cohort study, we identified patients diagnosed with first primary prostate cancer between 1995 and 2019, with follow-up until Dec 31, 2019, using population-based cancer registries' data from the Surveillance, Epidemiology, and End Results (SEER) Program. We calculated the cumulative incidence of death for each racial/ethnic group (Black, white, Hispanic, Asian or Pacific Islander [API], and American Indian or Alaska Native [AI/AN] people), by diagnostic period and cause of death. We quantified absolute disparities using rate changes for the 5-year cumulative incidence of death between racial/ethnic groups and diagnostic periods. We estimated relative (Hazard ratios [HR]) racial/ethnic disparities and the percentage of potential factors contributed to racial/ethnic disparities using Cox regression models.

Findings Despite a decreasing trend in the cumulative risk of death across five racial/ethnic groups, AI/AN and Black patients consistently had the highest rate of death between 1995 and 2019 with an adjusted HR of 1.48 (1.40–1.58) and 1.40 (1.38–1.42) respectively. The disparities in all-cause mortality between AI/AN and white patients increased over time, with adjusted HR 1.32 (1.17–1.49) in 1995–1999 and 1.95 (1.53–2.49) in 2015–2019. Adjustment of stage at diagnosis, initial treatment, tumor grade, and household income explained 33% and 24% of the AI/AN-white and

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Black-white disparities in all-cause death among patients with prostate cancer.

Interpretation The enduring racial/ethnic disparities in patients with prostate cancer, call for new interventions to eliminate health disparities. Our study provides important evidence and ways to address racial/ethnic inequality.

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Keywords: Prostate cancer; Racial/ethnic disparities; Cause-specific death; The United States

Research in context

Evidence before this study

Though racial/ethnic disparities in prostate cancer have received significant attention in the United States (US), relatively few studies have assessed long-term trends and potential causes of disparities in death among patients with prostate cancer. We searched MEDLINE, Embase, PubMed, and Google Scholar using the search terms ("racial disparity" or "racial inequity" or "racial and ethnic disparities" or "racial/ethnic disparities" or "racial and ethnic inequities" or "racial/ethnic inequities") and ("prostate neoplasm" or "prostate cancer" or "prostate tumor" or "prostate tumour") on November 10, 2022. We found the major racial/ethnic focus had been on disparities between Black and white people. We found no studies reporting trends and underlying causes of all-cause and cause-specific death over the last three decades among white, Black, Hispanic, Asian or Pacific Islander (API), and Indian or Alaska Native (AI/AN) patients with prostate cancer in the US.

Added value of this study

To our knowledge, this study is the first to compare all-cause and cause-specific death among white, Black, Hispanic, API, and AI/AN patients with prostate cancer in the US over 25 years. These data provide the most comprehensive and longest-running trend of racial/ethnic disparities in the causes of death among patients with prostate cancer. We also provide a detailed assessment of changes and potential causes of racial/ethnic disparities. These findings underscore the serious problem of racial/ethnic inequality in patients with prostate cancer. Especially, stage at diagnosis, initial treatment, and household income were potentially modifiable causes of racial/ethnic disparities. The findings provided valuable clues for explaining disparities in patients with prostate cancer and may further guide precise preventive measures to reduce racial/ethnic disparities.

Implications of all the available evidence

Our findings indicate that racial/ethnic disparities persist in patients with prostate cancer in the US. The continued disparity in all-cause and cause-specific mortality, particularly among Black and AI/AN patients, as compared to white patients, highlights the need for stronger measures to address these inequalities. Factors such as socioeconomic status, stage at diagnosis, and initial treatment have contributed to these disparities. Changes in prostate specific antigen (PSA) screening guidelines had made a big impact in the trends and patterns of racial/ethnic disparities. However, it is also important to acknowledge that the long history of structural racism and social injustice have perpetuated adverse social determinants of health, leading to persistent racial/ethnic disparities in healthcare.

Introduction

In the United States (US), prostate cancer is the most common cancer and the second leading cause of cancer death among men.[1] Although prostate cancer has a high 5-year survival rate, this favorable prognosis is not observed equally in all populations.[1,2] Especially, those belonging to racial/ethnic minorities may experience higher rates of adverse effects and a poorer quality of life resulting from a cancer diagnosis.[3] Therefore, racial/ethnic inequity remains a serious problem that affects the outcome of prostate cancer survivors. Identifying trends and potential causes of racial/ethnic disparities among patients with prostate cancer is a critical step toward improving survival and promoting health equity for all races/ethnicities.

Competing risk of death should be considered when analysing the racial/ethnic disparities in patients with prostate cancer. With survival improvement, prostate cancer survivors face an increased risk of non-prostate-cancer-specific death. The causes of death after a diagnosis of prostate cancer vary greatly according to the stage at diagnosis, patient characteristics, and period of diagnosis.[4] For example, among men diagnosed with local/regional disease, deaths from causes

other than prostate cancer were more than 4-fold compared to those who died of prostate cancer.[4] Especially, Black patients with prostate cancer experienced both higher prostate cancer-specific mortality and other-cause mortality than white patients.[5] The root causes of racial/ethnic disparities in patients with prostate cancer are multi-dimensional. A growing body of evidence suggests that race-defining biological differences do not fully explain prostate cancer health disparities. Dess et al. found that, with similar access to care and standardised treatment, Black men with nonmetastatic prostate cancer appeared to have comparable prostate cancer-specific mortality to white men.[5] In addition, most studies focused on the disparities between the Black and white populations, excluding other racial/ethnic populations such as Hispanic, Asian and Pacific Islander (API), and American Indian or Alaska Native (AI/AN) people. However, understanding trends and patterns in patients with prostate cancer of other races/ethnicities is quite important for enhancing health equity for all. We found no studies reporting trends of racial/ethnic disparities of cause-specific mortality among white, Hispanic, API, and AI/AN patients with prostate cancer over the last three decades in the US.

To identify how racial/ethnic disparities were developing over time and their underlying causes, we comprehensively analysed trends and patterns of racial/ethnic disparities in patients with prostate cancer according to the cause of death in the US over 25 years, using up-to-date population-based data. We further quantified potential factors that may drive racial/ethnic disparities. Our study results will add evidence for more appropriate interventions to bridge the gap of racial/ethnic disparities in prostate cancer care in the US.

Methods

Study design and data sources

This study used data from the Surveillance, Epidemiology, and End Results (SEER) database. Data were retrieved from 12 registries (San Francisco-Oakland SMSA, Connecticut, Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, Atlanta (Metropolitan), San Jose-Monterey, Los Angeles, Alaska Natives, Rural Georgia) (November 2021 submission), covering approximately 12.24% of the US population (based on 2010 census). The cancer registries' staff regularly retrieved the patients' demographic information (e.g., sex) from the medical records. We only included male patients with first, primary adenocarcinoma of the prostate (International Classification of Diseases for Oncology, 3rd Edition ICD-O-3: C61.9; histological code: 8140) diagnosed between 1995 and 2019 using SEER*-Stat software version 8.4.0.1. We obtained ethical approval for this study from the institutional review board of the Cancer Hospital, Chinese Academy of Medical Sciences, and written informed consent was waived given the data from a public database.

We identified the following variables from the SEER database: race/ethnicity, year of diagnosis, age at diagnosis, sex, stage at diagnosis, tumor grade, cancer-directed surgery status, radiotherapy status, and median household income. According to the United States Census Bureau, race and Hispanic origin (ethnicity) are two separate concepts. People who are Hispanic may be of any race. People in each race group may be either Hispanic or not Hispanic. As the exposure variable, we reported race/ethnicity in five mutually exclusive categories according to the SEER original coding standard of race/ethnicity: Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian/Pacific Islander (API), Non-Hispanic American Indian/Alaska Native (AI/AN), and Hispanic. We classified the stage at diagnosis based on "SEER historic stage A (1973–2015)" and "Combined Summary Stage (2004+)". We defined localised/regional stage cancer as non-metastatic cancer and distant stage cancer as metastatic cancer.[6] Tumor grade was classified into Grade I (well-differentiated), Grade II (moderately-differentiated), Grade III (poorly-differentiated), Grade IV (undifferentiated), and unknown based on Gleason Score.[7] Cancer-directed surgery status and radiotherapy status during the first course of therapy were determined according to the SEER coding. We retrieved median household income at census-tract county level.

Outcomes

The follow-up of the patients was from the date of cancer diagnosis until death or censored on December 31, 2019, whichever came first. The causes of death were coded according to two revisions of International Classification of Diseases editions (ICD), ninth (ICD-9) for the years 1995–1998 and tenth (ICD-10) for 1999 to 2019, respectively. We classified the causes of death into prostate-cancer-specific death and other-cause death. The latter included cardiovascular disease (CVD), other (non-prostate) cancers, chronic obstructive pulmonary disease (COPD), diabetes, and other specific causes. The six clusters of cause-specific death are mutually exclusive and comprehensive (appendix Supplementary Table S1).

Statistical analysis

The outcomes of interest were all-cause death and cause-specific death. We used the Fine and Gray model to calculate the cumulative incidence of death at 5 years and 10 years of follow-up, overall, and by race/ethnicity, stage, and diagnostic period, accounting for competing risks of death.[8] We categorised the year of diagnosis into five periods: 1995–1999, 2000–2004, 2005–2009, 2010–2014, and 2015–2019. Given that the white

population was the majority population in the US, and we focused on disparities from the majority population, we selected white patients as the reference group over time in pairwise racial/ethnic comparisons. To retrieve a more comprehensive picture of racial/ethnic disparities over time, we estimated both absolute and relative racial/ethnic disparities. We quantified absolute racial/ethnic disparities using absolute rate difference for the 5-year cumulative incidence of death between the period 1995–1999 and the period 2010–2014 (the most recent period for such data that are available). We quantified the relative disparities using adjusted hazard ratios (HRs) with the cause-specific hazard regression model with the adjustment for age as a categorical variable (<55, 55–64, 65–74, 75+ years), though strict proportionality was not established (appendix Supplementary Tables S1, S6–S9). To test whether relative racial/ethnic disparities had changed over time, we added a multiplicative interaction term between race/ethnicity and diagnostic period in regression models. The product term treated the diagnostic period as a continuous variable. The diagnostic period in the main effect was considered a continuous variable, which is the same as that in the interaction term.

To evaluate the potential association between the candidate covariables associated with all-cause and cause-specific death, we used a series of multivariable cause-specific hazard regression models. We conducted a mediation analysis to estimate the relative contribution of each covariable to racial/ethnic disparities in all-cause death and cause-specific death.[9] We selected the candidate covariables based on prior knowledge and data availability, including stage at diagnosis, tumor grade, the performance of cancer-directed surgery, radiotherapy performance, and annual household income.[10] The baseline model was defined as race/ethnicity plus age. The influence of each covariable on racial/ethnic disparities was initially tested in a baseline model: race/ethnicity plus age plus covariable one by one. We ranked the covariables in order of their significance of influence on racial/ethnic disparities (how much the HR decreased when included in the model). We then added the covariables to the baseline model in a sequence of multivariable models, in the order of their significance of influence. We calculated the change in HR as a measure of the proportion of disparity explained by the covariable.[11]

To further understand the association of baseline characteristic differences with outcomes, we conducted several subgroup analyses by income level, stage at diagnosis, and initial treatment modalities. We further presented the distribution of stage at diagnosis, tumor grade, cancer-directed surgery, radiotherapy performance, and annual household income for each diagnostic period. All statistical analyses were performed with R software (version 4.2.0). All reported P values were 2-sided and the level of significance was set at 0.05. This study followed the STROBE reporting guidelines for observational studies.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data and approved the final manuscript for publication.

Results

Cohort information

We included 492,052 men diagnosed with prostate cancer in the covering registries. The racial/ethnic distribution was as follows: white 69.3% (341,016), Black 12.0% (59,087), Hispanic 10.5% (51,614), API 7.7% (37,866), and AI/AN patients 0.5% (2469). The median follow-up time was 8.9 years (interquartile range: 3.6–13.2). Overall, 38.0% (187,022) of the total study population died, including 10.3% (50,837) from prostate cancer and 26.9% (132,131) from causes other than prostate cancer. 4054 patients (0.8%) were present with unknown causes of death; results for these patients were not reported in subsequent analysis. The mean age at diagnosis was 66.9 years (standard deviation [SD] 9.3), with the youngest age at onset in Black patients. There were 91.2% (448,631) of patients diagnosed with localised/regional stages. White patients had the lowest proportion of distant disease (Table 1).

The cumulative incidence of all-cause and cause-specific death during 1995–2019 is presented in Fig. 1 (appendix Supplementary Table S2). The 5-year cumulative incidence of death from prostate cancer was 5.9%, followed by CVD at 3.9% (Table 2, Fig. 2A). With the extension of follow-up, the 10-year cumulative incidence of CVD death (8.5%) approached the estimates of death from prostate cancer (9.8%) (Fig. 2B, appendix Supplementary Table S3). AI/AN patients had the highest 5-year cumulative incidence of death from all causes, with estimates of 22.1%, followed by Black patients (17.1%), white patients (14.9%), API patients (14.9%), and Hispanic patients (14.7%). Between 1995 and 2019, there were decreasing trends in the cumulative risk of death across five racial/ethnic groups (Table 2).

At each time period, the cumulative incidence of all-cause death was highest among AI/AN patients, followed by Black patients (Table 2, Supplementary Figs. S1 and S2). Between Black and white patients, the absolute disparity for the 5-year cumulative incidence of all-cause death in 1995–1999 was 3.9% and it decreased to 2.1% in 2010–2014. However, the absolute disparity in all-cause death between AI/AN and white patients of increased substantially (from 4.4% in 1995–1999 to 10.9% in 2010–2014). For Hispanic-white comparisons, we found the absolute disparity in death from prostate cancer was slightly widening (from 0.8% in 1995–1999 to 1.1% in 2010–2014) (Table 3).

	Overall	white	Black	Hispanic	API	AI/AN
	(N = 492,052)	(N = 341,016)	(N = 59,087)	(N = 51,614)	(N = 37,866)	(N = 2469)
Median follow-up (years) (IQR)	8.9 (3.6, 13.2)	9.1 (3.8, 13.5)	8.2 (3.1, 12.3)	8.2 (3.0, 12.4)	8.3 (3.2, 12.5)	7.8 (2.8, 11.6)
Diagnostic year						
1995–1999	89,348 (18.2)	66,187 (19.4)	9530 (16.1)	7496 (14.5)	5781 (15.3)	354 (14.3)
2000–2004	101,942 (20.7)	72,753 (21.3)	11,052 (18.7)	10,007 (19.4)	7669 (20.3)	461 (18.7)
2005–2009	108,777 (22.1)	75,284 (22.1)	13,053 (22.1)	11,450 (22.2)	8428 (22.3)	562 (22.8)
2010–2014	94,840 (19.3)	63,174 (18.5)	12,220 (20.7)	11,289 (21.9)	7634 (20.2)	523 (21.2)
2015–2019	97,145 (19.7)	63,618 (18.7)	13,232 (22.4)	11,372 (22.0)	8354 (22.0)	569 (23.0)
Vital status, n (%)						
Alive	305,030 (62.0)	208,440 (61.1)	37,038 (62.7)	34,130 (66.1)	24,015 (63.4)	1407 (57.0)
Dead from prostate cancer	50,837 (10.3)	34,823 (10.2)	6921 (11.7)	5389 (10.4)	3340 (8.8)	364 (14.7)
Dead from causes other than prostate cancer	132,131 (26.9)	96,012 (28.2)	14,740 (25.0)	11,090 (21.5)	9606 (25.4)	684 (27.7)
CVD	51,701 (10.5)	37,278 (10.9)	6054 (10.2)	4269 (8.3)	3865 (10.2)	235 (9.5)
Other cancers	25,036 (5.1)	18,064 (5.3)	2815 (4.8)	2136 (4.1)	1916 (5.1)	105 (4.3)
COPD	4114 (0.8)	2476 (0.7)	684 (1.2)	617 (1.2)	306 (0.8)	31 (1.3)
Diabetes	8051 (1.6)	6139 (1.8)	854 (1.4)	543 (1.1)	471 (1.2)	44 (1.8)
Other specific causes	43,229 (8.8)	32,055 (9.4)	4333 (7.3)	3524 (6.8)	3048 (8.0)	269 (10.9)
Dead with unknown causes	4054 (0.8)	1741 (0.5)	388 (0.7)	1006 (1.9)	905 (2.4)	14 (0.6)
Age at diagnosis (years), n (%)						
Mean (SD)	66.88 (9.3)	67.22 (9.3)	63.80 (9.2)	66.48 (9.3)	69.21 (9.0)	66.67 (9.3)
<55	45,359 (9.2)	28,690 (8.4)	9284 (15.7)	5166 (10.0)	1989 (5.3)	230 (9.3)
55–64	152,933 (31.1)	104,317 (30.6)	22,403 (37.9)	16,095 (31.2)	9313 (24.6)	805 (32.6)
65–74	190,648 (38.7)	133,597 (39.2)	20,025 (33.9)	20,263 (39.3)	15,808 (41.7)	955 (38.7)
75+	103,112 (21.0)	74,412 (21.8)	7375 (12.5)	10,090 (19.5)	10,756 (28.4)	479 (19.4)
Stage, n (%)						
Localised/regional	448,631 (91.2)	315,040 (92.4)	52,816 (89.4)	44,798 (86.8)	33,866 (89.4)	2111 (85.5)
Distant	25,133 (5.1)	15,607 (4.6)	3756 (6.4)	3215 (6.2)	2320 (6.1)	235 (9.5)
Unknown	18,288 (3.7)	10,369 (3.0)	2515 (4.3)	3601 (7.0)	1680 (4.4)	123 (5.0)
Tumor grade, n (%)						
Well	45,654 (9.3)	31,241 (9.2)	5298 (9.0)	5609 (10.9)	3244 (8.6)	262 (10.6)
Moderate	248,150 (50.4)	176,144 (51.7)	29,211 (49.4)	25,045 (48.5)	16,670 (44.0)	1080 (43.7)
Poorly	177,537 (36.1)	120,113 (35.2)	21,718 (36.8)	18,395 (35.6)	16,415 (43.4)	896 (36.3)
Undifferentiated	994 (0.2)	679 (0.2)	133 (0.2)	105 (0.2)	74 (0.2)	3 (0.1)
Unknown	19,717 (4.0)	12,839 (3.8)	2727 (4.6)	2460 (4.8)	1463 (3.9)	228 (9.2)
Surgery, n (%)						
Yes	193,930 (39.4)	139,563 (40.9)	19,405 (32.8)	20,813 (40.3)	13,302 (35.1)	847 (34.3)
No	292,298 (59.4)	197,946 (58.0)	38,965 (65.9)	30,101 (58.3)	23,704 (62.6)	1582 (64.1)
Unknown	5824 (1.2)	3507 (1.0)	717 (1.2)	700 (1.4)	860 (2.3)	40 (1.6)
Radiotherapy, n (%)						
Yes	160,115 (32.5)	110,599 (32.4)	20,728 (35.1)	14,139 (27.4)	13,912 (36.7)	737 (29.9)
No/unknown	331,937 (67.5)	230,417 (67.6)	38,359 (64.9)	37,475 (72.6)	23,954 (63.3)	1732 (70.1)
Surgery/radiotherapy, n (%)						
Yes	339,565 (69.0)	240,119 (70.4)	38,627 (65.4)	33,455 (64.8)	25,857 (68.3)	1507 (61.0)
No/unknown	152,487 (31.0)	100,897 (29.6)	20,460 (34.6)	18,159 (35.2)	12,009 (31.7)	962 (39.0)
Median household income, n (%)						
<$59999	70,143 (14.3)	56,220 (16.5)	5281 (8.9)	7238 (14.0)	466 (1.2)	938 (38.0)
$60000–$74999	233,864 (47.5)	152,108 (44.6)	35,766 (60.5)	32,081 (62.2)	13,295 (35.1)	614 (24.9)
$75000+	187,778 (38.2)	132,503 (38.9)	18,031 (30.5)	12,226 (23.7)	24,103 (63.7)	915 (37.1)
Unknown	267 (0.1)	185 (0.1)	9 (0.0)	69 (0.1)	2 (0.0)	2 (0.1)

API = Asian or Pacific Islander; AI/AN = American Indian/Alaska Native; IQR = interquartile range; SD = standard deviation; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease.

Table 1: **Characteristics of the study population.**

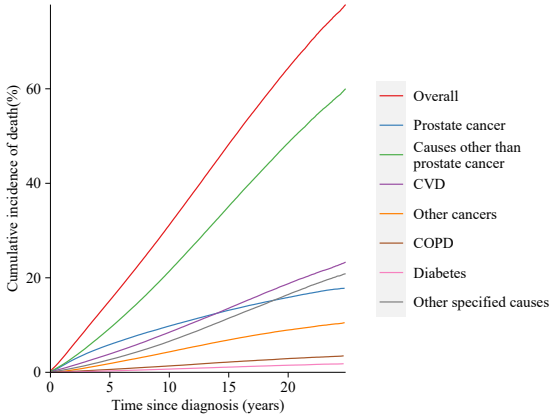

Fig. 1: Cumulative incidence of all-cause and cause-specific death in patients with prostate cancer. Abbreviations: CVD = cardiovascular disease. COPD = chronic obstructive pulmonary disease.

For relative disparities, AI/AN and Black patients consistently had the highest risk of death between 1995 and 2019, with adjusted HR of 1.48 (1.40–1.58) and 1.40 (1.38–1.42), respectively. Furthermore, both the crude and the adjusted HRs for all-cause death, death from causes other than prostate cancer, and death from CVD in Black patients increased from 1995–1999 to 2015–2019 (appendix Supplementary Table S4, Table 3). Similarly, we found the adjusted HR of AI/AN-white disparities for all-cause mortality increased from 1.32 (1.17–1.49) in 1995–1999 to 1.95 (1.53–2.49) in 2015–2019, indicating a widening disparity. In addition, we observed a widening relative disparity between AI/AN and white patients both in outcomes of death from prostate cancer and death from causes other than prostate cancer. However, in comparisons between Hispanic and white patients, the relative disparities only increased in death from prostate cancer.

Given that stage at diagnosis, tumor grade, receipt of cancer-directed surgery, receipt of radiotherapy, and household income were associated with the risk of death from all causes or specific causes (appendix Supplementary Table S5), we further quantified the relative contributions of these factors to racial/ethnic disparities between white patients and Black and AI/AN patients, for all-cause and cause-specific mortality (Table 4). The stage at diagnosis had the largest effect on Black-white and AI/AN-white disparities in prostate cancer-specific death, which explained 35% and 39% of disparities. Household income explained 21% of AI/AN disparities in CVD death. Initial treatment contributed to both Black-white and AI/AN-white disparities in death from prostate cancer and other causes. Adjustment for all covariables explained 24% of the Black-white disparities and 33% of the AI/AN-white disparities in all-cause death.

Since stage at diagnosis, tumor grade, initial treatment modalities, and annual household income were related to racial/ethnic disparities, we further presented the distribution of these factors by race/ethnicity and diagnostic period (appendix Supplementary Figs. S3–S8). Among all races/ethnicities, AI/AN patients consistently had the highest proportion of metastatic disease, whereas Hispanic and Black patients presented with a lower household income. Table 5 lists the adjusted HRs for death in patients with prostate cancer according to the stage at diagnosis, initial treatment, and household income. The adjusted HRs for Black-white and AI/AN-white disparities were higher in patients with localised/regional disease than in those with distant disease. By income level, we found the relative Black-white and AI/AN-white disparities still existed across different income categories.

Discussion

To our knowledge, this study is the first to compare trends in all-cause and cause-specific death among white, Black, Hispanic, API, and AI/AN patients with prostate cancer in the US over 25 years. These data provide the most comprehensive, and longest-running trend of racial/ethnic disparities in the cause of death among patients with prostate cancer in the US. We identified the perpetuation of poorer outcomes in patients with prostate cancer, particularly among Black and AI/AN patients as compared to white patients. We further demonstrated that the stage at diagnosis, initial treatment, and household income as significantly modifiable contributors to racial/ethnic disparities. Our study may provide important scientific evidence to address racial/ethnic inequalities in prostate cancer and promote health equity.

Previous studies had uncovered racial/ethnic inequalities of death in patients with prostate cancer.[3,12,13] Similarly, we found AI/AN and Black patients had worse all-cause and cause-specific death than the white patients. For the first time to our knowledge, we found that the benefits of a gradual decline in all-cause mortality among patients with prostate cancer have not been equitably benefited by all races/ethnicities, resulting in increasingly severe inequalities between AI/AN and white patients. In particular, larger reductions in all-cause mortality in white than in AI/AN patients between 1995 and 2019, resulted in widening AI/AN-white disparities both on an absolute scale and relative scale. With regard to Black-white disparities, we found Black patients experienced a larger decline in the absolute rate of all-cause mortality during 1995–2019 compared to white patients, resulting in a narrowing of absolute disparities, but a slight increase in relative disparities. These findings underscore the methodological importance of reporting both absolute and relative measures of disparities to provide a clear picture of health disparity change across races/ethnicities.[14,15] To be noted, even though the absolute Black-white disparities

	5-year cumulative incidence of death (95%CI), %						
	Overall	Prostate cancer	Causes other than prostate cancer	CVD	Other cancers	COPD	Diabetes
All patients							
1995–2014	15.2 (15.2–15.2)	5.9 (5.9–5.9)	9.3 (9.3–9.3)	3.9 (3.9–3.9)	1.9 (1.9–1.9)	0.3 (0.3–0.3)	0.6 (0.6–0.6)
1995–1999	19.8 (19.8–19.8)	7.0 (7.0–7.0)	12.7 (12.7–12.7)	6.2 (6.2–6.2)	2.3 (2.3–2.3)	0.4 (0.4–0.4)	0.9 (0.9–0.9)
2000–2004	16.1 (16.1–16.1)	5.5 (5.5–5.5)	10.5 (10.5–10.5)	4.5 (4.5–4.5)	2.1 (2.1–2.1)	0.3 (0.3–0.3)	0.7 (0.7–0.7)
2005–2009	13.4 (13.4–13.4)	5.0 (5.0–5.0)	8.4 (8.4–8.4)	3.2 (3.2–3.2)	1.8 (1.8–1.8)	0.3 (0.3–0.3)	0.5 (0.5–0.5)
2010–2014	12.6 (12.6–12.6)	5.6 (5.6–5.6)	7.0 (7.0–7.0)	2.6 (2.6–2.6)	1.5 (1.5–1.5)	0.2 (0.2–0.2)	0.4 (0.4–0.4)
Absolute change (%)[a]	−7.2	−1.4	−5.7	−3.6	−0.8	−0.2	−0.5
white							
1995–2014	14.9 (14.9–14.9)	5.6 (5.6–5.6)	9.4 (9.4–9.4)	3.9 (3.9–3.9)	1.9 (1.9–1.9)	0.2 (0.2–0.2)	0.6 (0.6–0.6)
1995–1999	19.3 (19.3–19.3)	6.7 (6.7–6.7)	12.6 (12.6–12.6)	6.1 (6.1–6.1)	2.2 (2.2–2.2)	0.3 (0.3–0.3)	0.9 (0.9–0.9)
2000–2004	15.7 (15.7–15.7)	5.2 (5.2–5.2)	10.4 (10.4–10.4)	4.5 (4.5–4.5)	2.1 (2.1–2.1)	0.3 (0.3–0.3)	0.7 (0.7–0.7)
2005–2009	13.0 (13.0–13.0)	4.7 (4.7–4.7)	8.3 (8.3–8.3)	3.1 (3.1–3.1)	1.8 (1.8–1.8)	0.2 (0.2–0.2)	0.6 (0.6–0.6)
2010–2014	12.3 (12.3–12.3)	5.3 (5.3–5.3)	7.0 (7.0–7.0)	2.6 (2.6–2.6)	1.5 (1.5–1.5)	0.2 (0.2–0.2)	0.4 (0.4–0.4)
Absolute change (%)[a]	−7.0	−1.4	−5.6	−3.5	−0.7	−0.1	−0.5
Black							
1995–2014	17.1 (17.1–17.1)	7.1 (7.1–7.1)	10.1 (10.1–10.1)	4.3 (4.3–4.3)	2.0 (2.0–2.0)	0.4 (0.4–0.4)	0.6 (0.6–0.6)
1995–1999	23.2 (23.2–23.2)	9.1 (9.1–9.1)	14.1 (14.1–14.1)	6.8 (6.8–6.8)	2.6 (2.6–2.6)	0.6 (0.6–0.6)	0.9 (0.9–0.9)
2000–2004	18.4 (18.4–18.4)	6.9 (6.9–6.9)	11.6 (11.6–11.6)	5.1 (5.1–5.1)	2.3 (2.3–2.3)	0.5 (0.5–0.5)	0.7 (0.7–0.7)
2005–2009	15.2 (15.2–15.2)	6.0 (6.0–6.0)	9.2 (9.2–9.2)	3.7 (3.7–3.7)	2.0 (2.0–2.0)	0.4 (0.4–0.4)	0.5 (0.5–0.5)
2010–2014	14.5 (14.5–14.5)	6.6 (6.6–6.6)	7.9 (7.9–7.9)	3.1 (3.1–3.1)	1.4 (1.4–1.4)	0.3 (0.3–0.3)	0.5 (0.5–0.5)
Absolute change (%)[a]	−8.7	−2.5	−6.2	−3.7	−1.2	−0.3	−0.4
Hispanic							
1995–2014	14.7 (14.7–14.7)	6.6 (6.6–6.6)	8.1 (8.1–8.1)	3.3 (3.3–3.3)	1.6 (1.6–1.6)	0.5 (0.5–0.5)	0.4 (0.4–0.4)
1995–1999	19.4 (19.4–19.4)	7.5 (7.5–7.5)	11.8 (11.8–11.8)	5.9 (5.9–5.9)	1.9 (1.9–1.9)	0.7 (0.7–0.7)	0.6 (0.6–0.6)
2000–2004	15.5 (15.5–15.6)	6.2 (6.2–6.2)	9.4 (9.4–9.4)	3.8 (3.8–3.8)	1.8 (1.8–1.8)	0.6 (0.6–0.6)	0.5 (0.5–0.5)
2005–2009	13.2 (13.2–13.2)	5.8 (5.8–5.8)	7.3 (7.3–7.4)	2.8 (2.8–2.8)	1.5 (1.5–1.5)	0.4 (0.4–0.4)	0.3 (0.3–0.3)
2010–2014	12.3 (12.3–12.3)	6.4 (6.4–6.4)	6.0 (6.0–6.0)	2.0 (2.0–2.0)	1.5 (1.5–1.5)	0.3 (0.3–0.3)	0.2 (0.2–0.2)
Absolute change (%)[a]	−7.1	−1.1	−5.8	−3.9	−0.4	−0.4	−0.4
API							
1995–2014	14.9 (14.9–14.9)	5.4 (5.4–5.4)	9.5 (9.5–9.5)	4.0 (4.0–4.0)	2.1 (2.1–2.1)	0.3 (0.3–0.3)	0.6 (0.6–0.6)
1995–1999	19.8 (19.8–19.8)	6.5 (6.5–6.5)	13.3 (13.3–13.3)	7.0 (7.0–7.0)	2.4 (2.4–2.4)	0.3 (0.3–0.3)	0.9 (0.9–0.9)
2000–2004	16.9 (16.9–16.9)	5.3 (5.3–5.3)	11.6 (11.6–11.6)	5.1 (5.1–5.1)	2.3 (2.3–2.3)	0.4 (0.4–0.4)	0.7 (0.7–0.7)
2005–2009	13.4 (13.4–13.4)	4.6 (4.6–4.6)	8.8 (8.8–8.8)	3.3 (3.3–3.3)	2.1 (2.1–2.1)	0.4 (0.4–0.4)	0.4 (0.4–0.4)
2010–2014	11.5 (11.5–11.5)	4.8 (4.8–4.8)	6.7 (6.7–6.7)	2.3 (2.3–2.3)	1.6 (1.6–1.6)	0.4 (0.4–0.4)	0.5 (0.5–0.5)
Absolute change (%)[a]	−8.3	−1.7	−6.6	−4.7	−0.8	0.1	−0.4
AI/AN							
1995–2014	22.1 (22.1–22.1)	9.7 (9.7–9.7)	12.4 (12.4–12.4)	4.4 (4.4–4.4)	1.9 (1.9–1.9)	0.5 (0.5–0.5)	0.9 (0.9–0.9)
1995–1999	23.7 (23.6–23.8)	9.7 (9.7–9.8)	14.0 (13.9–14.1)	6.0 (6.0–6.0)	1.7 (1.7–1.7)	0.6 (0.6–0.6)	1.1 (1.1–1.1)
2000–2004	19.8 (19.7–19.8)	8.7 (8.6–8.7)	11.1 (11.1–11.2)	4.9 (4.9–4.9)	1.3 (1.3–1.3)	0.4 (0.4–0.4)	1.3 (1.3–1.3)
2005–2009	20.7 (20.6–20.8)	7.6 (7.6–7.6)	13.1 (13.0–13.1)	4.4 (4.3–4.4)	2.7 (2.7–2.7)	0.4 (0.4–0.4)	1.1 (1.1–1.1)
2010–2014	23.2 (23.1–23.3)	12.3 (12.2–12.3)	10.9 (10.9–11.0)	4.1 (4.1–4.1)	2.0 (1.9–2.0)	0.2 (0.2–0.2)	0.2 (0.2–0.2)
Absolute change (%)[a]	−0.5	2.6	−3.1	−1.9	0.3	−0.4	−0.9

CI = confidence interval; API = Asian or Pacific Islander; AI/AN = American Indian/Alaska Native; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease. [a]The absolute changes for the 5-year cumulative incidence of death were calculated between the period 1995–1999 and the period 2010–2014 (the most recent data for such data available).

Table 2: **5-year cumulative incidence of all-cause and cause-specific death in patients with prostate cancer overall, by race/ethnicity and diagnostic period, 1995–2019.**

in patients with prostate cancer decreased over the study period, much remains to be done. Black patients still had a 1.4-fold increased risk of all-cause death compared with white patients with prostate cancer during 2015–2019, the most recent years for which such data are available.

It is noteworthy that a significant number of patients with prostate cancer died of noncancer causes.[16] Measures of racial/ethnic disparities in all-cause death may mask substantial disparities in death from some specific causes. For example, though we observed similar 5-year cumulative incidence of all-cause death between

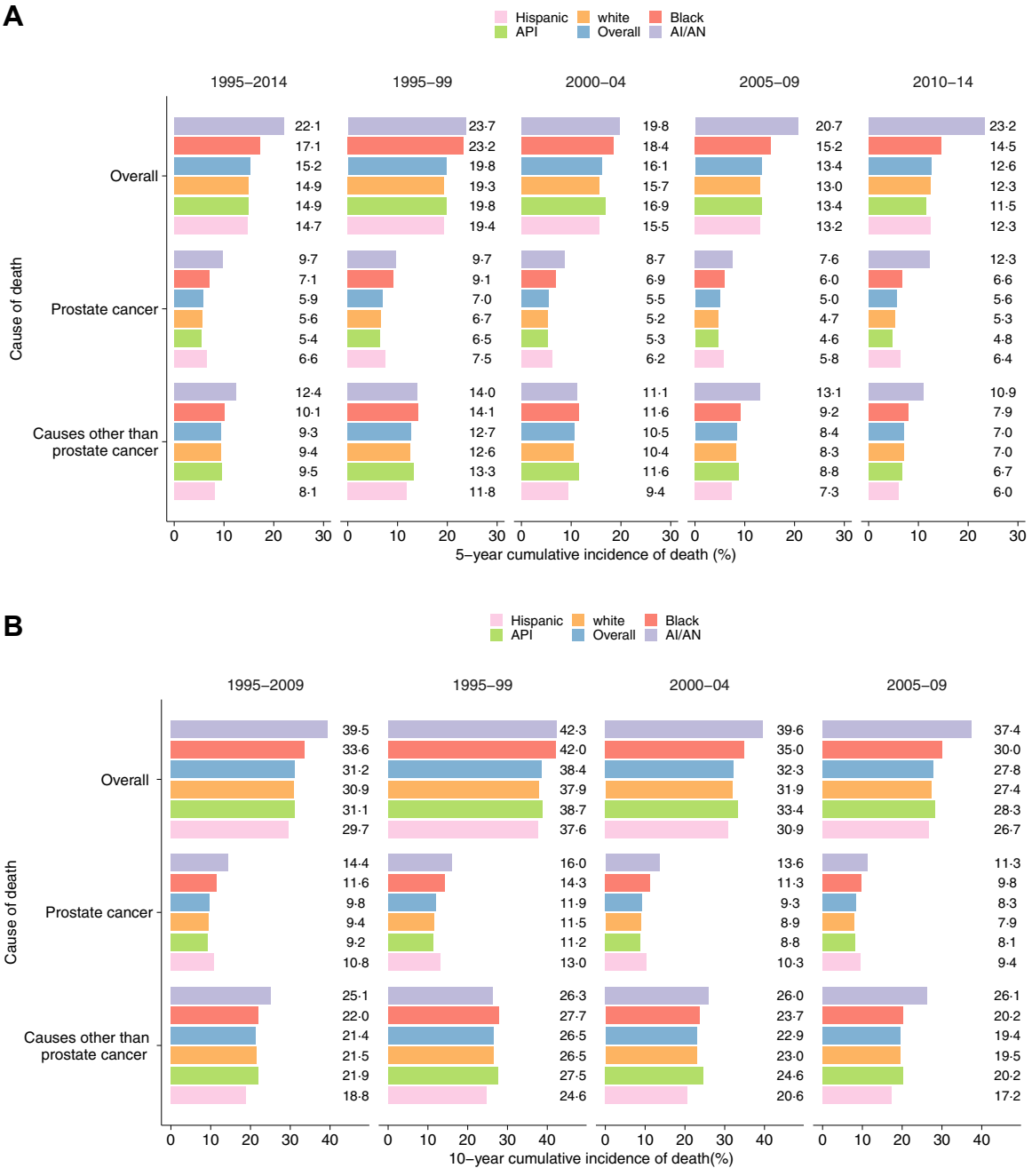

Fig. 2: 5-year and 10-year cumulative incidence of all-cause and cause-specific death in patients with prostate cancer overall, and by race/ethnicity and diagnostic period. (A) 5-year cumulative incidence of all-cause and cause-specific death and (B) 10-year cumulative incidence of all-cause and cause-specific death. Abbreviations: API = Asian or Pacific Islander. AI/AN = American Indian/Alaska Native. CVD = cardiovascular disease. COPD = chronic obstructive pulmonary disease.

Hispanic and white patients, for the first time, we identified widening Hispanic-white disparities of prostate-cancer-specific death both in absolute and relative terms. Disentangling the racial/ethnic disparities by cause of death may also provide more precise information which may further mitigate the gaps. We especially observed widening disparities in death both from prostate cancer and from other causes in AI/AN patients. This finding means anticancer efforts cannot be made in isolation and need to consider other

	Overall[a]		Prostate cancer[a]		Causes other than prostate cancer[a]		CVD[a]	
	Hazard ratio (95%CI)	Absolute disparity (%)[b]	Hazard ratio (95%CI)	Absolute disparity (%)[b]	Hazard ratio (95%CI)	Absolute disparity (%)[b]	Hazard ratio (95%CI)	Absolute disparity (%)[b]
Black vs white								
1995–2019	1.40 (1.38–1.42)	2.18	1.54 (1.50–1.58)	1.49	1.34 (1.32–1.36)	0.70	1.46 (1.42–1.50)	0.42
1995–1999	1.36 (1.32–1.39)	3.91	1.54 (1.47–1.61)	2.41	1.29 (1.25–1.33)	1.51	1.38 (1.32–1.44)	0.71
2000–2004	1.40 (1.37–1.44)	2.78	1.58 (1.50–1.66)	1.62	1.35 (1.30–1.39)	1.17	1.50 (1.42–1.57)	0.62
2005–2009	1.43 (1.39–1.47)	2.13	1.52 (1.44–1.61)	1.23	1.39 (1.34–1.44)	0.89	1.56 (1.47–1.66)	0.58
2010–2014	1.51 (1.44–1.57)	2.11	1.57 (1.47–1.68)	1.30	1.47 (1.39–1.55)	0.80	1.67 (1.53–1.83)	0.54
2015–2019	1.43 (1.33–1.54)		1.45 (1.32–1.60)		1.41 (1.27–1.57)		1.64 (1.38–1.94)	
P for trend[c]	<0.0001		0.52		<0.0001		<0.0001	
Hispanic vs white								
1995–2019	0.98 (0.96–1.00)	−0.28	1.18 (1.15–1.21)	0.98	0.90 (0.89–0.92)	−1.25	0.90 (0.87–0.93)	−0.60
1995–1999	1.01 (0.98–1.04)	0.06	1.17 (1.11–1.24)	0.83	0.95 (0.92–0.99)	−0.76	0.96 (0.91–1.01)	−0.18
2000–2004	0.98 (0.95–1.01)	−0.11	1.17 (1.11–1.24)	0.94	0.92 (0.89–0.95)	−1.05	0.94 (0.89–1.00)	−0.67
2005–2009	0.96 (0.93–0.99)	0.13	1.19 (1.12–1.26)	1.09	0.88 (0.84–0.91)	−0.97	0.98 (0.85–1.14)	−0.30
2010–2014	0.99 (0.94–1.04)	−0.01	1.20 (1.12–1.29)	1.08	0.86 (0.81–0.92)	−1.09	0.78 (0.70–0.88)	−0.64
2015–2019	1.17 (1.08–1.27)		1.29 (1.16–1.43)		1.04 (0.92–1.18)		1.17 (0.97–1.42)	
P for trend[c]	0.20		0.025		0.013		0.060	
API vs white								
1995–2019	0.85 (0.83–0.86)	−0.01	0.84 (0.81–0.87)	−0.18	0.85 (0.83–0.87)	0.18	0.86 (0.83–0.89)	0.13
1995–1999	0.88 (0.85–0.91)	0.52	0.87 (0.81–0.93)	−0.18	0.88 (0.85–0.91)	0.71	0.92 (0.87–0.97)	0.98
2000–2004	0.86 (0.83–0.89)	1.20	0.84 (0.78–0.90)	0.03	0.87 (0.84–0.90)	1.17	0.88 (0.83–0.94)	0.69
2005–2009	0.85 (0.82–0.89)	0.36	0.87 (0.80–0.94)	−0.09	0.85 (0.81–0.89)	0.44	0.85 (0.79–0.91)	0.23
2010–2014	0.81 (0.76–0.85)	−0.83	0.81 (0.73–0.89)	−0.49	0.81 (0.75–0.87)	−0.34	0.78 (0.69–0.88)	−0.31
2015–2019	0.90 (0.82–0.98)		0.90 (0.80–1.02)		0.89 (0.78–1.02)		0.85 (0.68–1.07)	
P for trend[c]	0.42		0.18		0.15		0.019	
AI/AN vs white								
1995–2019	1.48 (1.40–1.58)	7.14	1.78 (1.60–1.97)	4.12	1.37 (1.27–1.48)	3.03	1.22 (1.08–1.39)	0.49
1995–1999	1.32 (1.17–1.49)	4.41	1.58 (1.27–1.96)	3.01	1.23 (1.07–1.42)	1.41	1.15 (0.92–1.45)	−0.06
2000–2004	1.46 (1.30–1.64)	4.12	1.81 (1.46–2.23)	3.43	1.34 (1.17–1.55)	0.69	1.39 (1.11–1.74)	0.44
2005–2009	1.59 (1.41–1.80)	7.65	1.66 (1.32–2.09)	2.89	1.57 (1.36–1.82)	4.76	1.26 (0.95–1.65)	1.25
2010–2014	1.71 (1.46–2.00)	10.86	2.19 (1.75–2.75)	6.97	1.41 (1.13–1.76)	3.88	1.43 (0.99–2.07)	1.50
2015–2019	1.95 (1.53–2.49)		1.79 (1.27–2.52)		2.15 (1.53–3.01)		0.86 (0.36–2.08)	
P for trend[c]	<0.0001		0.041		0.0059		0.70	

CI = confidence interval; API = Asian or Pacific Islander; AI/AN = American Indian/Alaska Native; CVD = cardiovascular disease. [a]All cause-specific Cox regression models were adjusted for age as a categorical variable (<55, 55–64, 65–74, 75+ years). [b]The absolute disparities for the 5-year cumulative incidence of death were calculated using white patients as the reference category. [c]P for trend values were calculated by the interaction term between race/ethnicity and diagnostic period in regression models.

Table 3: **Adjusted hazard ratios (HR) and absolute disparities for all-cause and cause specific death in Black, Hispanic, API, and AI/AN patients with prostate cancer compared with White patients with prostate cancer in the US, 1995–2019.**

comorbidities/disorders. Cancer health equality cannot be achieved without significant efforts to control CVD, diabetes, and other diseases across all races/ethnicities.[17]

Disparities in early detection of cancer can lead to increased cancer diagnoses at advanced stage when cancer is harder to treat and thus substantially contributes to the disproportionate burden of death in racial/ethnic minorities.[18,19] A previous study found that the stage at diagnosis had the largest effect in explaining Black-white cancer-specific survival disparities of prostate cancer. Another study also reported AI/AN men had the highest proportion of distant-stage disease, contributing to 31% higher prostate cancer mortality among AI/AN men than among white men.[1] Similarly, we found the stage at diagnosis had the largest effect on Black-white and AI/AN-white disparities in death from prostate cancer, which explained 35% and 39% of disparities. Stage is itself influenced by a myriad of factors, which include socioeconomic status, cancer awareness, health insurance, uptake of prostate specific antigen (PSA) screening, access to health care, cultural attitudes towards screening, healthcare provider biases, and biological factors.[20] Lower PSA screening prevalence among AI/AN men and Black men than among white men likely contributes to the lower proportion of

All causes			Prostate cancer			Causes other than prostate cancer			CVD		
Covariable	Hazard ratios (95% CI)	Contribution, %	Covariable	Hazard ratios (95% CI)	Contribution, %	Covariable	Hazard ratios (95% CI)	Contribution, %	Covariable	Hazard ratios (95% CI)	Contribution, %
Black vs white											
Baseline[a]	1.37 (1.35–1.39)		Baseline[a]	1.48 (1.44–1.52)		Baseline[a]	1.33 (1.31–1.36)		Baseline[a]	1.45 (1.41–1.49)	
Stage at diagnosis	1.32 (1.30–1.34)	14	Stage at diagnosis	1.31 (1.28–1.35)	35	Initial treatment	1.30 (1.27–1.32)	9	Initial treatment	1.40 (1.36–1.45)	9
Initial treatment	1.29 (1.27–1.31)	8	Initial treatment	1.27 (1.23–1.31)	8	Stage at diagnosis	1.29 (1.27–1.32)	3	Stage at diagnosis	1.40 (1.36–1.44)	0
Grade	1.28 (1.26–1.30)	3	Grade	1.24 (1.21–1.28)	6	Grade	1.29 (1.27–1.31)	0	Grade	1.40 (1.36–1.44)	0
Income	1.28 (1.26–1.30)	0	Income	1.24 (1.21–1.28)	0	income	1.29 (1.27–1.31)	0	Income	1.40 (1.36–1.44)	0
All adjustments		24	All adjustments		50	All adjustments		12	All adjustments		9
AI/AN vs white											
Baseline[a]	1.43 (1.34–1.53)		Baseline[a]	1.62 (1.43–1.83)		Baseline[a]	1.33 (1.31–1.36)		Baseline[a]	1.24 (1.08–1.42)	
Stage at diagnosis	1.37 (1.28–1.46)	14	Stage at diagnosis	1.38 (1.22–1.56)	39	Income	1.32 (1.22–1.43)	11	Income	1.19 (1.03–1.36)	21
Income	1.33 (1.24–1.42)	9	Initial treatment	1.35 (1.20–1.52)	5	Initial treatment	1.30 (1.20–1.41)	6	Initial treatment	1.17 (1.02–1.34)	8
Initial treatment	1.31 (1.22–1.40)	5	Grade	1.33 (1.17–1.50)	3	Stage at diagnosis	1.30 (1.20–1.40)	0	Stage at diagnosis	1.16 (1.01–1.33)	4
Grade	1.29 (1.21–1.38)	5	Income	1.29 (1.15–1.46)	7	Grade	1.29 (1.19–1.40)	3	Grade	1.16 (1.01–1.33)	0
All adjustments		33	All adjustments		53	All adjustments		19	All adjustments		33

CI = confidence interval; AI/AN = American Indian/Alaska Native; CVD = cardiovascular disease. [a]The baseline model is adjusted for age as a categorical variable (<55, 55–64, 65–74, 75+ years).

Table 4: **Percentage contribution of covariables to overall Black-white and AI/AN-white disparities in all-cause and cause-specific death 1995–2019.**

localised disease diagnosis, which subsequently contributes to racial/ethnic disparities in death among patients with prostate cancer.[21,22] In 2012, the US Preventive Services Taskforce (USPSTF) recommended against screening for prostate cancer in men of all ages. In 2018, USPSTF recommended PSA screening for ages 55–69 based on a share-decision making.[23] The magnitude of the impact of changes in screening recommendation differed across racial/ethnic groups, with the steepest decline of PSA screening in AI/AN, followed by Black, white, Hispanic, and API men during 2012–2018.[22] The heterogeneity of its impact by race/ethnicity was likely associated with the changing trends of racial/ethnic disparities in death among patients with prostate cancer.[24] As an example, we observed a fast rise in prostate cancer-specific death during 2010–2014 after changes in screening recommendations, which exacerbated the AI/AN-white disparities in patients with prostate cancer. Given that men with metastasized disease had similar mortality risks among race/ethnicity, and effective and curable treatment options are still lacking for metastatic prostate cancer, therefore, closing gaps in PSA screening, early detection, and follow-up care is of key importance in addressing racial/ethnic disparities in patients with prostate cancer.

Racial/ethnic minorities continue to experience more frequent and higher severity of multiple barriers to quality cancer care including treatment delays, lack of access to guideline-concordant treatment, and implicit bias.[25] Definitive treatment with radical prostatectomy or radiation improves high-risk prostate cancer survival, especially in those without metastasis.[26] In our study, we persistently found racial/ethnic minorities experienced a lower proportion of qualitative cancer treatment uptake, which may at least partly contribute to disparities between white patients and Black and AI/AN patients. Similarly, Kratzer et al. found that lower treatment access contributed to AI/AN men having an 86% 5-year relative survival rate for regional-stage disease, which approaches 100% among white.[27] Several recent studies have also shown that in the situation with equitable access to standard treatment, racial/ethnic disparities in outcomes of prostate cancer can be eliminated.[5,28,29] Therefore, providing all people with the quality medical care that they need will help to improve health equity.

Evidence has shown that structural racism is a root cause of racial health inequities.[25] Structural racism refers to the totality of ways in which societies foster racial discrimination, through mutually reinforcing inequitable systems (education, employment, income, health care, and so on) that in turn reinforce discriminatory beliefs, values, and distribution of resources, which together affect the risk of adverse health outcomes and perpetuate racial group inequity.[30] American Cancer Society recently published a framework for understanding and addressing social determinants to advance

	Hazard ratio (95%CI)			
	Overall[a]	Prostate cancer[a]	Causes other than prostate cancer[a]	CVD[a]
Black vs white				
Stage at diagnosis				
Localised/regional	1.34 (1.31–1.37)	1.42 (1.37–1.48)	1.31 (1.28–1.34)	1.45 (1.40–1.50)
Distant	1.08 (1.03–1.12)	1.05 (1.00–1.10)	1.19 (1.09–1.31)	1.18 (1.03–1.35)
Initial treatment				
Surgery/radiotherapy	1.34 (1.31–1.36)	1.43 (1.37–1.48)	1.31 (1.28–1.34)	1.44 (1.39–1.50)
No/unknown	1.33 (1.30–1.36)	1.42 (1.37–1.47)	1.28 (1.25–1.32)	1.37 (1.31–1.43)
Median household income				
<$59999	1.33 (1.26–1.40)	1.41 (1.29–1.55)	1.28 (1.20–1.37)	1.33 (1.19–1.48)
$60000–$74999	1.42 (1.39–1.44)	1.60 (1.54–1.65)	1.35 (1.32–1.38)	1.48 (1.43–1.54)
$75000+	1.40 (1.37–1.44)	1.51 (1.44–1.58)	1.36 (1.32–1.40)	1.44 (1.37–1.52)
Hispanic vs white				
Stage at diagnosis				
Localised/regional	0.97 (0.95–0.99)	1.13 (1.09–1.18)	0.91 (0.89–0.94)	0.91 (0.88–0.95)
Distant	0.94 (0.90–0.99)	0.96 (0.91–1.01)	0.87 (0.78–0.96)	0.87 (0.74–1.02)
Initial treatment				
Surgery/radiotherapy	0.97 (0.95–0.99)	1.13 (1.09–1.18)	0.92 (0.89–0.94)	0.91 (0.88–0.95)
No/unknown	0.93 (0.91–0.96)	1.10 (1.06–1.15)	0.84 (0.82–0.87)	0.83 (0.79–0.87)
Median household income				
<$59999	1.04 (1.00–1.08)	1.20 (1.12–1.29)	0.97 (0.93–1.02)	0.89 (0.82–0.96)
$60000–$74999	0.95 (0.93–0.97)	1.17 (1.13–1.22)	0.87 (0.85–0.89)	0.91 (0.87–0.94)
$75000+	0.97 (0.94–1.00)	1.15 (1.08–1.22)	0.90 (0.87–0.94)	0.82 (0.77–0.88)
API vs white				
Stage at diagnosis				
Localised/regional	0.83 (0.81–0.85)	0.79 (0.75–0.83)	0.84 (0.81–0.86)	0.86 (0.83–0.90)
Distant	0.75 (0.71–0.79)	0.71 (0.67–0.76)	0.85 (0.77–0.95)	0.92 (0.79–1.06)
Initial treatment				
Surgery/radiotherapy	0.83 (0.81–0.85)	0.79 (0.75–0.83)	0.84 (0.82–0.87)	0.87 (0.83–0.91)
No/unknown	0.90 (0.87–0.92)	0.91 (0.87–0.96)	0.88 (0.85–0.92)	0.86 (0.82–0.91)
Median household income				
<$59999	0.77 (0.64–0.94)	1.14 (0.85–1.51)	0.61 (0.47–0.79)	0.59 (0.39–0.91)
$60000–$74999	0.84 (0.81–0.86)	0.88 (0.83–0.94)	0.82 (0.79–0.85)	0.84 (0.80–0.89)
$75000+	0.90 (0.88–0.92)	0.87 (0.83–0.91)	0.91 (0.89–0.94)	0.92 (0.88–0.96)
AI/AN vs white				
Stage at diagnosis				
Localised/regional	1.45 (1.34–1.58)	1.69 (1.45–1.98)	1.38 (1.25–1.51)	1.31 (1.11–1.54)
Distant	1.09 (0.94–1.27)	1.01 (0.85–1.21)	1.43 (1.06–1.92)	1.05 (0.63–1.75)
Initial treatment				
Surgery/radiotherapy	1.46 (1.35–1.59)	1.70 (1.45–1.98)	1.39 (1.26–1.53)	1.33 (1.13–1.57)
No/unknown	1.37 (1.25–1.51)	1.60 (1.39–1.84)	1.26 (1.11–1.42)	1.01 (0.82–1.25)
Median household income				
<$59999	1.46 (1.33–1.60)	2.00 (1.73–2.32)	1.24 (1.10–1.40)	1.08 (0.88–1.33)
$60000–$74999	1.30 (1.14–1.49)	1.30 (1.01–1.68)	1.30 (1.11–1.53)	1.30 (1.01–1.67)
$75000+	1.50 (1.35–1.66)	1.58 (1.30–1.91)	1.47 (1.29–1.66)	1.29 (1.04–1.60)

CI = confidence interval; API = Asian or Pacific Islander; AI/AN = American Indian/Alaska Native; CVD = cardiovascular disease. [a]All cause-specific Cox regression models were adjusted for age as a categorical variable (<55, 55–64, 65–74, 75+ years).

Table 5: **Adjusted hazard ratios (HRs) for all-cause and cause-specific death among Black, Hispanic, API, and AI/AN compared with white patients by stage at diagnosis, initial treatment, and median household income, 1995–2019.**

cancer health equity. And it also showed that health-related disparities stem from social-structural factors.[31] Especially, Black and AI/AN populations living in rural areas, experience greater poverty, have lower educational attainment, and lack access to quality care, which adversely impacts personal lifestyle factors,

screening, diagnosis, treatment, and survivorship.[32,33] Similarly, we found Black and AI/AN patients with prostate cancer consistently had lower household income, lower attainment of education, and lack of standardised treatment than white patients in our study. We did not find that area-level income made a significant difference in disparities between Black and white patients. It may well be that area-level income alone does not pick up all of the socioeconomic-related issues at the individual level. However, we still observed contextual, area-level effects of income on AI/AN-white disparities. Taken together, it is undeniable that a long history of structural racism and other social and institutional injustice have contributed to the adverse social determinant of health, which in turn perpetuates cancer disparities in racial/ethnic minorities. Our findings highlight the urgent need to address the structural, intersectional, and internalised barriers faced by these minorities over such a long period of time.

Prostate cancer health disparities are a complex and multifaced problem. The observation that Black men are more likely to develop prostate cancer at a younger age, and their tumours are more likely to progress to a metastatic state suggest that biological determinant may at least play a part in racial/ethnic disparities. Though we cannot rule out biologic differences in explaining some of the racial/ethnic disparities, a genetic predisposition for prostate cancer is not deterministic for poorer cancer outcomes. Studies have found that adhering to a healthy lifestyle was associated with a decreased rate of lethal prostate cancer among men at increased genetic risk for prostate cancer risk.[34,35] The modifiable lifestyle risk factors include smoking, alcohol consumption, diet, and limited physical activity, and are often shaped by a person's socioeconomic status as well as the social environment. It is noteworthy that these modifiable risk factors also contribute to other chronic diseases, such as CVD and diabetes. Notably, the influences of environmental, dietary, and social influences affect races/ethnicities differently. Therefore, evidence-based and population-specific intervention strategies that remove adverse behavioural, environmental and social risks which are preventable may provide effective approaches for improving outcomes and health equity in patients with prostate cancer.

The analysis covered more than two decades and preceded the COVID-19 pandemic. All kinds of health inequalities have been especially apparent during the COVID-19 pandemic, which has disproportionately affected racial/ethnic minorities owing to the underlying social, structural, and environmental factors.[36,37] Although the impact of the COVID-19 pandemic on prostate cancer is unknown, based on the current situation, it is therefore likely that the adverse impact of COVID-19 may further exacerbate the racial/ethnic disparities in patients with prostate cancer.

Our study has several strengths. First, our study was the first one, to our knowledge, to quantify trends of racial/ethnic disparities in the all-cause and cause-specific death among white, Black, Hispanic, API, and AI/AN patients with prostate cancer in the US over time. The cohort we used in our study had diverse races/ethnicities with a follow-up of up to 25 years, which allows us to capture a more comprehensive picture of the relationship between races/ethnicities and prostate cancer outcomes. We used both absolute and relative measures to quantify trends and the magnitude of racial/ethnic disparities. Our in-depth analyses provide a clear picture to monitor racial/ethnic disparity trends by using the most updated data within the US. Second, we quantified the contributors that drive the racial/ethnic disparities, which provide strong evidence that disparities can be eliminated through modifiable factors such as stage at diagnosis and qualitative treatment access, and interventions should be an important public health imperative in prostate cancer survivors. For example, given that Black men are at increased risk of developing the disease at a younger age, and more likely than others to be presented with advanced stage at diagnosis, our findings should motivate considering more intensive screening among Black men than others. It is important that people consult with their health care providers to develop a personalised prostate cancer screening plan that considers their risk of developing prostate cancer and their tolerance for the potential harms of PSA screening, especially for Black and AI/AN populations.

Our study has some limitations. First, we were unable to obtain socioeconomic data at the individual level such as insurance status, household income, and attainment of education, which limited us to further exploring socioeconomic factors that influence racial/ethnic disparities. Second, confounders such as biological factors, lifestyle factors, comorbid conditions, and more specific treatment regimens may partially explain the racial/ethnic disparities. However, these detailed data were not available. Therefore, a large proportion of disparities remained unexplained. We were not able to estimate the relative contribution of biological factors. Third, we did not explore the temporal differences in each racial/ethnic group regarding the characteristics of PSA screening uptake, which would be an important factor in explaining the racial/ethnic disparities. Fourth, potential misclassification of the cause of death, and race/ethnicity by population-based cancer registries cannot be ruled out. However, we did not include patients with unknown causes of death to minimise this misclassification. Fifth, we only quantified racial/ethnic disparities in prostate cancer outcomes in the US. Prostate cancer is a global disease with rising epidemiological significance.[2] Characterising a global outlook of the magnitude of the association between race/ethnicity and prostate cancer outcomes is needed. And this study

is an important step for future studies to understand the effect of race/ethnicity on prostate cancer outcomes globally.

In conclusion, population-level racial/ethnic disparities in prostate cancer outcomes are a major and persistent public health challenge in the US. The worse outcomes of prostate cancer in underserved racial/ethnic groups over time highlight the urgent need for multifaceted interventions to reduce racial/ethnic inequalities.

Contributors

HZ, HP, and ELG contributed to the conception and design of the study. MX, TS, YX, and XR did the literature search and construction of tables and figures. MX, XR, HZ, and TS verified the underlying data. HZ, ELG, and HP contributed to the administration and supervision. HZ, MX, and YX drafted the paper. HZ, YX, SN, JM, YW, LL, XQY, CMA, JSJ, XY, KC-Q, YL, TW, BL, and ELG interpreted the results. CX contributed to the methodology. All authors contributed to data interpretation and rewriting of the paper. All authors reviewed and approved the final version. All authors had full access to all the data. The corresponding authors were responsible for the decision to submit the manuscript.

Data sharing statement

All supporting data were obtained from the SEER database. The study group welcomes potential collaboration to maximise the use of data. Data extraction rules, the detailed protocol, and the R program are available upon reasonable request to the corresponding author of Hongmei Zeng (hongmeizeng@cicams.ac.cn).

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102138.

References

1 Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7–33.
2 Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN Estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249.
3 Islami F, Guerra CE, Minihan A, et al. American cancer society's report on the status of cancer disparities in the United States, 2021. *CA Cancer J Clin*. 2022;72(2):112–143.
4 Weiner AB, Li EV, Desai AS, Press DJ, Schaeffer EM. Cause of death during prostate cancer survivorship: a contemporary, US population-based analysis. *Cancer*. 2021;127(16):2895–2904.
5 Dess RT, Hartman HE, Mahal BA, et al. Association of black race with prostate cancer-specific and other-cause mortality. *JAMA Oncol*. 2019;5(7):975–983.
6 Lee C, Light A, Alaa A, Thurtle D, van der Schaar M, Gnanapragasam VJ. Application of a novel machine learning framework for predicting non-metastatic prostate cancer-specific mortality in men using the Surveillance, Epidemiology, and End Results (SEER) database. *Lancet Digit Health*. 2021;3(3):e158–e165.
7 Surveillance, Epidemiology, and End results (SEER) program. Instructions for Coding Grade for 2014. https://seer.cancer.gov/tools/grade/. Accessed April 10, 2022.
8 Latouche A, Allignol A, Beyersmann J, Labopin M, Fine JP. A competing risks analysis should report results on all cause-specific hazards and cumulative incidence functions. *J Clin Epidemiol*. 2013;66(6):648–653.
9 Ellis L, Canchola AJ, Spiegel D, Ladabaum U, Haile R, Gomez SL. Racial and ethnic disparities in cancer survival: the contribution of tumor, sociodemographic, institutional, and neighborhood characteristics. *J Clin Oncol*. 2018;36(1):25–33.
10 de Glas NA, Kiderlen M, Vandenbroucke JP, et al. Performing survival analyses in the presence of competing risks: a clinical example in older breast cancer patients. *J Natl Cancer Inst*. 2016;108(5):djv366.
11 Yu XQ, Goldsbury D, Yap S, Yap ML, O'Connell DL. Contributions of prognostic factors to socioeconomic disparities in cancer survival: protocol for analysis of a cohort with linked data. *BMJ Open*. 2019;9(8):e030248.
12 Aizer AA, Wilhite TJ, Chen MH, et al. Lack of reduction in racial disparities in cancer-specific mortality over a 20-year period. *Cancer*. 2014;120(10):1532–1539.
13 Siegel DA, O'Neil ME, Richards TB, Dowling NF, Weir HK. Prostate cancer incidence and survival, by stage and race/ethnicity - United States, 2001-2017. *MMWR Morb Mortal Wkly Rep*. 2020;69(41):1473–1480.
14 Harper S, Lynch J, Meersman SC, Breen N, Davis WW, Reichman ME. An overview of methods for monitoring social disparities in cancer with an example using trends in lung cancer incidence by area-socioeconomic position and race-ethnicity, 1992-2004. *Am J Epidemiol*. 2008;167(8):889–899.
15 Harper S, Lynch J. *Methods for measuring cancer disparities: using data relevant to healthy people 2010 cancer-related objectives*. Bethesda: National Cancer Institute (NCI); 2005.
16 Cho H, Mariotto AB, Mann BS, Klabunde CN, Feuer EJ. Assessing non-cancer-related health status of US cancer patients: other-cause survival and comorbidity prevalence. *Am J Epidemiol*. 2013;178(3):339–349.
17 Paller CJ, Wang L, Brawley OW. Racial inequality in prostate cancer outcomes-socioeconomics, not biology. *JAMA Oncol*. 2019;5(7):983–984.
18 Williams PA, Zaidi SK, Sengupta R. AACR cancer disparities progress report 2022. *Cancer Epidemiol Biomarkers Prev*. 2022;31(7):1249–1250.
19 Deuker M, Knipper S, Pecoraro A, et al. Prostate cancer characteristics and cancer-specific mortality of Native American patients. *Prostate Cancer Prostatic Dis*. 2020;23(2):277–285.
20 Riviere P, Kalavacherla S, Banegas MP, et al. Patient perspectives of prostate cancer screening vary by race following 2018 guideline changes. *Cancer*. 2023;129(1):82–88.
21 Wenzel M, Wurnschimmel C, Nocera L, et al. The effect of race/ethnicity on cancer-specific mortality after salvage radical prostatectomy. *Front Oncol*. 2022;12:874945.
22 Kensler KH, Pernar CH, Mahal BA, et al. Racial and ethnic variation in PSA testing and prostate cancer incidence following the 2012 USPSTF recommendation. *J Natl Cancer Inst*. 2021;113(6):719–726.
23 Fenton JJ, Weyrich MS, Durbin S, Liu Y, Bang H, Melnikow J. Prostate-specific antigen-based screening for prostate cancer: evidence report and systematic review for the US preventive services task force. *JAMA*. 2018;319(18):1914–1931.
24 Hall WJ, Chapman MV, Lee KM, et al. Implicit racial/ethnic bias among health care professionals and its Influence on health care outcomes: a systematic review. *Am J Public Health*. 2015;105(12):e60–e76.
25 Phelan JC, Link BG, Tehranifar P. Social conditions as fundamental causes of health inequalities: theory, evidence, and policy implications. *J Health Soc Behav*. 2010;51(Suppl):S28–S40.
26 Schaeffer E, Srinivas S, Antonarakis ES, et al. NCCN guidelines insights: prostate cancer, version 1.2021. *J Natl Compr Canc Netw*. 2021;19(2):134–143.
27 Kratzer TB, Jemal A, Miller KD, et al. Cancer statistics for American Indian and Alaska Native individuals, 2022: including increasing disparities in early onset colorectal cancer. *CA Cancer J Clin*. 2022;73:120–146.

28 McNamara MA, George DJ, Ramaswamy K, et al. Overall survival by race in chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) patients treated with abiraterone acetate or enzalutamide. *J Clin Oncol*. 2019;37(7_suppl):212.
29 Spratt DE, Chen YW, Mahal BA, et al. Individual patient data analysis of randomized clinical trials: impact of Black race on castration-resistant prostate cancer outcomes. *Eur Urol Focus*. 2016;2(5):532–539.
30 Krieger N. Theories for social epidemiology in the 21st century: an ecosocial perspective. *Int J Epidemiol*. 2001;30(4):668–677.
31 Alcaraz KI, Wiedt TL, Daniels EC, Yabroff KR, Guerra CE, Wender RC. Understanding and addressing social determinants to advance cancer health equity in the United States: a blueprint for practice, research, and policy. *CA Cancer J Clin*. 2020;70(1):31–46.
32 Oake JD, Harasemiw O, Tangri N, et al. The association between income status and treatment selection for prostate cancer in a universal health care system: a population-based analysis. *J Urol*. 2021;206(5):1204–1211.
33 Wang DS, Jani AB, Tai CG, et al. Severe lack of comprehension of common prostate health terms among low-income inner-city men. *Cancer*. 2013;119(17):3204–3211.
34 Loeb S, Peskoe SB, Joshu CE, et al. Do environmental factors modify the genetic risk of prostate cancer? *Cancer Epidemiol Biomarkers Prev*. 2015;24(1):213–220.
35 Plym A, Zhang Y, Stopsack KH, et al. A healthy lifestyle in men at increased genetic risk for prostate cancer. *Eur Urol*. 2023;83(4):343–351.
36 Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet*. 2020;395(10241):1907–1918.
37 Rossen LM, Ahmad FB, Anderson RN, et al. Disparities in excess mortality associated with COVID-19 - United States, 2020. *MMWR Morb Mortal Wkly Rep*. 2021;70(33):1114–1119.