Single black men have the worst prognosis with localized prostate cancer

Sijun Liu, MD,[1,2] Zongwei Wang, PhD,[1] Xingbo Long, MD,[3] Aaron Fleishman, PhD,[1] Xiangchun Huang, BC,[4] Qingguang Wu, BC,[2] Boris Gershman, MD,[1] Aria F. Olumi MD[1]

[1]Division of Urologic Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA
[2]School of Pharmaceutical Sciences, Guangzhou University of Chinese Medicine, Guangzhou, PR China
[3]Department of Urology, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, PR China
[4]The Fourth People's Hospital of Yiyang, Hunan, PR China

LIU S, WANG Z, LONG X, FLEISHMAN A, HUANG X, WU Q, GERSHMAN B, OLUMI AF. Single black men have the worst prognosis with localized prostate cancer. *Can J Urol* 2022;29(1): 10992-11002.

Introduction: *To determine whether marital status combined with race serve as prognostic factors for survival in localized prostate cancer.*

Materials and methods: *Patients with localized prostate cancer were retrospectively extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Chi-square test was used to investigate the association between marital status combined with race and other variables. Gray's test was used to compare the cumulative incidence function of different variables. Multivariable analysis was conducted to assess prognostic factors after adjusting for other variables.*

Results: *A total of 207,219 patients with localized prostate cancer from the SEER database from 2010 to 2016 were eligible. We found that black or single patients had the highest risk of mortality ($p < 0.001$). When marital status and race were combined, single black patients had the worst prognosis after adjusting for other variables (hazard ratio = 1.93, 95% confidence interval: 1.58-2.35; $p < 0.001$). Married status had a prognostic advantage in all races. In the same marital groups, whites and Asians had lower risk of prostate cancer-specific mortality and other-cause mortality than blacks with married and single status ($p < 0.001$).*

Conclusions: *Marital status and race serve as prognostic factors for localized prostate cancer. Blacks or single individuals had higher risk of mortality when considered independently, and single black patients had the worst prognosis. Furthermore, married status was an advantage in the same race group, and whites and Asians had lower risk than blacks with married and single status. Accordingly, the interaction between race and marital status on prostate cancer prognosis in clinical practice should be assessed carefully.*

Key Words: marital status, race, localized prostate cancer, prognosis

Accepted for publication November 2021

Funding
This work was supported by National Natural Science Foundation of China (No. 81973497, No. 81673619)

Address correspondence to Dr. Aria F. Olumi, Urologic Surgery at Beth Israel Deaconess Medical Center, 330 Brookline Ave, Rabb 440, Boston, MA 02215 USA

Introduction

Prostate cancer is the second most common cancer in men worldwide. Most cases are localized and will be diagnosed in one out of seven men in his lifetime in the United States. One in 39 men will die from the disease.[1] Findings in current literature show that race is an independent prognostic factor for survival in prostate

cancer. Akinyemiju et al revealed that black patients had higher rate ratios of prostate cancer mortality than white patients in the United States.[2] A similar study showed that prostate cancer mortality rate per 100,000 was 17.9 for white men and 38.7 for black men in the United States.[3] Blacks had higher risk of prostate cancer compared with whites, adjusted hazard ratio (HR): 1.86, 95% confidence interval (CI): 1.75-1.98.[2] Black men may be more prone to a more aggressive type of prostate cancer, which could contribute to their later stage diagnosis.[4-7] Many prostate cancer–associated genes are differentially expressed between African-American and Caucasian-American men.[8,9] In contrast, a prior report showed that there was no significant association between race and prostate size after adjusting for either demographic characteristics or demographic and cancer-specific characteristics,[10] and black race was not associated with worse outcomes after radical prostatectomy across Gleason grades when men had equal access to care.[11] These apparent differences might be due to misclassification and statistical adjustment which are not precise enough to mitigate unmeasured confounding factors to find a small absolute difference between race groups.[12]

In addition to race, the possible association between marital status and prostate cancer risk remains controversial. Previous studies found that marital status was strongly associated with improved health and longevity.[13] Further studies indicated that unmarried men had a higher risk of prostate cancer mortality compared with married men. However, Randi et al suggested that marital status was not materially associated with cancer incidence risk.[14] Marital status did not affect the clinical and pathologic characteristics of patients that underwent radical prostatectomy. Furthermore, marital status did not affect biochemical recurrence-free and metastasis-free survival after radical prostatectomy.[15]

No consideration of the interaction between race and marital status may be an important reason for different conclusions from other studies. Several socioeconomic status indicators such as education, employment, income, and marital status were found to be associated with the reduced risk of morbidity and mortality.[16,17] The unequal gain of resources across the racial groups is attributed to a number of social processes such as differential access to the opportunity structure and different distributions of societal and everyday barriers in the daily lives of racial/ethnic groups.[18] A significant interaction was found between race and marital status on self-rated physical health, suggesting a larger association for blacks compared with whites.[19]

In this study we hypothesized that there are interactions between race and marital status and survival among patients with localized prostate cancer. We examined the associations of marital status and race on prostate cancer mortality in SEER, the large nationwide cancer registry using robust statistical methods to adjust for competing risks of death and potential confounding variables.

Materials and methods

Data source

We used the SEER database, which routinely collects information on cancer patients including demographics, primary tumor site, cancer stage, treatment, and follow up information for survival, and collected data on March 15, 2020 (submission of the SEER database; https://seer.cancer.gov/; SEER ID: 10587-Nov2019).

Clinicopathologic characteristics

The following variables were collected from the SEER database: marital status, age at diagnosis, race, diagnosis time, pathologic grade, tumor node metastasis phase, SEER stage, T stage (American Joint Committee on Cancer,), radiation recode, surgery recode, vital status, cause-specific death classification, other cause of death classification, and survival time. In this study, we categorized marital status as divorced/separated (referred to as divorced), married, single/never married (referred to as single), and widowed.[20,21] Patient age was stratified into five groups using a 10-year age interval: < 49, 50-59, 60-69, 70-79, and ≥ 80 years. Patient race was stratified into four groups: white, black, Asian, and other. We removed the other race group in the analysis given small number of patients in this group. Tumor grade was separated into five levels: Grade I (well differentiated), Grade II (moderately differentiated), Grade III (poorly differentiated), Grade IV (undifferentiated), and unknown. T stage was grouped into three categories: T1, T2, and unknown. Surgery recode was represented as yes (radical prostatectomy), no, and other or unknown. Radiation therapy recode was represented as refused, beam radiation, radioactive implants, combination of beam with implants or isotopes, and unknown. Vital status was categorized as alive or dead, and cause-specific death classification was further categorized as dead of other cause and death attributable to localized prostate cancer.

Inclusion criteria

ICD-O-3 (International Classification of Diseases for Oncology, 3rd edition) morphology codes were used

with SEER*Stat software version 8.3.6 to identify prostate cancer in recent 7 years between 2010 and 2016. Time frame of 2010 to 2016 was chosen, in order to focus on the more contemporary cases of prostate cancer management. The inclusion criteria were as follows: (a) known marital status and survival months; (b) localized prostate cancer (cT1-T2 N0 M0); (c) age at diagnosis older than 18 years; (d) cause of death and number of months survived known.

Statistical analyses

Baseline characteristics of patients with different marital status were summarized and compared using chi-square test. We regarded other causes of death as competing events in our analysis of competing risks. Comparison between the cumulative incidences of the groups is checked by Gray's test. Univariable analysis was performed using the cumulative incidence function (CIF) of prostate cancer mortality to show the probability of each event and Gray's test to estimate the difference in the CIF between groups. Multivariable analyses were conducted to estimate the effect of marital status and race independently and synergistically after adjusting for age, grade groups, T-stage rating, surgery and radiation recode, which revealed the HR and exact 95% CI presented with forest plot. Further subgroup analyses were conducted using two-way interaction terms: race and marital status with a composite HR estimated for each relevant level after adjusting for other variables to assess the risk of prostate cancer-specific mortality (PCSM) and other-cause mortality (OCM) more specifically. The p value was two-sided, and $p < 0.05$ was deemed as statistical significance. All statistical analyses were performed using SPSS version 25.0 (SPSS, Inc., USA) and R statistical software (version 3.5.0; https: //www.r-proje ct.org/). The "cmprsk, survival, survminer" R package was used.

Results

Baseline demographic and clinical characteristics

A total of 207,219 eligible patients with localized prostate cancer were extracted from the SEER database in the period from 2010 to 2016, Figure 1. Among them, 18,002 (8.69%) were divorced or separated, 154,401 (74.51%) were married, 26,122 (12.61%) were single/never married, and 8,694 (4.20%) were widowed. As shown in Table 1, baseline characteristics of patients with localized prostate cancer, individual variables and the relation between the variable and marital status were summarized. Using the chi-square test, we found significant differences in demographics and characteristics of patients with localized prostate cancer,

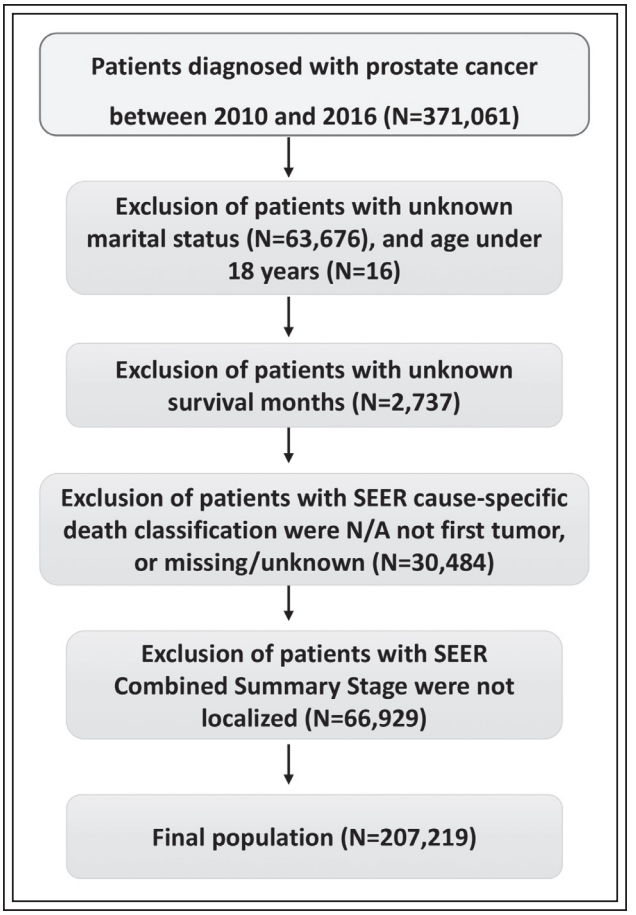

Figure 1. Flow diagram of the study population.

which were observed in all subgroups ($p < 0.001$). With respect to age at diagnosis, patients diagnosed in the age group of 50 to 80 years comprised the majority, the ratio of 49-59 years group was 22.19%, the ratio of 59-69 years group was 43.71%, and the ratio of 69-79 years group was 25.37%. Specifically, compared with other marital status, the proportion of married patients accounted for over 50% in each group. Moreover, the proportion of widowed patients increased in the older population; the 18-49 years group was 0.52%, the 49-59 years group was 1.16%, the 59-69 years group was 2.75%, and the 69-79 years group was 6.60%. After age 80 years, widowed patients had the highest proportion, which accounted for 17.89%. In this respect, marital status changed with age.

Univariable analysis of the prognosis of localized prostate cancer

We regarded other causes of death as competing events in Gray's test analysis. Median follow up for the cohort was 41.18 months. The CIF for all variables

TABLE 1. **Baseline characteristics of patients with localized prostate cancer (n, %)**

Variables	Total	Divorced/ Separated	Married	Single/Never Married	Widowed	p value
Marital status	207219	18002	154401	26122	8694	
	(100.00)	(8.69)	(74.51)	(12.61)	(4.20)	
Age (years)						< 0.001
18-49	5949	476	4184	1258	31	
	(2.87)	(8.00)	(70.33)	(21.15)	(0.52)	
50-59	45975	4448	32901	8093	533	
	(22.19)	(9.67)	(71.56)	(17.60)	(1.16)	
60-69	90569	8696	68193	11192	2488	
	(43.71)	(9.60)	(75.29)	(12.36)	(2.75)	
70-79	52572	3760	40654	4690	3468	
	(25.37)	(7.15)	(77.33)	(8.92)	(6.60)	
≥ 80	12154	622	8469	889	2174	
	(5.87)	(5.12)	(69.68)	(7.31)	(17.89)	
Race						< 0.001
Black	34955	4602	20750	8045	1558	
	(16.87)	(13.17)	(59.36)	(23.02)	(4.46)	
White	158134	12556	122306	16611	6661	
	(76.31)	(7.94)	(77.34)	(10.50)	(4.21)	
Asian	9862	453	8215	863	331	
	(4.76)	(4.59)	(83.3)	(8.75)	(3.36)	
Others/ Unknown	4268	391	3130	603	144	
	(2.06)	(9.16)	(73.34)	(14.13)	(3.37)	
Grade groups						< 0.001
I	30630	2563	22804	4200	1063	
	(14.78)	(8.37)	(74.45)	(13.71)	(3.47)	
II	92535	7894	69650	11647	3344	
	(44.66)	(8.53)	(75.27)	(12.59)	(3.61)	
III	78287	7045	57853	9518	3871	
	(37.78)	(9.00)	(73.90)	(12.16)	(4.94)	
IV	177	22	123	23	9	
	(0.09)	(12.43)	(69.49)	(12.99)	(5.08)	
Unknown	5590	478	3971	734	407	
	(2.70)	(8.55)	(71.04)	(13.13)	(7.28)	
T-stage rating						< 0.001
T1	89287	8541	64215	12027	4504	
	(43.09)	(9.57)	(71.92)	(13.47)	(5.04)	
T2	91122	7213	70356	10410	3143	
	(43.97)	(7.92)	(77.21)	(11.42)	(3.45)	
Unknown	26810	2248	19830	3685	1047	
	(12.94)	(8.38)	(73.96)	(13.74)	(3.91)	
Surgery						< 0.001
Yes	79397	5625	62563	6763	2446	
	(38.32)	(7.09)	(78.80)	(8.52)	(3.08)	
No	125376	12138	90147	16922	6169	
	(60.50)	(9.68)	(71.90)	(13.50)	(4.92)	
Unknown	2446	239	1691	437	79	
	(1.18)	(9.77)	(69.13)	(17.87)	(3.23)	

TABLE 1 (Cont'd). **Baseline characteristics of patients with localized prostate cancer (n, %)**

Variables	Total	Divorced/ Separated	Married	Single/Never Married	Widowed	p value
Radiation record						< 0.001
Refused	1036 (0.50)	100 (9.65)	705 (68.05)	168 (16.22)	63 (6.08)	
Beam	53740 (25.93)	5281 (9.83)	38702 (72.02)	6867 (12.78)	2890 (5.38)	
Combination	7544 (3.64)	629 (8.34)	5760 (76.35)	864 (11.45)	291 (3.86)	
Implants or isotopes	12888 (6.22)	1146 (8.89)	9814 (76.15)	1484 (11.51)	444 (3.45)	
Unknown	132011 (63.71)	10846 (8.22)	99420 (75.31)	16739 (12.68)	5006 (3.79)	

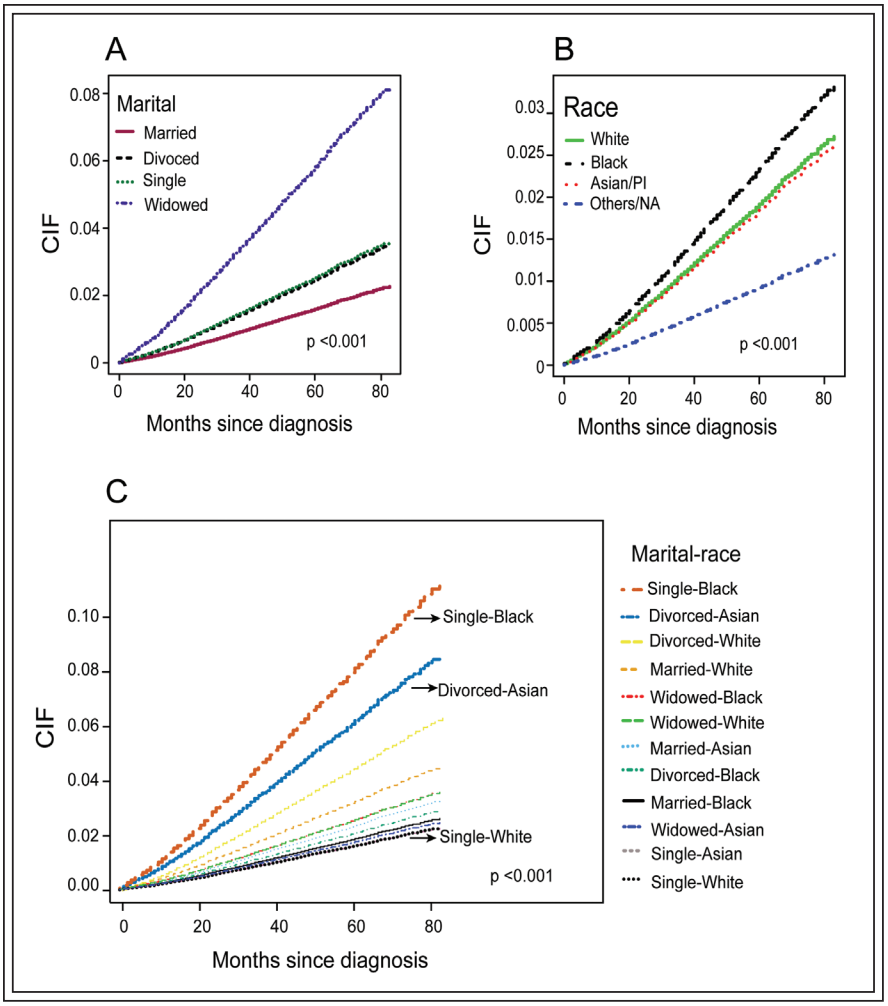

Figure 2. Competing-risk model depicting cumulative incidence function (CIF) of prostate cancer-specific mortality. **(A)** Categorized by marital status; **(B)** Categorized by race; **(C)** Categorized by marital status combined with race.

were analyzed for total of 80 months by 20 months intervals, and increased over 20, 40, 60, and 80 months. During follow up, a total of 2,869 patients died from prostate cancer, while 11,012 died of other causes. The results of Gray's test showed that marital status, race and marital status combined with race had statistically significant effects on localized prostate cancer mortality ($p < 0.001$). Patients who were widowed, black, age ≥ 80 years, with tumor Grade IV and T1 stage, and who refused radiation therapy had higher CIF within the follow up time of 80 months, Table 2. When race and marital status were considered separately widowed or black patients had the highest CIF, Figure 2a and 2b. When marital status and race were combined, single black patients had the highest CIF, Figure 2c, which was 2.2%, 5.1%, 7.9%, and 10.8% in the follow up time at 20, 40, 60, and 80 months, respectively, Table 2. Interestingly, calculating the Cumulative Incidence Function (CIF) of Prostate Cancer Mortality (i.e.: calculated risk of mortality) from 207,219 eligible

TABLE 2. **Univariate analysis using competing risk model**

Variables	Gray's test	p value	Cumulative incidence function of prostate cancer mortality			
			20 months	40 months	60 months	80 months
Marital status	605.924	< 0.001				
Married			0.004	0.010	0.016	0.022
Divorced/separated			0.007	0.016	0.025	0.034
Single/never married			0.007	0.016	0.025	0.035
Widowed			0.016	0.037	0.058	0.080
Race	35.093	< 0.001				
Black			0.005	0.012	0.019	0.026
White			0.006	0.015	0.023	0.032
Asian			0.005	0.012	0.018	0.025
Others/unknown			0.003	0.006	0.009	0.013
Combined marital status and race	659.598	< 0.001				
Married-Black			0.005	0.012	0.018	0.025
Married-White			0.009	0.020	0.032	0.044
Married-Asian			0.006	0.015	0.023	0.032
Divorced-Black			0.006	0.013	0.020	0.028
Divorced-White			0.012	0.029	0.045	0.061
Divorced-Asian			0.017	0.039	0.061	0.083
Single-Black			0.022	0.051	0.079	0.108
Single-White			0.004	0.010	0.016	0.022
Single-Asian			0.004	0.010	0.016	0.022
Widowed-Black			0.007	0.016	0.025	0.035
Widowed-White			0.007	0.016	0.025	0.035
Widowed-Asian			0.005	0.011	0.017	0.024
Age (years)	3651.028	< 0.001				
18-49			0.002	0.004	0.007	0.009
50-59			0.002	0.005	0.007	0.010
60-69			0.003	0.007	0.011	0.016
70-79			0.007	0.017	0.027	0.037
≥ 80			0.029	0.066	0.102	0.139
Grade groups	1450.361	< 0.001				
I			0.002	0.004	0.006	0.008
II			0.002	0.005	0.007	0.010
III			0.009	0.020	0.030	0.041
IV			0.034	0.072	0.109	0.146
Unknown			0.018	0.039	0.059	0.080
T-stage rating	43.058	< 0.001				
T1			0.006	0.014	0.022	0.030
T2			0.005	0.011	0.017	0.024
Unknown			0.005	0.010	0.016	0.023
Surgery	236.081	< 0.001				
Yes			0.003	0.008	0.013	0.018
No			0.007	0.015	0.024	0.033
Unknown			0.006	0.013	0.020	0.028

TABLE 2 (Cont'd). **Univariate analysis using competing risk model**

Variables	Gray's test	p value	Cumulative incidence function of prostate cancer mortality			
			20 months	40 months	60 months	80 months
Radiation record	130.222	< 0.001				
Refused			0.010	0.024	0.037	0.051
Beam			0.006	0.013	0.021	0.029
Combination			0.003	0.007	0.011	0.015
Implants or isotopes			0.002	0.004	0.007	0.010
Unknown			0.006	0.013	0.021	0.029

TABLE 3. **Univariate analysis of combined marital status and race using competing risk model**

Variables	Gray's test	p value	Cumulative incidence function of prostate cancer mortality			
			1 month (30 days)	20 months	40 months	60 months
Combined marital status and race		< 0.001				
Married-Black			0.000	0.003	0.007	0.010
Married-White			0.000	0.006	0.012	0.017
Married-Asian			0.000	0.006	0.011	0.016
Divorced-Black			0.000	0.006	0.011	0.017
Divorced-White			0.001	0.016	0.032	0.046
Divorced-Asian			0.002	0.020	0.039	0.056
Single-Black			0.003	0.040	0.078	0.112
Single-White			0.000	0.003	0.007	0.010
Single-Asian			0.000	0.004	0.009	0.013
Widowed-Black			0.000	0.005	0.010	0.014
Widowed-White			0.000	0.006	0.011	0.017
Widowed-Asian			0.001	0.007	0.013	0.019

patients with localized prostate cancer, we found that amongst surgically treated patients, single black men had the highest CIF in the follow up time at 30 days, 20 months, 40 months and 60 months compared to other groups, Table 3.

Multivariable analysis

When race and marital status were considered separately, the multivariable analysis with Fine-Gray model indicated that black or single patients were associated with a survival disadvantage after adjusting for age, grade groups, T-stage rating, surgery and radiation recode. When race was considered individually, black patients had the highest risk of mortality after adjusting for other variables (HR = 1.283, 95% CI: 1.165-1.414; p < 0.001, Figure 3a). When marital status was considered individually, single patients had the highest risk of mortality after adjusting for other variables (HR = 1.716, 95% CI: 1.542-1.909; p < 0.001, Figure 3a). With combined marital status and race, single black patients had the worst prognosis after adjusting for other variables (HR = 1.929, 95% CI: 1.583-2.35; p < 0.001, Figure 3b).

Subgroup analysis

We conducted further subgroup analysis using two-way interaction terms: race and marital status with a composite HR to estimate each relevant level after adjusting for other variables, Table 4. In the same race group, the results showed that divorced and single patients had higher risk of PCSM and OCM than that of married black patients (p < 0.001). Divorced, single, and widowed patients had higher risk of PCSM and

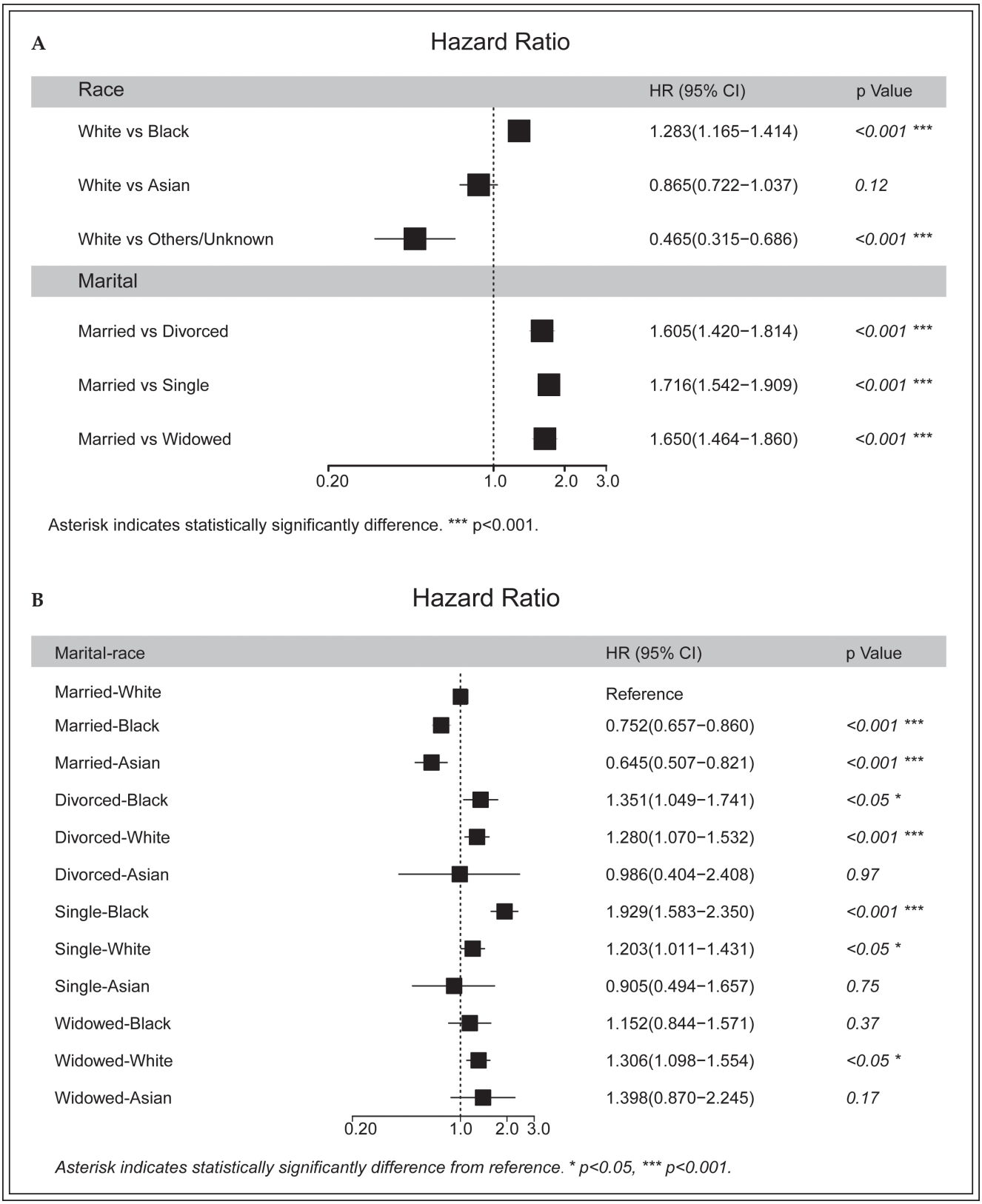

Figure 3. **(A)** Multivariate analysis forest plot when race and marital status were considered separately; **(B)** Multivariable analysis forest plot with combined marital status and race.

TABLE 4. **Subgroup analysis in multivariable competing risks regression model stratified by race and marital status**

Variables	Marital status	Cancer-specific mortality		Other-cause mortality	
		HR (95% CI)	p value	HR (95% CI)	p value
Race group					
Black					
	Married	Ref.		Ref.	
	Divorced	1.367 (1.0632, 1.758)	0.015	1.402 (1.240, 1.585)	0.000
	Single	1.954 (1.6056, 2.379)	0.000	1.573 (1.418, 1.744)	0.000
	Widowed	1.348 (0.979, 1.855)	0.067	1.683 (1.447, 1.957)	0.000
White					
	Married	Ref.		Ref.	
	Divorced	1.782 (1.547, 2.053)	0.000	1.797 (1.674, 1.929)	0.000
	Single	1.667 (1.458, 1.906)	0.000	1.553 (1.448, 1.666)	0.000
	Widowed	1.730 (1.514, 1.977)	0.000	1.642 (1.526, 1.768)	0.000
Asian					
	Married	Ref.		Ref.	
	Divorced	1.53 (0.615, 3.820)	0.360	1.19 (0.689, 2.050)	0.530
	Single	1.43 (0.760, 2.680)	0.270	1.43 (1.020, 2.020)	0.041
	Widowed	2.06 (1.220, 3.460)	0.007	1.33 (0.916, 1.940)	0.130
Marital status					
Married					
	Black	Ref.		Ref.	
	White	0.709 (0.619, 0.811)	0.000	0.673 (0.630, 0.719)	0.000
	Asian	0.608 (0.477, 0.774)	0.000	0.490 (0.431, 0.557)	0.000
Divorced					
	Black	Ref.		Ref.	
	White	0.924 (0.7128, 1.200)	0.550	0.894 (0.786, 1.016)	0.085
	Asian	0.703 (0.2826, 1.750)	0.450	0.431 (0.251, 0.740)	0.002
Single					
	Black	Ref.		Ref.	
	White	0.633 (0.5163, 0.775)	0.000	0.682 (0.612, 0.760)	0.000
	Asian	0.476 (0.2572, 0.882)	0.018	0.472 (0.339, 0.659)	0.000
Widowed					
	Black	Ref.		Ref.	
	White	1.110 (0.824, 1.500)	0.490	0.763 (0.658, 0.885)	0.000
	Asian	1.180 (0.703, 1.990)	0.530	0.496 (0.345, 0.715)	0.000

OCM than that of married white patients ($p < 0.001$), and widowed patients had higher risk of PCSM and OCM than that of married Asian patients ($p < 0.001$). In addition, white and Asian patients in the married or single status had lower risk of PCSM and OCM than that of black patients. ($p < 0.001$).

Discussion

The protective effects of marriage on cancer stage at presentation and survival have been demonstrated across several major cancer sites, including breast, prostate, ovarian, and colon cancers.[22-25] In our study, we found that with marital status and race combined, single black patients had the worst prognosis after adjusting for age, grade groups, T-stage rating, surgery and radiation recode. Many explanations exist for why unmarried status is associated with poorer survival. For instance, the marriage protection theory states that marriage provides a protective health effect through access to a network of personal social relationships, improved socioeconomic status and support, and promotion of healthy lifestyle

and behavioral choices.[26] Potential limitations should be considered although our results show that race and marital status have interacting effects. Marital status is not a static entity, and marriage may dissolve and reform. In our study we showed that the proportion of single patients gradually decreased with increasing age. Secondly, elder patients with localized prostate cancer (≥ 80 years) had higher CIF at the follow up time of 20, 40, 60, and 80 months, respectively, which suggests that age is a prognostic factor for outcomes from localized prostate cancer. Meanwhile, previous studies indicated that older patients were less emotionally affected by the change of marital status, and older widowed men were less affected by bereavement than younger ones.[27] Therefore, a more comprehensive prospective analysis with appropriate psychosocial assessment of emotion and quality of life may help us better understand the effect of marital status on survival in prostate cancer patients.

Previous studies reported that black men in the United States had a higher risk of being diagnosed with and dying from prostate cancer compared with nonblack men.[28] In our study, we found that single black patients have a survival disadvantage and had the highest risk of mortality with Fine-Gray model. Moreover, our subgroup analyses showed that divorced and single black patients have higher risk of PCSM and OCM than married black patients. The genetic diversity between black men and others may at least partly explain the above findings. In African-American men, the increased levels of a specific set of pro-inflammatory molecules in stromal cells of tumor microenvironment may promote the progression of prostate cancer when compared with European-American men.[29] Meanwhile, prior genome-wide studies have identified common molecular subtypes based on gene fusions.[30] Many prostate cancer-associated genes are differentially expressed between African-American and Caucasian-American men.[9,10] In addition to possible genetic variations in different races associated with prostate cancer, social factors can also complement progression of prostate cancer. For example, marital status is associated with household composition and living arrangements, which partially explain why there are observed differences in health status according to marital status. Moreover, marital termination is a potential stressor that changes immunological, hormonal and neural control systems in divorced and widowed individuals.[31]

There are several limitations that should be addressed, and results of this study should be interpreted with caution. First, marital status was checked only once since we could not account for marital history and transitions with SEER database. This is particularly true for elderly patients with localized prostate cancer who may have been married at the time of diagnosis, but widowed or divorced at the time of death. Meanwhile, in SEER database single only means not married, but the patients may have been in a relationship. On the other hand, married status does not assure a relationship with partners who live together. Second, although we adjusted for a multitude of confounding factors, the influence of unmeasured potential confounding factors still cannot be measured, including physical activity, healthy dietary choices, smoking cessation, education, insurance status, and social support. Further studies with long term follow up are needed to examine whether marital transition and marital quality impact mortality in prostate cancer patients. Finally, since our data was extracted from SEER comprising only data on population within the US, our results may not be generalizable for the population outside of the USA.

Conclusions

Marital status and race may serve as important prognostic factors for localized prostate cancer. Married individuals have a survival advantage when diagnosed with localized prostate cancer. Whites and Asians diagnosed with prostate cancer have lower risk of mortality than blacks with married and single status. Most importantly, single black men with localized prostate cancer have the highest risk of mortality. □

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