The impact of marriage on the overall survival of prostate cancer patients: A Surveillance, Epidemiology, and End Results (SEER) analysis

Yu Liu[1*]; Qi Xia[1*]; Jianling Xia[1]; Hua Zhu[2]; Haihong Jiang[3]; Xiangjian Chen[4;]; Yuancai Zheng[3]; Fangyi Zhang[3*]; Shi Li[3*]

[1]Cancer Center, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, Hospital of the University of Electronic Science and Technology of China, Chengdu, Sichuan, China; [2]Department of Obstetrics and Gynecology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China; [3]Department of Urology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China; [4]Department of General Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China

[*]Authors contributed equally to this work.

Acknowledgements: *The authors acknowledge the efforts of the SEER program in the creation of the SEER database. This work was financially supported by the National Natural Science Foundation of China (No. 81702321), and the Scientific and Technological Projects of Wenzhou, China (No. Y20170183).*

Cite as: *Can Urol Assoc J* 2018 October 15; Epub ahead of print. http://dx.doi.org/10.5489/cuaj.5413

Published online October 15, 2018

***

Abstract

Introduction: Marital status has long been associated with positive patient outcomes in several malignances; however, little is known about its influence on prostate cancer. We analyzed data from the Surveillance, Epidemiology, and End Results (SEER) database to evaluate whether married patients with prostate cancer had a better prognosis than the unmarried.

Methods: We identified 824 554 patients diagnosed with prostate cancer between 1973 and 2012 in the SEER database. Using the Cox proportional hazard models, we analyzed the impact of marital status (single, married, divorced/separated, and

widowed) on survival after diagnosis with prostate cancer. Chi-square tests were used to analyze the association between marital status and other variables, and the Kaplan–Meier method was used to estimate survival curves.
Results: Married men were more likely to be diagnosed with a lower Gleason score and undergo surgery than patients in the other groups ($p<0.001$). The married group had a lower risk of mortality caused by prostate cancer than the other groups. The five-year survival rate for married patients was higher than that for patients in the other groups.
Conclusions: Marital status is a prognostic factor for the survival of prostate cancer patients, as being married was associated with better outcomes.

Introduction

Social support is a major protective factor for mental and physical health and mortality, with an effect comparable to that of smoking cessation.[1, 2] Various studies have demonstrated that social interaction is beneficial in alleviating loneliness and promoting self-management of chronic diseases.[3, 4] Marriage is one the most important types of social support, which has a strong effect on various physiological mechanisms.[5] Because of the emotional support and social interaction provided by marriage, married patients are more likely to maintain healthy behaviors, such as having better diets, participating in more physical activities, and receiving more preventive healthcare and more aggressive treatments.[6-8]

Among the cancer patient population, marriage has proved to be a prognostic factor for a variety of cancers, such as colon adenocarcinoma,[9] bladder cancer,[10] breast cancer,[11] lung cancer,[12] and gastric cancer.[13] However, only one study has demonstrated the survival benefits of marriage in prostate cancer patients.[14] One of the reasons why married cancer patients may have better outcomes is that they are more likely to be diagnosed at an earlier stage of the disease and receive more intensive therapies.[15,16] Meanwhile, the benefits of marriage are greater among male cancer patients than among female patients.[17,18] Since prostate cancer is the most common male-specific cancer,[19] it is of interest to investigate the relationship between marital status and prostate cancer. We addressed this issue based on data in the Surveillance, Epidemiology, and End Results (SEER) database from 1973 to 2012. In this study, we focus on a more detailed analysis of prostate cancer, to determine the association of marital status and cancer outcomes, including early-stage diagnosis, possibility of undergoing surgery, and overall survival in patients. Furthermore, we offer new insights into how marriage plays a prominent role through subgroup analysis using the Gleason score.

Methods

Study population

The National Cancer Institute's SEER program contains information on cancer statistics of the U.S. population since 1973. We collected data from the May 3, 2017 submission of the SEER Database (https://seer.cancer.gov/). Prostate cancer cases were identified by the International Classification of Disease for Oncology, Third Edition, (ICD-O-3/WHO2008) code C61.9. All prostate cancer patients who were reported to cancer registries by hospitals were included. Patients with insufficient Gleason score information were excluded from our study. Thus, a total of 824554 patients were evaluated (Fig.1). This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Statistical methods

We obtained information routinely recorded at diagnosis for each patient, including marital status (married, single, divorced/separated, widowed), age (<70 and ≥70), race (white, black, other), Gleason score (≤7, >7), surgery (yes, no), and survival months. Chi-square tests were used to assess the association between two categorical variables. The Kaplan–Meier method was used to estimate 5-year survival rates. The Cox proportional hazard models were used to evaluate the effect of marital status on the risk of death from prostate cancer. The Cox model was adjusted for age, race, marriage, Gleason score, and surgery, and 95% confidence intervals were calculated for each hazard ratio. All statistical analyses were performed using the Stata/SE 12.0 statistical software.

Results

Patient demographics

We identified 824554 prostate cancer patients from the SEER database (Fig.1). In the cohort, 9.4% were single (i.e., never married), 76.8% were married, and 6.8% were widowed. Those separated and divorced were grouped together as the divorced/separated group (7.0%). Patient characteristics are presented in Table 1. The mean age of married men was higher than that of patients in the single and divorced/separated groups ($p<0.0001$). Married men had a median age of 68 years, while the single and divorced/separated groups had a median age of 65 years (Table 1). The widowed group had the oldest age at diagnosis with a median age of 76).

The Gleason score act was a significant biomarker for the prediction of prostate cancer at the pathological stage.[20] We obtained the Gleason score dates from the SEER database and used it in our analysis. Married patients were more likely to be diagnosed at a low-risk stage (Gleason score≤7) than the single, divorced/separated,

and widowed groups ($p<0.0001$). Among married men, 37.1% were diagnosed at a high-risk stage (Gleason score>7), while 40.6% single, 41.3% divorced/separated, and 39.4% widowed patients were diagnosed at a high-risk stage ($p<0.0001$).

Furthermore, a significantly higher proportion of married patients (52.6%) underwent surgery compared with those in the other groups ($p<0.0001$). Surgery was performed on 46.5% of single men, 46.1% of divorced/separated men, and 45.1% of widowed men.

Impact of marital status on overall survival rate

The Kaplan–Meier survival curves are presented in Fig.2. Log-rank tests showed that married patients (the upper most line) had best survival compared with all the other groups ($p<0.001$). The 5-year survival rate was 81.5% for married, 77.9% for single, 77.3% for divorced/separated, and 58.5% for widowed groups. The overall 5-year survival rate for the unmarried group was 71.8% and approximately 6.1 percentage points lower than that of the married group.

In the Cox proportional hazard models, marital status served as a significant predictor of the risk of death from prostate cancer ($p<0.001$). This prognostic effect was independent of age, race, Gleason score, and surgery status ($p<0.01$ for all). Married men had a lower risk of death from prostate cancer than single patients (HR: 0.8736, 95%CI: 0.8632–0.8840). The widowed men were most likely to die because of cancer, with a relative risk of death of 1.4270 (95%CI: 1.4164–1.4377, $p<0.0001$). Increasing age, being black, elevated Gleason score, and no surgery were significantly correlated with a higher risk of death due to prostate cancer ($p<0.0001$ for all).

We have demonstrated that married people were more likely to be diagnosed at a lower Gleason score level. Furthermore, we suspect that marriage had a protective effect on patients with the same Gleason score. To further investigate this, we conducted subgroup analysis within the same Gleason score level. Five-year survival rates for married people were significantly higher than that of all other groups for different Gleason score levels. Among patients with Gleason scores ≤ 7, the 5-year survival rate was 94.5% for married patients, 93.3% for single patients, 92.4% for divorced/ separated patients, and 90.9% for widowed patients (Fig. 3A). Similarly, the 5-year survival rate for married patients in the subgroup with Gleason scores >7 was 81.1%, while it was 76.9% for single, 74.5% for separated/divorced, and 72.2% for widowed patients (Fig. 3B). Meanwhile, we can infer from Fig.3 that married patients were more likely to be diagnosed 3 years older in median age compared with single or divorced/separated patients in prostate cancer. This phenomenon may be explained by two opposing effects: a delay in the onset of the disease or a delay in detection of the disease. We believe that since marriage had a positive protective effect on prostate

cancer patients, diagnosis of the disease in married patients at an older age may result from a later onset of the disease.

Discussion

We identified 824554 cancer patients from the SEER database. In this study, we demonstrated that marriage served as a protective factor for prostate cancer patients. The Kaplan–Meier survival curves showed that married patients had significantly higher 5-year survival rates than single, divorced/separated, and widowed patients. Furthermore, in the Cox proportional hazard models, we observed that marital status served as a significant predictor of risk of death from prostate cancer ($p<0.001$).

Why does marital status result in such favorable outcomes for prostate cancer patients? The benefits can be explained in two points. First, health plays a major role in marital transitions. Men who enjoy robust health are more likely to have a happy marriage.[21] Furthermore, married people who benefit from well-balanced lifestyles and social interactions could obtain a favorable prognosis. Previous studies have observed this outcome in various human malignancies.[9-13] In this study, a higher proportion of married patients underwent surgery compared to other groups. Encouragement from their spouse may enable prostate cancer patients to have a stronger will to live, and they are more likely to receive aggressive and standard treatments. This is also in accordance with previous studies.[6-8] When patients were first diagnosed with prostate cancer, a significant number of married patients were detected at an earlier stage. This suggests that marriage helps men monitor their health and undergo a routine medical checkup.

Although all unmarried groups showed poorer survival expectations compared to the married group, the widowed group showed the poorest prognosis. We believe that this phenomenon demonstrates that marriage provides men with a strong social support system to improve their prognosis after being diagnosed with a malignancy. Single and separated patients are more prepared to establish social relationships other than marriage compared with widowed patients. Depression is widely documented in the widowed population; therefore, the widowed group had the worst prognosis. Previous studies have confirmed that social support is significantly associated with biological processes that may alleviate the harmful effects caused by stress. Stress, especially depressive symptoms, can stimulate tumor progression via immunological and neuroendocrine pathways.[6,7,22] Breast cancer studies showed that married patients had higher levels natural cell activity, while the immune capacity of the unmarried patients was reduced.[23,24] Most single or divorced patients retain or develop an additional source of social support, whereas widowed patients lack this. Our data further emphasized the important protective effects of marriage on prostate cancer prognosis. Meanwhile, it is easy to understand that elderly patients have poor

prognosis. As people age, their healthy immune system gradually declines, and they accumulate more oxidative stress and senescent cells.[25]

Our study has some strengths. We controlled data for the different stages of cancer progression at baseline and divided the patients into two groups according to their Gleason scores. Using this, we observed that marriage exerted a protective effect in these two groups. Furthermore, the protective effect of marriage is more evident in patients with cancer in the initial stage.

However, our study also had some limitations. First, although the SEER database provided abundant and representative data, an obvious limitation is that the data were simple demographics rather than specific control variables. We could not acquire variables such as education, wealth, and social status, which are also significantly associated with prostate cancer prognosis.[26] Furthermore, it is possible that men with good financial conditions and higher social status are more likely to get married. Meanwhile, tobacco use was associated with incidences of highly malignant prostate cancer.[27] In addition, married men are more likely to refuse smoking;[28] therefore, a better survival rate of married patients in our study is a result of multiple factors. Third, information on marital transition since diagnosis is not available in the database. Therefore, the marital status was analyzed as a baseline variate rather than a time-varying covariate.

Despite these potential limitations, we have demonstrated that marriage is significantly associated with better survival outcomes for prostate cancer patients, and could be assessed by clinicians as a predicator of survival in cancer patients. Taken together, our study suggests that, because of the protective role of marriage in prostate cancer patients, additional social and community support should be strengthened in prostate cancer patients, especially in unmarried patients; nevertheless, future research is needed to uncover the underlying causes of the benefits of marriage.

References

1. House JS, Landis KR, Umberson D. Social relationships and health. Science. 1988;241:540-545.
2. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. PLoS medicine. 2010;7:e1000316.
3. Saito T, Kai I, Takizawa A. Effects of a program to prevent social isolation on loneliness, depression, and subjective well-being of older adults: a randomized trial among older migrants in Japan. Archives of gerontology and geriatrics. 2012;55:539-547.
4. Pitkala KH, Routasalo P, Kautiainen H, Sintonen H, Tilvis RS. Effects of socially stimulating group intervention on lonely, older people's cognition: a randomized, controlled trial. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2011;19:654-663.
5. Uchino BN. Social support and health: a review of physiological processes potentially underlying links to disease outcomes. Journal of behavioral medicine. 2006;29:377-387.
6. Manzoli L, Villari P, Pirone GM, Boccia A. Marital status and mortality in the elderly: a systematic review and meta-analysis. Social science & medicine. 2007;64:77-94.
7. Rendall MS, Weden MM, Favreault MM, Waldron H. The protective effect of marriage for survival: a review and update. Demography. 2011;48:481-506.
8. Seeman TE. Health promoting effects of friends and family on health outcomes in older adults. American Journal of Health Promotion. 2000;14:362-370.
9. Liu M, Li L, Yu W, et al. Marriage is a dependent risk factor for mortality of colon adenocarcinoma without a time-varying effect. Oncotarget. 2017;8:20056-20066.
10. Nelles JL, Joseph SA, Konety BR. The impact of marriage on bladder cancer mortality. Urol Oncol. 2009;27:263-267.
11. Osborne C, Ostir GV, Du X, Peek MK, Goodwin JS. The influence of marital status on the stage at diagnosis, treatment, and survival of older women with breast cancer. Breast cancer research and treatment. 2005;93:41-47.
12. Jatoi A, Novotny P, Cassivi S, et al. Does marital status impact survival and quality of life in patients with non-small cell lung cancer? Observations from the mayo clinic lung cancer cohort. The oncologist. 2007;12:1456-1463.
13. Shi RL, Chen Q, Yang Z, et al. Marital status independently predicts gastric cancer survival after surgical resection--an analysis of the SEER database. Oncotarget. 2016;7:13228-13235.
14. Brody S. Marriage and mortality in prostate cancer. The Journal of urology. 1997;158552-158553.
15. Aizer AA, Chen M-H, McCarthy EP, et al. Marital status and survival in patients with cancer. Journal of clinical oncology. 2013;31:3869-3876.
16. Kissane DW. Marriage is as protective as chemotherapy in cancer care.

Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31:3852-3853.
17. Manzoli L, Villari P, G MP, Boccia A. Marital status and mortality in the elderly: a systematic review and meta-analysis. Social science & medicine (1982). 2007;64:77-94.
18. Rendall MS, Weden MM, Favreault MM, Waldron H. The protective effect of marriage for survival: a review and update. Demography. 2011;48:481-506.
19. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016;66:2712-2789.
20. Partin AW, Kattan MW, Subong ENP, et al. Combination of prostate-specific antigen, clinical stage, and gleason score to predict pathological stage of localized prostate cancer - A multi-institutional update. JAMA-J Am Med Assoc. 1997;277:1445-1451.
21. Fu H, Goldman N. Incorporating health into models of marriage choice: Demographic and sociological perspectives. Journal of Marriage and the Family. 1996:740-758.
22. Spiegel D, Sephton SE, Terr AI, Stites DP. Effects of psychosocial treatment in prolonging cancer survival may be mediated by neuroimmune pathways. Annals of the New York Academy of Sciences. 1998;840:674-83.
23. Levy SM, Herberman RB, Whiteside T, Sanzo K, Lee J, Kirkwood J. Perceived social support and tumor estrogen/progesterone receptor status as predictors of natural killer cell activity in breast cancer patients. Psychosomatic medicine. 1990;52:73-85.
24. Kiecolt-Glaser JK, Fisher LD, Ogrocki P, Stout JC, Speicher CE, Glaser R. Marital quality, marital disruption, and immune function. Psychosomatic medicine. 1987;49:13-34.
25. Hoeijmakers JH. DNA damage, aging, and cancer. New England Journal of Medicine. 2009;361:1475-1485.
26. Brodszky V, Varga P, Gimesi-Orszagh J, et al. Long-term costs and survival of prostate cancer: a population-based study. International urology and nephrology. Int Urol Nephrol. 2017;49:1707-1714.
27. Tang B, Han CT, Gan HL, et al. Smoking increased the risk of prostate cancer with grade group >= 4 and intraductal carcinoma in a prospective biopsy cohort. Prostate. 2017;77:984-989.
28. Tong EK, Gildengorin G, Nguyen T, et al. Smoking prevalence and factors associated with smoking status among Vietnamese in California. Nicotine Tob Res. 2010;12:613-621.

Figures and Tables

Fig, 1. Flow chart of patients' cohort definition.

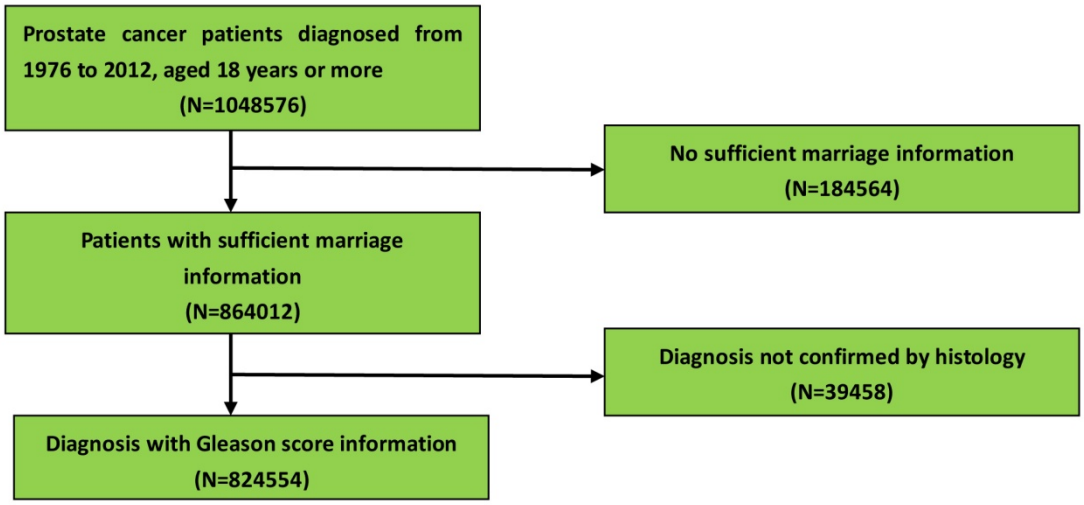

Fig. 2. Kaplan-Meier plots of survival curves by marital status. The five-year survival rate was 81.5% for married, 77.9% for single, 77.3% for divorced/separated, and 58.5% for widowed groups.

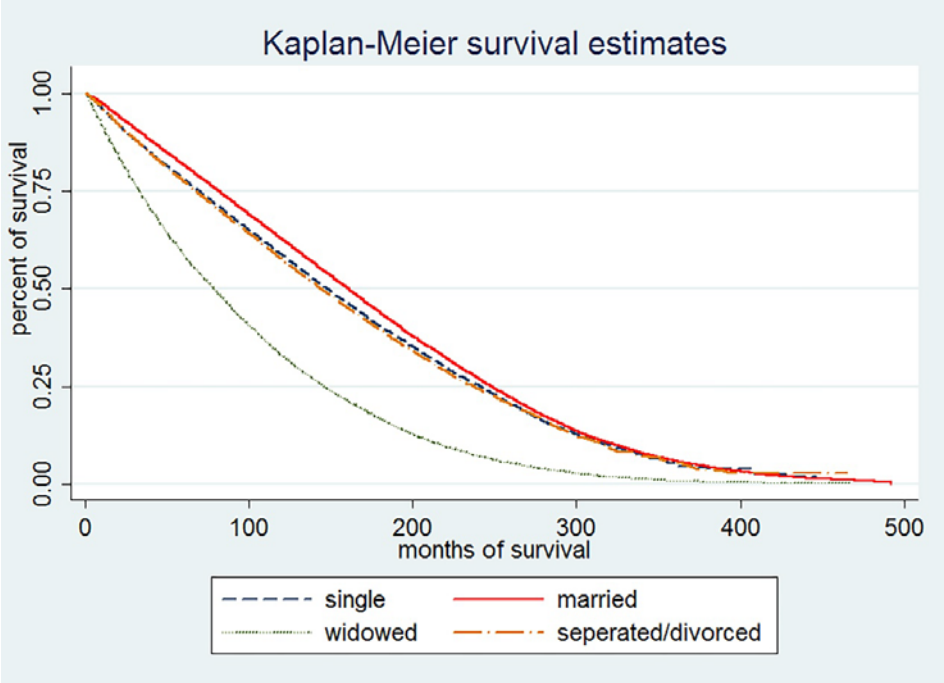

Fig. 3. Median age at diagnosis and five-year survival rates by Gleason score and marital status. ***(A)*** Five-year survival rate and median age among patients with Gleason scores ≤7; ***(B)*** five-year survival rate and median age among patients with Gleason scores >7.

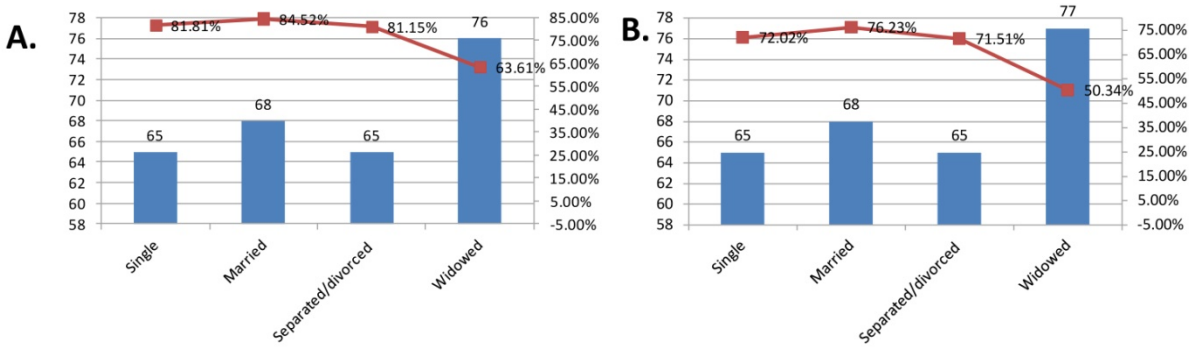

Table 1. Baseline characteristics of the prostate cancer patients according to marital status (n=824 554)

Variable	Single	Married	Divorced/ separated	Widowed	p
Total	77 831	633 175	57 443	56 105	
Age, years					<0.0001
Mean ± SD	65.3±9.8	67.6±9.1	65.4±8.7	76.0±8.6	
Median	65	68	65	76	
Race, n (%)					<0.0001
White	55 939 (71.9)	530 732 (83.8)	42 435 (73.9)	45 551 (81.2)	
Black	17 517 (22.5)	58 497 (9.3)	12 421 (21.6)	7213 (12.9)	
Other	4375 (5.6)	43 946 (6.9)	2587 (4.5)	3341 (5.9)	
Gleason score, n (%）					<0.0001
Low-risk (≤7)	46 202 (59.4)	398 028 (62.9)	33 718 (58.7)	33 998 (60.6)	
High-risk (8+)	31 628 (40.6)	234 908 (37.1)	23 725 (41.3)	22 107 (39.4)	
Surgery, n (%)					<0.0001
Yes	36 168 (46.5)	333 043 (52.6)	26 484 (46.1)	25 314 (45.1)	
No	41 663 (53.5)	300 132 (47.4)	30 959 (53.9)	30 791 (54.9)	

Table 2. Hazard ratios of risk of death by Cox proportional hazard model		
Variable	**HR (95% CI)**	**p**
Age	1.0936 (1.0931–1.0940)	<0.0001
≥70 years (ref: <70)		
Race (ref: White)		
Black	1.0899 (1.0787–1.1012)	<0.0001
Other	0.9568 (0.9499–0.9637)	<0.0001
Marital status (ref: single)		
Married	0.8736 (0.8632–0.8840)	<0.0001
Divorced/separated	1.0082 (1.0025–1.0139)	0.005
Widowed	1.4270 (1.4164–1.4377)	<0.0001
Gleason score (ref: ≤7)		
>8	1.4554 (1.4451–1.4657)	<0.0001
Surgery (ref: no)		
Yes	0.6875 (0.6829–0.6921)	<0.0001

CI: confidence interval; HR: hazard ratio.