Original Article

Association between preoperative prostate-specific antigen levels and mortality in high- and intermediate-grade prostate cancer patients who received radical prostatectomy: Findings from the SEER database

Joshua Ikuemonisan [a, *], Olaoluwa Lediju [b], Adeniyi Togun [c], Oluwakayode Adejoro [d]

[a] Masonic Cancer Center, University of Minnesota, Minneapolis, MN, 55414, USA
[b] Department of Family Medicine, Hennepin County Medical Center, Minneapolis, MN, 55408, USA
[c] University of Minnesota School of Public Health, Minneapolis, MN, 55455, USA
[d] Department of Urology, University of Minnesota, Minneapolis, MN, 55455, USA

A R T I C L E   I N F O

A B S T R A C T

Background: The degree of expression of prostate-specific antigen (PSA) has been applied for the purpose of screening and monitoring the progression of prostate cancer. The goal of this study was to evaluate the association between preoperative PSA levels and mortality outcomes in men with high- and intermediate-grade prostate cancer who received radical prostatectomy.
Methods: The 2004—2014 files of the Surveillance, Epidemiology, and End Result database were analyzed. A total of 97,357 patients with non-metastatic high- and intermediate-grade adenocarcinoma of the prostate who received radical prostatectomy were identified. Using Kaplan—Meier estimates and multivariable Cox proportional hazard models, the relationship between preoperative PSA values and cancer-specific mortality outcomes in men with high- and intermediate-grade prostate cancer who received radical prostatectomy was tested.
Results: Of 97,357 patients with high- and intermediate-grade prostate cancer who received radical prostatectomy from 2001 to 2014, there were 983 cancer-specific deaths, and the average follow-up time for the cohort was 85.0 (34.6) months. Preoperative PSA values > 10 ng/ml were associated with greater risk of cancer-specific mortality (hazard ratio 2.3, $P < 0.0001$) when compared to the referent/normal values for preoperative PSA (<4 ng/ml). Individuals with preoperative PSA values 4—10 ng/ml had lower risk of prostate cancer-specific mortality (hazard ratio 0.80, $P = 0.03$) when compared to individuals with normal preoperative PSA values.
Conclusions: Individuals with preoperative PSA values 4—10 ng/ml had 20% lower risk of prostate cancer-specific mortality when compared to individuals with preoperative PSA values of <4 ng/dl. The findings from this study suggest that low or normal preoperative PSA values may not always mean that prostate cancer is indolent, and more work needs to be done to better classify risk in men with prostate cancer.

1. Introduction

Prostate-specific antigen (PSA) is a protein produced by both normal and malignant cells of the prostate gland. PSA has been used for screening and prognostication of prostate cancer. Although several benign conditions can cause some elevation of blood levels of PSA, values > 10 ng/dl have been associated with prostate cancer diagnosis and cancer-specific mortality (CSM).[1] Although elevated PSA blood levels raise suspicion of prostate cancer, there have been cases of high- and intermediate-grade prostate cancer (Gleason score 7—10 observed in patients with PSA levels <4 ng/ml.[2] Some possible explanations for finding low PSA levels in individuals with high- and intermediate-grade prostate cancer may be that poorly differentiated/aggressive prostate tumors that are known to express lower amounts of PSA,[3,4] other associated factors are older age and low serum-free testosterone/androgen levels, which result in the production of low amounts of PSA.[5,6]

* Corresponding author.
 E-mail address: ikuem001@umn.edu (J. Ikuemonisan).

High- and intermediate-grade prostate cancer (Gleason score 7−10)[7] refer to prostate cancer tissue that appears grossly different from normal tissue, tends to grow rapidly and may be associated with higher mortality rates. Low grade/well-differentiated prostate cancer (Gleason score 6 or less) refers to prostate cancer tissue that looks more like normal tissue and tends to grow more slowly and is associated with a lower mortality rate.[8]

Radical prostatectomy is a common surgical treatment for prostate cancer. However, some patients who receive radical prostatectomy could experience biochemical recurrence of prostate cancer, tumor recurrence, and/or metastasis.[9,10]

Higher risk of prostate cancer recurrence, and other less-than-desired outcomes are associated with factors such as higher PSA levels at initial diagnosis and preoperatively, higher Gleason score at initial diagnosis and short PSA doubling time or high PSA velocity after diagnosis.[11,12] A lack of the ability to identify individuals with elevated risk will lead to poorer outcomes of prostate cancer management in this group of individuals. We queried the Surveillance, Epidemiology and End Results (SEER) data, to assess the relationship between preoperative PSA levels and mortality in high- and intermediate-grade prostate cancer patients who received radical prostatectomy.

2. Materials and Methods

2.1. Data Source

The SEER data file of patients diagnosed with adenocarcinoma of the prostate from 2004 to 2014 was used to conduct this study. The SEER program is a product of the National Cancer Institute and it contains specific information on patients diagnosed with cancer from the SEER tumor registries in the United States. The SEER data report information on demographic characteristics of patients, pathologic features of tumors, cancer-directed surgery from diagnosis through the first 6 months post-diagnosis and death data from January 1, 2004 until the end of study date (December 31, 2014). This sample of the SEER data did not contain information on receipt of radiotherapy. As of 2014, the SEER registry covered approximately 28% of the population of the United States[13].

2.2. Cohort Selection and Study Population

A total of 98,365 men diagnosed with non-metastatic high- and intermediate-grade adenocarcinoma of the prostate from 2004 to 2014 who received radical prostatectomy within 6 months of their prostate cancer diagnoses were identified.

Table 1
Description of study cohort characteristics, in general and compared by preoperative prostatectomy PSA

Preoperative PSA values (ng/ml)				
Total, N (%)	< 4, N (%)	4–<10, N (%)	>10, N (%)	P
Year of diagnosis				<0.0001
2004	6701 (6.87)	769 (6.13)	4556 (6.85)	1376 (7.45)
2005	6466 (6.63)	794 (6.34)	4422 (6.65)	1250 (6.76)
2006	8485 (8.70)	1140 (9.10)	5774 (8.68)	1571 (8.50)
2007	10473 (10.7)	1443 (11.52)	7192 (10.81)	1838 (9.95)
2008	10807 (11.08)	1571 (12.54)	7395 (11.12)	1841 (9.96)
2009	1294 (11.58)	1545 (12.33)	7797 (11.72)	1952 (10.56)
2010	11092 (11.37)	1492 (11.91)	7601 (11.42)	1999 (10.82)
2011	11317 (11.60)	1491 (11.90)	7786 (11.70)	2040 (11.04)
2012	9780 (10.03)	1164 (9.29)	6659 (10.01)	1957 (10.59)
2013	8755 (8.98)	923 (7.37)	5959 (8.96)	1873 (10.14)
2014	2367 (2.43)	195 (1.56)	1390 (2.09)	782 (4.23)
Age, (years)				<0.0001
<45	847 (0.87)	222 (1.77)	468 (0.70)	157 (0.85)
45–54	15174 (15.56)	2527 (20.17)	9698 (14.58)	2949 (15.95)
55–64	45626 (46.78)	5952 (47.51)	31719 (47.68)	7955 (43.05)
65–74	33507 (34.35)	3584 (28.61)	23150 (34.80)	6773 (36.65)
≥75	2383 (2.44)	242 (1.93)	1496 (2.25)	645 (3.49)
Race				<0.0001
White	79269 (81.27)	10826 (86.42)	54365 (81.71)	14078 (76.18)
Black	12270 (12.58)	1179 (9.41)	8110 (12.19)	2981 (16.13)
Asian or PI	4917 (5.04)	372 (2.97)	3331 (5.01)	1214 (6.57)
Am. Indian	1081 (1.11)	150 (1.20)	725 (1.10)	206 (1.11)
Region				<0.0001
Midwest	11670 (11.96)	1764 (14.08)	7852 (11.80)	2054 (11.12)
Northeast	13998 (14.35)	2476 (19.77)	9443 (14.20)	2079 (11.25)
South	18841 (19.32)	2542 (20.29)	12773 (19.20)	3526 (19.08)
West	53028 (54.37)	5745 (45.86)	36463 (54.81)	10820 (58.55)
Clinical tumor stage				<0.0001
T1	60090 (61.61)	6038 (48.20)	43306 (65.10)	10746 (58.15)
T2	34516 (35.39)	6136 (49.00)	21650 (32.54)	6730 (36.41)
T3	2512 (2.58)	289 (2.31)	1371 (2.10)	852 (4.61)
T4	108 (0.11)	17 (0.14)	34 (0.05)	57 (0.31)
Unknown	311 (0.32)	47 (0.38)	170 (0.3)	94 (0.51)
CSM				<0.0001
Yes	983 (1.01)	126 (12.82)	497 (50.56)	360 (37)
ACM				<0.0001
Yes	5268 (5.40)	554 (10.52)	3277 (62.21)	1437 (28)
Median survival (number at risk)				
	87 (12527)	85 (66531)	79 (18479)	<0.0001

%, percentage; ACM, all-cause mortality; Am. Indian, American Indian; CSM, cancer-specific mortality; N, frequency; PI, Pacific Islander; PSA, prostate-specific antigen.
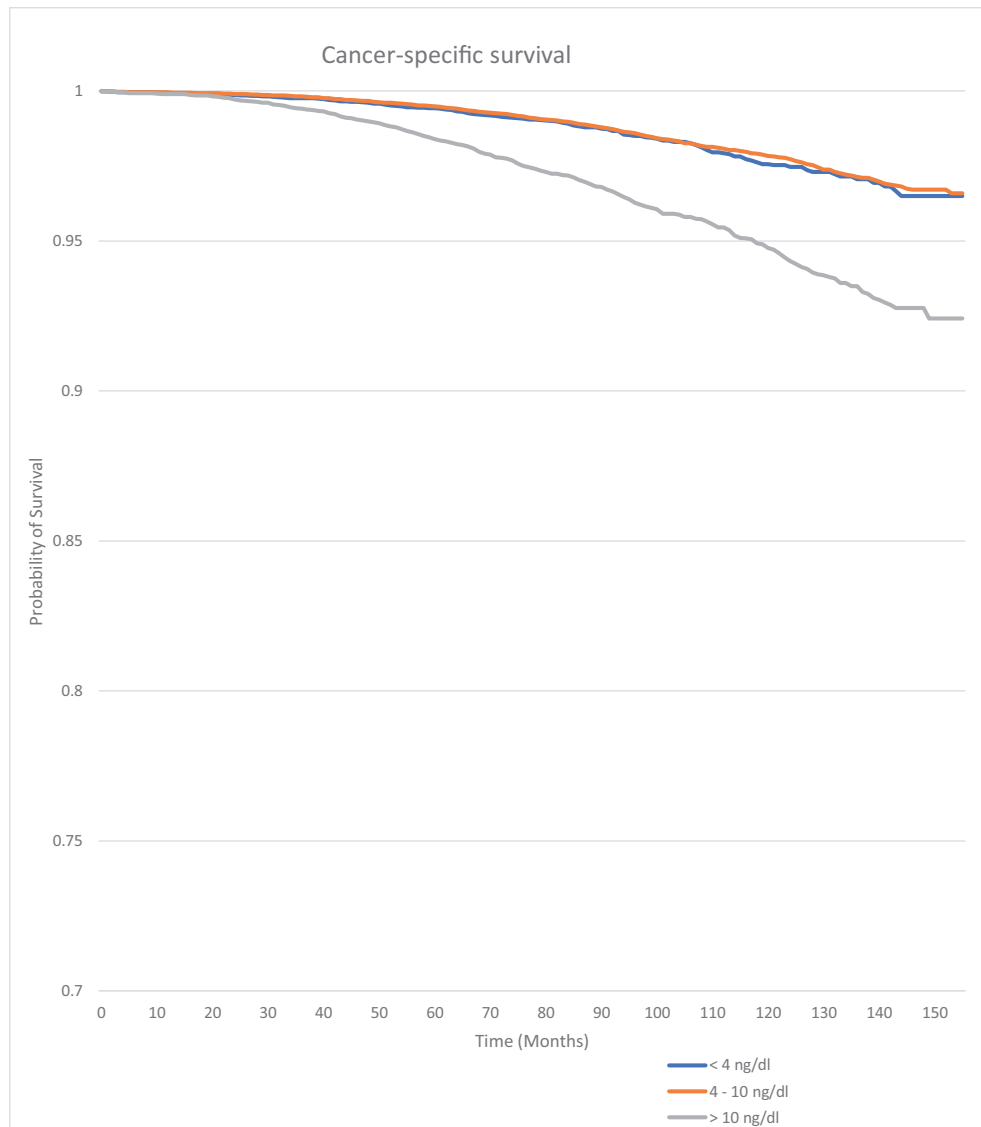
Fig. 1. Kaplan–Meier curves demonstrating the unadjusted cancer-specific survival by prostate-specific antigen (PSA) categories.

Inclusion of subjects was limited to adenocarcinoma of the prostate because it is the most common prostate cancer histology type. Also by design, we limited the study cohort to men who received radical prostatectomy because: (1) these patients have pathologic rather than clinical staging of their disease and pathological staging has been shown to be more accurate than clinical staging,[13,14] (2) it helps to study a more homogenous population of perhaps more fit patients with favorable performance profile and limit the selection bias from treatment choices (e.g. radiotherapy, hormone therapy watchful waiting) to limit selection bias, thus ensuring that all the patients are fit enough to have surgery and to ensure that all the patients in the study had pathological staging information available. Men whose reporting sources were nursing/convalescent homes/autopsy/death certificate ($n = 460$) with possible limited follow-up time and those diagnosed in the State of Louisiana in 2005 ($n = 368$) were excluded because of missing data from the impact of Hurricane Katrina in 2005. This cohort selection yielded a study population of 97,537 patients with non-metastatic high- and intermediate-grade prostate cancer treated early with radical prostatectomy. Study outcomes were reviewed from the date of

prostate cancer diagnosis until the earlier of the date of death or end of study date—December 31, 2014.

2.3. Variables

Age (10-year increments), race (White, Black, Asian, and Pacific Islander), geographic location of SEER registry (Midwest, Northeast, South and West), pathologic tumor stage (T1, T2, T3, T4, and unknown) based on SEER recoded extent of disease, tumor grade (low, moderate, high, and anaplastic), preoperative PSA (<4 ng/ml, 4–10 ng/ml, and >10 ng/ml), death status (dead vs. alive) and cause of death (CSM vs. ACM) were reported. We relied on SEER whose registries use algorithms to classify the cause of death from death certificates to identify a distinct, disease-specific cause of death.

2.4. Outcomes

The patient was the unit of analysis. We sought to understand the influence of low preoperative PSA on CSM and all-cause mortality (ACM) among patients with high- and intermediate-grade disease who received radical prostatectomy. All-cause survival (i.e.
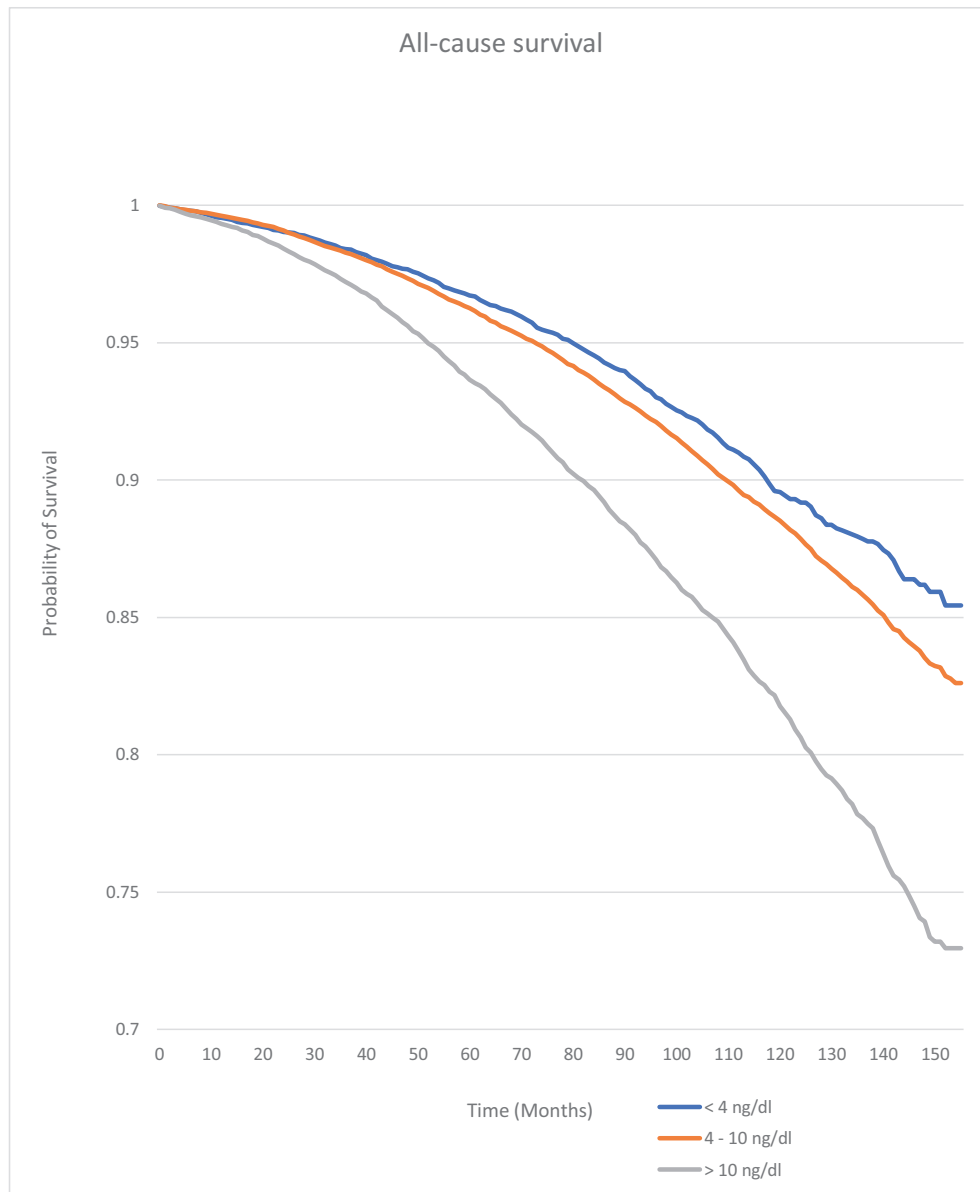
Fig. 2. Kaplan–Meier curves demonstrating the unadjusted all-cause survival by PSA categories.

overall survival—OS) was defined as the number of months from prostate cancer diagnosis to the earlier of death date or end of study date. Cancer-specific survival (CSS) was defined as the number of months from prostate cancer diagnosis to prostate cancer death date or end of study date, whichever occurs first; and patients with non-prostate cancer deaths were censored at the time of death. CSS and OS were operationalized as time to event variables.

2.5. Analysis

The univariate characteristics of the study patients were outlined. Comparisons of univariate characteristics of patients by preoperative PSA strata were performed using Chi-square statistical test. The Kaplan–Meier estimator was used to determine the unadjusted mortality risks of PSA-level strata and the log-rank test was applied to determine statistical significance. Multivariable Cox proportional hazard models were fitted to determine the influence

of PSA on CSS and OS while controlling for known confounders (patient demographics and tumor characteristics). Analysis was conducted using SAS 9.3 software (SAS Institute Inc, Cary, NC, USA). The level of statistical significance was set at $P < 0.05$.

3. Results

The mean (standard deviation—SD) follow-up of the cohort was 85.0 (34.6) months. The mean (SD) age of the cohort was 61.7 (7.1) years; the mean (SD) follow-up of men with PSA of <4 ng/ml, 4–10 ng/ml, and >10 ng/dl were 60.3 (7.4) months, 61.8 (6.9) months, and 62.0 (7.4) months, respectively.

Table 1 summarizes the univariate characteristics of the study population and the comparison of the study population stratified based on preoperative PSA values. Men with low PSA values (<4 ng/ml) constituted 12.8% ($n = 12,527$) of the study population. Men with PSA values of 4–10 ng/ml and >10 ng/ml represented 68.2%

Table 2
Multivariable Cox proportional hazard model demonstrating the influence of preoperative PSA on the adjusted risk of cancer-specific mortality

Covariates		95% CI	P
Year of diagnosis	0.953	0.920 - 0.987	0.0074
Age (years)			
<45 (reference)			
45—54	0.736	0.387—1.402	0.3518
55—64	0.886	0.472—1.661	0.7049
65—74	1.066	0.567—2.004	0.8421
75—84	1.759	0.879—3.522	0.1107
≥85	6.924	1.505—31.85	0.0129
Race			
White (reference)			
Black	1.083	0.894—1.312	0.4177
Asian or Pacific Islander	0.649	0.459—0.918	0.0146
American Indian	0.201	0.050—0.804	0.0233
Region			
Midwest (reference)			
Northeast	1.036	0.806—1.333	0.7816
South	1.111	0.877—1.408	0.3838
West	1.013	0.823—1.247	0.8999
PSA, (ng/ml)			
< 4 (reference)			
4—10	0.803	0.659—0.978	0.0294
>10	2.307	1.776—2.998	<0.0001
Clinical tumor stage			
T1 (reference)			
T2	1.459	1.275—1.669	<0.0001
T3	4.099	3.26—5.153	<0.0001
T4	8.066	4.614—14.102	<0.0001
Unknown	1.844	0.76—4.472	0.1761

This analysis adjusted for year of diagnosis, patient demographics, and tumor stage. CI, confidence interval; PSA, prostate-specific antigen.

($n = 66{,}531$) and 14.2% ($n = 18479$), respectively. The frequency distribution of age at diagnosis, pathologic tumor stage, CSM, and ACM across PSA strata differed significantly ($P < 0.0001$). The median survival (and the number at risk) for study participants with PSA values of <4 ng/ml, 4—10 ng/ml, and >10 ng/ml was 87 months (12,527), 85 months (66,531), and 79 months (18,479), respectively.

Figs. 1 and 2 depict the unadjusted Kaplan-Meier estimates of the risks of CSM and ACM across PSA strata. There were significant differences in the unadjusted risk of CSM (<0.0001) and ACM (<0.0001) by PSA strata.

Table 2 summarizes the adjusted mortality risks of the study patients. Compared to men with PSA of <4 ng/ml, the risks of CSM was 2.3 times higher among patients with PSA of >10 ng/ml. The risk of CSM among patients with PSA of 4-10 ng/ml was 20% lower than patients with PSA of <4 ng/ml ($P = 0.03$). The risk of CSM was 6.9 times higher among patients aged ≥85 years compared with patients aged <45 years. The risk of CSM was 35% lower among Asians/Pacific Islanders relative to Whites. Compared with clinical tumor stage 1, the risk of CSM increased as clinical tumor stage advanced; 46%, 310%, and 707% for clinical stages 2, 3, and 4, respectively.

Table 3 The risks of ACM were 1.1 times and 1.7 times higher among patients with 4–10 ng/ml and >10 ng/ml, respectively, compared to patients with PSA of <4 ng/ml. The risk of OS increased with age; and the risk of ACM was 26.2 times higher among patients aged ≥85 years compared with patients aged <45 years. The risk of ACM was 40% higher in Blacks, whereas 30% lower among American Indians and 24% lower among Asians/Pacific Islanders relative to Whites. Finally, a positive correlation was observed between the levels of PSA and clinical stage of disease (r = . XY, 0.174, $P < 0.0001$).

4. Discussion

This retrospective study examined the influence of preoperative PSA levels on mortality in high- and intermediate-grade prostate cancer patients who received radical prostatectomy in the United States between 2004 and 2014. Having controlled for baseline characteristics, we found that the risks of CSM was higher among men with PSA of >10 ng/ml than men with PSA of <4 ng/ml, similar to findings in recent studies.[15,16] In this study, we also found that men with PSA levels of 4-10 ng/ml had significantly lower CSM than men with PSA values <4 ng/ml, suggesting that the relationship between preoperative PSA and CSM may not be linear. In men with high- and intermediate-grade prostate cancer, it is likely the tumor is so poorly differentiated that the epithelial cells fail to express the PSA coding gene and produce only a small amount of PSA, this may cause individuals with high- and intermediate-grade disease to have normal or near normal PSA levels.[17,18]

Patients with preoperative PSA values <4 ng/ml are generally adjudged to be low risk and may be less likely to be offered surgery or advanced management treatment. Most methods of risk classification help in making a treatment decision and evaluating the risk of recurrence after treatment. With most classifications relying on PSA values, they would assume less risk for men with PSA <4 ng/ml. Although over diagnosing is avoided, some types of poorly differentiated prostate cancers could be misclassified leading to poor but avoidable outcomes, this opinion is supported by studies demonstrating higher rates of non-organ confined disease in patients with extremely low levels of PSA.[19–21]

The strength of this study comprises the use of data from a registry that is nationally representative of the US population and contains information on histologically confirmed cancer cases. The

Table 3
Cox proportional hazards model demonstrating the influence of preoperative PSA on the adjusted risk for all-cause mortality

Covariates	Hazard ratio	95% CI	P
Year of diagnosis	0.973	0.960—0.987	0.0002
Age (years)			
<45 (reference)			
45—54	1.182	0.770—1.814	0.4442
55—64	1.966	1.291—2.994	0.0016
65—74	3.360	2.206—5.117	<0.0001
75—84	6.566	4.256—10.132	<0.0001
≥85	26.153	13.34—51.276	<0.0001
Race			
White (reference)			
Black	1.418	1.312—1.534	<0.0001
Asian and Pacific Islanders	0.757	0.658—0.871	0.0001
American Indians	0.697	0.497—0.976	0.0359
Region			
Midwest (reference)			
Northeast	0.948	0.847—1.061	0.3518
South	1.238	1.120—1.369	<0.0001
West	1.007	0.921—1.101	0.8780
PSA (ng/ml)			
< 4 (reference)			
4—10	1.098	1.002—1.203	0.0442
>10	1.738	1.603—1.883	<0.0001
Clinical tumor Stage			
T1 (reference)			
T2	1.200	1.134—1.270	<0.0001
T3	1.637	1.421—1.885	<0.0001
T4	2.711	1.778—4.133	<0.0001
Unknown	2.109	1.515—2.936	<0.0001

This analysis adjusted for year of diagnosis, patient demographics, and tumor stage. CI, confidence interval; PSA, prostate-specific antigen.

longitudinal nature of the data, availability of confirmed PSA values, as well as information on disease outcomes and causes of mortality are additional advantages. In addition, this study is representative of the US general adult male population and includes sub-populations like young and elderly men irrespective of insurance status or insurance type.

The results of this study are inherent to its retrospective design. The conclusions from this study are drawn from the findings of non-metastatic prostate cancer patients who received radical prosta-tectomy. The outcomes of patients with high- and intermediate-grade prostate cancer and low PSA levels who did not receive radical prostatectomy (i.e. radiation or watchful waiting or active surveil-lance) may differ from the findings in this study. Hence, the findings of this study may not be generalizable to all prostate cancer patients. Ascertainment of cause of death could be challenging and there is a possibility of misclassification in some patients.

8. Conclusion

Non-metastatic prostate cancer with low preoperative PSA may not always be indolent. It is important to take the non-linear rela-tionship between survival and PSA levels into consideration when making treatment decisions for prostate cancer patients: normal preoperative PSA results do not rule out advanced disease and the possibility of poor outcomes. It is important to take the findings of this study into consideration when using preoperative PSA levels to prognosticate or make treatment decisions in high- and interme-diate-grade prostate adenocarcinoma patients. Further studies on the natural history of this subset of prostate cancer is suggested.

Conflicts of interest

All authors have no conflict of interest to declare.

References

1. Oh W, Hurwitz M, D'Amico A, Richie J, Kantoff P. *Neoplasms of the Prostate Cancer Medicine*. Hamilton: BC Decker Inc.; 2003.
2. Izumi K, Ikeda H, Maolake A, Machioka K, Nohara T, Narimoto K, et al. The relationship between prostate-specific antigen and TNM classification or Gleason score in prostate cancer patients with low prostate-specific antigen levels. Prostate 2015;75(10):1034−42.
3. Mahal BA, Aizer AA, Efstathiou JA, Nguyen PL. Association of very low prostate-specific antigen levels with increased cancer-specific death in men with high-grade prostate cancer. Cancer 2016;122(1):78−83.
4. Sokoloff M, Yang XJ, Fumo M, Mhoon D, Brendler C. Characterizing prostatic adenocarcinomas in men with a serum prostate specific antigen level of< 4.0 ng/mL. BJU Int 2004;93(4):499−502.
5. MacKintosh FR, Sprenkle PC, Walter LC, Rawson L, Karnes RJ, Morrel CH, et al. Age and prostate-specific antigen level prior to diagnosis predict risk of death from prostate cancer. Front Oncol 2016;6:157.
6. D'Amico AV, Chen M-H, Malkowicz SB, Whittington R, Renshaw AA, Tomaszewski JE, et al. Lower prostate specific antigen outcome than expected following radical prostatectomy in patients with high grade prostate and a prostatic specific antigen level of 4 ng/ml. or less. J Urol 2002;167(5): 2025−31.
7. Scosyrev E, Messing J, Noyes K, Veazie P, Messing E. Surveillance Epidemiology and End Results (SEER) program and population-based research in urologic oncology: an overview. Papers Present Urolog Oncol Seminar Orig Invest 2012;30(2):126−32.
8. Egevad L, Granfors T, Karlberg L, Bergh A, Stattin P. Prognostic value of the Gleason score in prostate cancer. BJU Int 2002;89(6):538−42.
9. Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC, et al. Risk of prostate cancer−specific mortality following biochemical recur-rence after radical prostatectomy. JAMA 2005;294(4):433−9.
10. D'Amico AV, Chen M-H, Roehl KA, Catalona WJ. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. N Engl J Med 2004;351(2):125−35.
11. Egawa S, Arai Y, Tobisu K, Kuwao S, Kamoto T, Kakehi Y, et al. Use of pre-treatment prostate-specific antigen doubling time to predict outcome after radical prostatectomy. Prostate Cancer Prostatic Dis 2000;3(4):269−74.
12. D'Amico AV, Renshaw AA, Sussman B, Chen M-H. Pretreatment PSA velocity and risk of death from prostate cancer following external beam radiation therapy. JAMA 2005;294(4):440−7.
13. Institute NC. Surveillance, epidemiology, and end results program. http://seer.cancer.gov/registries/. Accessed.
14. Cosma G, Acampora G, Brown D, Rees RC, Khan M, Pockley AG. Prediction of pathological stage in patients with prostate cancer: a neuro-fuzzy model. PloS One 2016;11(6).
15. Perrapato SD, Carothers GG, Maatman TJ, Soechtig CE. Comparing clinical staging plus transrectal ultrasound with surgical-pathologic staging of prostate cancer. Urology 1989;33(2):103−5.
16. Lewinshtein D, Teng B, Valencia A, Gibbons R, Porter CR. The Association be-tween pre-operative PSA and prostate cancer-specific mortality in patients with long-term follow-up after radical prostatectomy. Prostate 2012;72(1): 24−9.
17. Pierorazio PM, Ross AE, Lin BM, Epstein JI, Han M, Walsh PC, et al. Preoperative characteristics of high-Gleason disease predictive of favourable pathological and clinical outcomes at radical prostatectomy. BJU Int 2012;110(8):1122−8.
18. McGuire BB, Helfand BT, Loeb S, Hu Q, O'Brien D, Cooper P, et al. Outcomes in patients with Gleason score 8−10 prostate cancer: relation to preoperative PSA level. BJU Int 2012;109(12):1764−9.
19. Weir EG, Partin AW, Epstein JI. Correlation of serum prostate specific antigen and quantitative immunohistochemistry. J Urol 2000;163(6):1739−42.
20. Berglund RK, Stephenson AJ, Cronin AM, Vickers AJ, Eastham JA, Klein EA, et al. Comparison of observed biochemical recurrence-free survival in patients with low PSA values undergoing radical prostatectomy and predictions of preop-erative nomogram. Urology 2009;73(5):1098−103.
21. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes ML, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level≤ 4.0 ng per milliliter. N Engl J Med 2004;350(22):2239−46.