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The association of marital status and mortality among men with early-stage prostate cancer treated with radical prostatectomy: insight into post-prostatectomy survival strategies

Saira Khan^{*,a}, Kenneth G. Nepple^{*,b}, Adam S. Kibel^c, Gurdarshan Sandhu^d, Dorina Kallogjeri^e, Seth Stroppe^f, Robert Grubb III^g, Kathleen Y. Wolin^h, Siobhan Sutcliffe^a

^aDivision of Public Health Sciences, Department of Surgery, Washington University in St. Louis School of Medicine, 660 S. Euclid Ave., Campus Box 8100, St. Louis, MO, 63110

^bDepartment of Urology, Carver College of Medicine, University of Iowa Health Care, 3228 RCP, Iowa City, IA 52242

^cDivision of Urology, Department of Surgery, Brigham and Women's Hospital, Harvard School of Medicine, 45 Francis St., ASB11-3, Boston, MA, 02115

^dMercy Clinic Urology, David C. Pratt Cancer Center, 607 S. New Ballas Rd., Suite 3100, St. Louis, MO 63141

^eDepartment of Otolaryngology, Washington University in St. Louis School of Medicine, 660 S. Euclid Ave., Campus Box 8042, St. Louis, MO 63110

^fUrology of St. Louis, 12855 North Forty Dr., Suite 375, St. Louis, MO, 63141

^gDepartment of Urology, Medical University of South Carolina, 135 Rutledge Ave., Charleston, SC 29425

^hInteractive Health Inc., 300 N. Elizabeth St., Chicago, IL, 60607

Abstract

Purpose: The purpose of this study was to determine the association of marital status, a marker of social support, with all-cause and prostate cancer-specific mortality in a cohort of men with early-stage prostate cancer treated with radical prostatectomy.

Correspondence: Saira Khan, PhD, MPH, Postdoctoral Research Scholar, Division of Public Health Sciences, Department of Surgery, Washington University in St. Louis School of Medicine, 660 S. Euclid Avenue, Campus Box 8100, St. Louis, MO 63110, khans@wustl.edu, Phone: 314-747-0964, Fax: 314-747-1020.

*Co-first authors

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

A waiver of informed consent was obtained from the Institutional Review Board of the Washington University in St. Louis School of Medicine.

The authors declare that they have no conflict of interest.

Methods: We conducted a retrospective cohort study of 3579 men treated for localized (stage 1–2) prostate cancer with radical prostatectomy at a single institution between 1994 and 2004. Marital status (not married vs. married) and marital history (never married, divorced, widowed vs. married) at the time of prostatectomy were examined in relation to (1) all-cause mortality and (2) prostate cancer-specific mortality using Cox proportional hazards regression.

Results: Not being married (vs. married) at the time of radical prostatectomy was associated with an increased risk of all-cause mortality (Hazard Ratio (HR): 1.42; 95% Confidence Interval (CI): 1.10, 1.85). Similarly, in analyses of marital history, never married men were at highest risk of all-cause mortality (HR: 1.77, 95% CI: 1.19, 2.63). Unmarried status (vs. married) was also associated with an increased risk of prostate cancer-specific mortality (HR: 1.97; 95% CI: 1.01, 3.83).

Conclusions: Unmarried men with prostate cancer were at greater risk for death after radical prostatectomy. Among married men with prostate cancer, marriage likely serves as a multi-faceted proxy for many protective factors including social support. Future studies should explore the mechanisms underlying these findings to inform the development of novel prostate cancer survival interventions for unmarried men and those with low social support.

Keywords

prostate cancer; radical prostatectomy; marital status; mortality; single; married

INTRODUCTION

Prostate cancer is the most common cancer among men in the United States with an estimated 164,690 new diagnoses in 2018 [1]. Although the overall survival rate for prostate cancer is high, 26,730 men had a death attributable to prostate cancer in 2018 [1]. Nonetheless, few risk factors have been established for prostate cancer incidence or survival beyond non-modifiable factors including age, race, family history [2], certain genetic polymorphisms [3], and tumor characteristics at diagnosis. This lack of modifiable risk factors has limited primary and secondary prevention efforts to date.

A possible, under-recognized and potentially modifiable risk factor for prostate cancer survival is social support, the primary source of which among older men with prostate cancer is usually a spouse [4]. Strong social support or marriage could potentially improve survival by several possible mechanisms, including reducing psychological distress, promoting earlier diagnosis at a less advanced stage, facilitating a healthier lifestyle with fewer medical comorbidities, encouraging definitive and pro-active treatments, ensuring that patients adhere to treatment and follow-up care plans, and providing logistical support (e.g. transportation) [4–10]. Indeed, in the small number of studies conducted to date, being unmarried has consistently been found to be associated with an increased risk of mortality after diagnosis with prostate cancer [5, 11–15]. However, the potential of these findings for improving prostate cancer survival has generally not been recognized by the prostate cancer community or translated into survival interventions (e.g., patient navigators or men’s health programs targeted to men most in need) [16, 17]. Therefore, to build the body of literature further on this topic, we examined the association of marital status, a marker of social

support, with all-cause and prostate cancer-specific death in men with prostate cancer. In addition, restriction of our cohort to men with early-stage prostate cancer treated by definitive therapy (radical prostatectomy) allowed us to explore whether marital status acts through earlier diagnosis and definitive prostate cancer treatment or whether post-diagnostic mechanisms may also play a role [18, 19]. Finally, availability of medical comorbidity data also allowed us to explore reduced comorbidity burden as an additional possible mechanism not examined in previous studies [20].

METHODS

The study population consisted of 3579 men treated for localized (stage 1–2) prostate cancer with radical prostatectomy at the Washington University in St. Louis School of Medicine between 1994 and 2004. Marital history, demographic factors, comorbidities, and disease specific factors (Prostate-Specific Antigen (PSA), clinical stage, biopsy Gleason grade) were retrieved from an institutional cancer registry. Marital status was assessed at the time of treatment by cancer registrars via review of the medical record. Date and cause of death were determined by chart review and linkage to the National Death Index, after which the dataset was de-identified. This study was approved by the Institutional Review Board of Washington University School of Medicine and a waiver of informed consent was received.

Our primary exposure of interest was marital status, which we examined as both a binary marital status variable (not married vs. married) and as marital history (never married, divorced, and widowed vs. married) at the time of radical prostatectomy. Covariates were selected based on variables known to be associated with the outcome, and included demographic and clinical factors. Age (<50, 51–55, 56–60, 61–65, 66–70, and >70 years) was analyzed as a categorical variable in our primary models and as a continuous variable in sensitivity analyses. Race (White, Other) was also analyzed as a categorical variable. Comorbidity severity was determined at the time of treatment by cancer registrars using the validated ACE-27 comorbidity index, and categorized as none, mild, and moderate/severe [20]. Key clinical covariates included biopsy Gleason grade, clinical stage, and pretreatment PSA. Biopsy Gleason grade (6, 7, 8–10) was analyzed as a categorical variable, whereas PSA was analyzed as a continuous log transformed variable. Our primary outcomes of interest were all-cause death and prostate cancer-specific death.

Cox proportional hazards models were used to assess the association between marital history, marital status (binary), and all-cause death. Multivariable models were adjusted for age, race, comorbidity status, PSA, and biopsy Gleason grade. Separate models were used to examine marital history and all-cause death.

Similar analyses were performed to investigate the association between marital status and prostate cancer-specific death. In analyses of prostate cancer-specific death, we were limited to examining marital status as a binary variable (not married vs. married) due to the small number of deaths attributable to prostate cancer.

Sensitivity analyses were performed among participants with a biopsy Gleason score ≥ 7 to further evaluate our results among men with both early-stage disease and favorable pathology (i.e. Gleason score ≥ 7).

RESULTS

Characteristics of the Study Population

The characteristics of our study population can be seen in Table 1. The majority of men in our cohort were married at the time of radical prostatectomy (86.8%). A similar proportion of men were divorced (5.3%) or never married (5.5%), with the smallest proportion of men widowed (2.4%). The mean age of men in our cohort was 60.4 years, with the largest proportion of men between 56–65 at the time of treatment. As expected, widowed men were somewhat older at diagnosis (66.0 years) than the cohort as a whole. The vast majority of men in our cohort were White (89.9%). White men were less likely to be divorced, widowed, or never married (11.8%) than men of other races (25.6%). Over half of the cohort had no comorbidities, and widowed men were more likely to have comorbidities than the cohort as a whole. The median PSA at radical prostatectomy was 5.5 ng/mL. Most men in our cohort were diagnosed with a biopsy Gleason grade ≤ 6 , with 19.5% diagnosed with a biopsy Gleason grade ≥ 7 .

All-cause and prostate-cancer specific mortality

The mean follow-up time was 10.2 years. Approximately twelve percent of our cohort had a death due to any cause by the end of follow-up (n=437) and about 2% had a death due to prostate cancer (n=62).

Not married status (vs. married) was associated with an increased risk of all-cause death in multivariable models adjusted for age, race, comorbidity, PSA, and biopsy Gleason grade (Hazard Ratio (HR): 1.42; 95% Confidence Interval (CI): 1.10, 1.85; Table 2). Similarly, in analyses of marital history, never married men were at an increased risk for all-cause death (HR: 1.77, 95% CI: 1.19, 2.63). Divorced (HR: 1.13; 95% CI: 0.74, 1.73) and widowed status (HR: 1.47; 95% CI: 0.91, 2.38) were also suggestive of an increased risk of all-cause death, but results were not statically significant. Finally, not married men (vs. married) were also at an increased risk of prostate cancer-specific death (HR: 1.97; 95% CI: 1.01, 3.83).

Sensitivity Analyses

Results were consistent when age was analyzed as a continuous variable (data not shown) and when we limited our cohort to men with Gleason score ≥ 7 for both all-cause mortality [Marital Status: Never married vs. married: (HR: 1.38; 95% CI: 1.05, 1.81); Marital History: Divorced (HR: 1.04; 95% CI: 0.66, 1.63), Widowed (HR: 1.47; 95% CI: 0.91, 2.38), and Never-Married (HR: 1.78; 95% CI: 1.17, 2.68)] and prostate cancer-specific mortality (Marital Status: Never married vs. married: HR: 1.95; 95% CI: 0.93, 4.12).

DISCUSSION

In this large study of men treated for early-stage prostate cancer with radical prostatectomy, we observed that being unmarried (vs. married) at the time of radical prostatectomy was associated with an increased risk of both all-cause and prostate cancer-specific death. Although our analyses suggested that divorced, widowed, and never married men were all at increased risk for all-cause mortality, the strongest association was observed for never married men. Our results, which are consistent with those from previous studies across both the United States and Europe [5, 11–15], were observed in men with early-stage prostate cancer treated by definitive therapy and after adjustment for comorbidities, suggesting that mechanisms besides these three factors were responsible for a large proportion of the associations observed in our and previous studies.

Additional possible mechanisms by which marriage may potentially enhance survival in men with prostate cancer include: (1) post-diagnostic psychosocial support; (2) adherence to follow-up prostate cancer care guidelines along with choice of adjuvant and secondary therapy, if necessary; and (3) healthier post-diagnostic lifestyles choices. First, married men receive psychosocial support from their partners [4, 6–8]. Indeed, men report that support from partners and one-to-one peer support are the most valued form of support they receive after diagnosis, and social support has been previously associated with an improved likelihood of survival [4, 16, 21]. Second, men's spouses may influence adherence to post-surgical prostate cancer guidelines (e.g. scheduling for transportation to follow-up visits with an urologist [22]) and receipt of adjuvant or secondary therapy (e.g. adjuvant or salvage radiation therapy, androgen deprivation therapy, or systemic therapies). Finally, married men may lead a healthier lifestyle post-diagnosis. Smoking and heavy drinking are more common in single, divorced, or widowed individuals, and physical inactivity is more common in men who report inadequate emotional support [10, 23]. These lifestyle factors are associated with all-cause mortality, and may also be associated with prostate cancer-specific mortality.

It is important to note that prostate cancer patients treated at our institution are primarily White. As such we did not have sufficient power to investigate the possible role that marriage may play in contributing to racial disparities in prostate cancer survival. However, we did observe that non-White men were more likely to be unmarried (25.6%) than White men (11.7%), consistent with national estimates [24]. Despite lower marriage rates in African American men, spouses remain a major source of support for them [25]. In fact, social support and pro-social coping may be of a particular importance for African American men with prostate cancer [26], as evidence suggests that African American men are more likely to experience emotional distress following prostate cancer treatment due to traditional perceptions of masculine norms and negative feelings regarding disease disclosure [26]. These factors can all potentially contribute to worse prostate cancer outcomes, an experience that may be exacerbated by the lower proportion of married African American than White men. Future analyses could thus examine whether marital status or the elements it represents explain at least part of the racial disparities that mark prostate cancer.

In addition to low representation of African-American men, our study was also limited by its lesser characterization of prostate cancer at diagnosis (i.e. missing pathologic grade and

stage and limited Gleason score categorization), leaving open the possibility that some of our observed association may have been explained by earlier diagnosis in married men. However, the fact that adjustment for PSA concentration at diagnosis and biopsy Gleason score, as well as restriction to men with biopsy Gleason score ≤ 7 , had minimal influence on our estimates suggests a lesser role for later diagnosis or worse pathology in explaining our findings. Our findings could also be strengthened by a more detailed socio-demographic characterization of the men in our study including the composition of the other race group and causes of death other than prostate cancer. Post-diagnostic mechanisms such as psychosocial support, logistical support, healthier post-diagnostic lifestyle choices (i.e. not smoking, physical activity, healthy diet etc.), adherence to follow-up care plans, and more pro-active adjuvant and secondary therapies should be explored in future studies. Finally, it is important to note that, although we used marital status as a marker of social support, married men may not always be in supportive marriages. Men in dysfunctional relationships are more likely to experience psychological distress than married men in supportive relationships [27, 28]. If some of the married men in our cohort were in unsupportive marriages, this would have likely biased our findings toward the null, as such men would not have received the supportive benefits of marriage. Nevertheless, we still observed a survival benefit for married men.

Despite the aforementioned limitations, our study had several key strengths. We had over 10 years of follow-up on a large cohort of men. In addition, we were able to explore the possible influence of important clinical characteristics including comorbidities, biopsy Gleason score, and receipt of definitive treatment. Crucially, we were able to show that even among a cohort with low-risk disease and high expected survival, marriage still conferred a survival benefit. Although marital status itself is not a factor that can be intervened upon, many avenues of support represented by marriage could be leveraged to support unmarried men with prostate cancer or those with low social support. These could range from connecting unmarried men diagnosed with prostate cancer to support groups or other prostate cancer patients to enhance their social support to connecting men to nurse navigators to help them navigate treatment decisions and follow-up care. Although several of these interventions currently exist to improve quality of life, their potential for improving survival is less well-recognized and -promoted. Importantly, these interventions do not need to increase the clinical burden for physicians; instead they could be accomplished by harnessing existing resources more effectively and channeling them to men most in need through targeted physician endorsement.

CONCLUSIONS

Our study adds to the small body of literature suggesting that marital status plays an important role in prostate cancer outcomes. Specifically, our study suggests that being unmarried at the time of radical prostatectomy may be associated with an increased risk of prostate cancer-specific and all-cause mortality. Men who are unmarried or who have low social support thus represent a high risk group that could potentially benefit from targeted prostate cancer survival interventions. Future studies should explore the mechanisms underlying our findings to inform the development of these interventions.

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Table 1.

Characteristics of men treated for localized prostate cancer with radical prostatectomy, 1994–2004 (n=3579)

Characteristic	All Men (n=3579) N(%)	Married (n=3107) N(%)	Divorced (n=189) N(%)	Widowed (n=87) N(%)	Never Married (n=196) N(%)	Not Married (n=472) N(%)
Age (years)						
Mean (SD)	60.4 (7.2)	60.5 (7.1)	59.7 (7.0)	64.3 (6.4)	57.4 (7.9)	59.6 (7.7)
Median	61.0	61.0	60.0	66.0	57.0	60.0
Age (years)						
<50	334 (9.3)	275 (8.9)	22 (11.6)	3 (3.5)	34 (17.4)	59 (12.5)
51–55	566 (15.8)	481 (15.5)	32 (16.9)	7 (8.1)	46 (23.5)	85 (18.0)
56–60	844 (23.6)	733 (23.6)	46 (24.3)	18 (20.7)	47 (24.0)	111 (23.5)
61–65	879 (24.6)	784 (25.2)	44 (23.3)	12 (13.8)	39 (19.9)	95 (20.1)
66–70	699 (19.5)	612 (19.7)	35 (18.5)	33 (37.9)	19 (9.7)	87 (18.4)
>70	257 (7.2)	222 (7.2)	10 (5.3)	14 (16.1)	11 (5.6)	35 (7.4)
Race						
White	3219 (89.9)	2839 (91.4)	152 (80.4)	69 (79.3)	159 (81.1)	380 (80.5)
Other	360 (10.1)	268 (8.6)	37 (19.6)	18 (20.7)	37 (18.9)	92 (19.5)
Comorbidity						
None	2118 (59.2)	1847 (59.4)	112 (59.3)	39 (44.8)	120 (61.2)	271 (57.4)
Mild	1193 (33.3)	1030 (33.2)	61 (32.3)	37 (42.5)	65 (33.2)	163 (34.5)
Moderate/Severe	268 (7.5)	230 (7.4)	16 (8.5)	11 (12.6)	11 (5.6)	38 (8.1)
Prostate-specific antigen concentration (ng/mL)						
Mean (SD)	6.8 (5.2)	6.7 (5.1)	7.1 (5.1)	8.7 (7.8)	6.9 (4.6)	7.3 (5.5)
Median	5.5	5.4	5.5	5.9	5.3	5.5
Biopsy Gleason grade						
6	2732 (76.3)	2355 (75.8)	147 (77.8)	74 (85.1)	156 (79.6)	377 (79.9)
7	698 (19.5)	618 (19.9)	36 (19.1)	10 (11.5)	34 (17.3)	80 (17.0)
8–10	149 (4.2)	134 (4.3)	6 (3.2)	3 (3.5)	6 (3.1)	15 (3.2)

^aNot married is a combined category consisting of divorced, widowed, and never married men

Table 2.

Association between marital status and mortality in patients treated for localized prostate cancer by radical prostatectomy, 1994 to 2004 (n=3579)

	Total person-time (years)	Number of Deaths (n=437)	All-Cause Death		Prostate Cancer-Specific Death		
			Unadjusted HR (95%)	Adjusted ^a HR (95% CI)	Number of Deaths (n=62)	Unadjusted HR (95%)	Adjusted ^b HR (95% CI)
Marital Status (binary)^c							
Married	31,608.6	369	Ref	Ref	51	Ref	Ref
Not Married	4502.2	68	1.35(1.04,1.75)	1.42 (1.10, 1.85)	11	1.57(0.82, 3.02)	1.97(1.01,3.83)
Marital History^c							
Married	31,608.6	369	Ref	Ref	51	---	---
Divorced	1834.3	23	1.10 (0.73,1.68)	1.13 (0.74,1.73)	4	---	---
Widowed	827.4	18	1.95 (1.21,3.12)	1.47 (0.91,2.38)	1	---	---
Never Married	1840.5	27	1.33 (0.90,1.97)	1.77 (1.19,2.63)	6	---	---

CI=confidence interval; HR=hazards ratio; PSA=prostate-specific antigen.

^aModel includes marital history (married, divorced, widowed, never married), age, race, comorbidity, log-transformed PSA, Biopsy Gleason grade

^bModel includes marital status (married vs. not married), age, race, comorbidity, log-transformed PSA, Biopsy Gleason grade

^cMarital status (binary) and marital history were analyzed in separate models.