Clinical-Prostate cancer

Contemporary analysis of the effect of marital status on survival of prostate cancer patients across all stages: A population-based study

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Abstract

Background: Marital status rates may have changed over time in prostate cancer (PC) patients and may have affected cancer-specific mortality (CSM) and other-cause mortality (OCM).

Methods: Within the Surveillance, Epidemiology, and End Results database (2004−2015), we identified PC patients who were either married ($n = 326,664$) or unmarried ($n = 106,533$). Temporal trends, cumulative incidence plots, as well as multivariable competing risks regression analyses focused on (1) the overall population, (2) D'Amico low-risk N0M0 PC, (3) D'Amico intermediate-risk N0M0 PC, (4) D'Amico high-risk N0M0 PC, (5) N1M0 PC, and (6) M1 PC patients.

Results: Of all, 24.6 % were unmarried and increased trend over time (23.0%−26.9%, $P < 0.001$). Unmarried men experienced higher CSM rates (9.8% vs. 6.3% in married men, $P < 0.001$) and OCM rates (24.3% vs. 17.1% in married men, $P < 0.001$) in the overall population, as well as in all subgroup analyses. Unmarried status represented an independent predictor of higher CSM (hazard ratio: 1.19, $P < 0.001$) and OCM (hazard ratio: 1.41, $P < 0.001$) in the overall cohort, as well as in all subgroup analyses except for the N1M0 subgroup, where marital status did not reach independent predictor status for CSM.

Conclusions: Unmarried PC patients are at higher risk of CSM and OCM. This relationship applies to all stage subgroups, except for the N1M0 subgroup. Consequently, unmarried individuals should ideally benefit of improved counseling, closer follow-up, as well as of other measures aimed at reducing the CSM and OCM disadvantages. © 2019 Elsevier Inc. All rights reserved.

Introduction

Sociodemographics, such as marital status, represent established predictors of better survival in many urological, as well as nonurological primaries [1−3]. In general, this effect is applicable to patients with localized, as well as with metastatic disease [1]. Specifically, unmarried men are disadvantaged in most comparisons relative to their married peers. The above statements apply to historical prostate cancer (PC) patients across all disease stages [4,5]. However, in contemporary institutional analyses, the protective

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effect of marital status was no longer identified, when a large European cohort of radical prostatectomy (RP) patients represented the focus of the analyses [6].

Based on the historical nature of virtually all available studies examining the effect of marital status on various cancer-control outcomes, including cancer-specific mortality (CSM), we decided to reassess the contemporary trends in marital status, as well as its effect on CSM and other-cause mortality (OCM). We hypothesized that the proportion of unmarried patients may have increased in more recent years. Moreover, we postulated that due to this effect the CSM benefit of marital status reported in historical studies may no longer be applicable to contemporary patients, as was suggested by the most recent European RP-based analysis [6]. For purpose of all analyses, we relied on the most contemporary Surveillance, Epidemiology, and End Results (SEER) database (2004−2015).

Material and methods

Study population

The SEER database samples 27.8% of the United States and approximates the United States in terms of demographic composition, as well as of cancer incidence [7]. Within the SEER database (2004−2015), we identified patients ≥18 years old, with known marital status, with histologically confirmed PC diagnosis (International Classification of Disease for Oncology [ICD-O-3] code 8140/3 site code C61.9) and with available prostatic-specific antigen (PSA) value. Patients with clinical stage T0 or unknown metastatic status were excluded.

We performed 6 sets of analyses that focused on CSM, which was defined as death attributable to PC. Conversely, OCM was defined as death attributable to other causes than PC. In all analyses, the predictor of interest consisted of married vs. unmarried status. First, we addressed the overall cohort across all disease stages. This resulted in 326,664 married and 106,533 unmarried eligible patients. Steps 2, 3, and 4, respectively, consisted of subgroup analyses according to the 3 D'Amico risk groups in N0M0 patients. The D'Amico low-risk group (87,848 married vs. 24,481 unmarried patients) included patients with PSA <10 ng/ml and/or Gleason score ≤6 and/or clinical T-stage ≤cT2a. The D'Amico intermediate-risk group (115,481 married vs. 35,904 unmarried men) included patients with PSA 10-20 ng/ml and/or Gleason score 7 and/or cT2b. The D'Amico high-risk group (67,419 married vs. 25,134 unmarried men) included patients with PSA >20 ng/ml and/or Gleason score ≥8 and/or cT2c. Step 5 focused on patients with N1M0 stage (5404 married vs. 1983 unmarried men) and step 6 focused on M1 stage (11,223 married vs. 7,195 unmarried men).

Finally, we performed sensitivity analyses in nonmetastatic RP patients (125,924 married vs. 29,812 unmarried men). Moreover, we performed sensitivity analyses

according to historical (2004−2009, 176.338 married vs. 54.404 unmarried men) vs. contemporary (2010−2015, 150.326 married vs. 52.129 unmarried men) year of diagnosis to further validate our findings.

Statistical analyses

Descriptive statistics included frequencies and proportions for categorical variables. Means, medians, and ranges were reported for continuously coded variables. The chi-square tested the statistical significance in proportions differences. The *t* test and Kruskal-Wallis test examined the statistical significance of means and median differences. Temporal trend analyses were performed with estimated annual percentage changes (EAPC) in the overall cohort, as well as in all subgroups.

In all analyses, we relied on cumulative incidence plots and subsequently fitted multivariable competing risks regression models testing the effect of marital status on CSM and OCM. All variables were adjusted for age at diagnosis, PSA, biopsy Gleason Grade Groups (GGG) [8], defined as GGG I (Gleason score 3 + 3), GGG II (Gleason score 3 + 4), GGG III (Gleason score 4 + 3), GGG IV (Gleason score 8), and GGG V (Gleason score 9−10) at diagnosis, clinical stage (≤cT2, ≥cT3), lymph node stage (cN0-cNX-cN1), metastatic status (cM0-cM1), treatment type (brachytherapy, external beam radiation therapy [EBRT], RP, combination therapy, no local treatment [NLT]), and race (Caucasian, African-American, and unknown/other).

For all statistical analyses, R software environment for statistical computing and graphics (version 3.4.3) was used. All tests were 2 sided with a level of significance set at $P<$ 0.05.

Results

Within the SEER database between years 2004 and 2015, 433,197 PC patients with known marital status were identified. In the overall cohort, 24.6% were unmarried (Table 1). Moreover, the rate of unmarried individuals increased in direct proportion to the D'Amico risk grouping with the highest proportion of unmarried individuals in M1 patients. Specifically, in the D'Amico low-risk group, the D'Amico intermediate-risk group, and the D'Amico high-risk group, 21.7%, 23.7%, and 27.1% were unmarried, respectively. In N1M0 patients, 26.8% were unmarried and in M1 patients 39.0% were unmarried (Table 2). Additionally, in N0M0 patients, the highest unmarried proportion was recorded in NLT patients (30.2%) followed by EBRT (26.7%) and RP (19.0%). Median follow-up within the overall cohort was 64 (interquartile range [IQR]: 32−98) months, within D'Amico low-risk group 68 (IQR: 39−103) months, within D'Amico intermediate-risk group 65 (IQR: 33−98) months, within D'Amico high-risk group 60 (IQR: 29−95) months, within N1M0 patients 45 (IQR: 19−77) months and within M1 patients 20 (IQR: 9−40) months.

Table 1
Descriptive characteristics of overall prostate cancer patients diagnosed within the Surveillance, Epidemiology, and End Results database from 2004 to 2015, stratified according to marital status (married vs. unmarried)

Variables	Overall (n = 433,197, 100%)	Married (n = 326,664, 75.4%)	Unmarried (n = 106,533, 24.6%)	P value
Age at diagnosis, years				
Mean	65.4	65.5	65.1	<0.001
Median	65	65	65	<0.001
Interquartile range	59−71	59−71	58−71	
Race, n (%)				
Caucasian	337,529 (77.9)	263,464 (80.7)	74,065 (69.5)	<0.001
African-American	67,305 (15.5)	40,153 (12.3)	27,152 (25.5)	
Other	28,363 (6.5)	23,047 (7.1)	5,316 (5)	
Socioeconomic status				
High	215,898 (49.8)	157,709 (48.3)	58,189 (54.6)	<0.001
Low	217,265 (50.2)	168,935 (51.7)	48,330 (45.4)	
Year of diagnosis				
Median	2009	2009	2009	<0.001
Interquartile range	2006−2012	2006−2012	2007−2012	
Prostate-specific antigen, ng/ml				
Mean	12.6	11.4	16.3	<0.001
Median	6.5	6.3	7.3	<0.001
Interquartile range	4.7−10.4	4.7−9.8	5.1−13.3	
Clinical tumor stage, n (%)				
≤T2	411,513 (95)	312,103 (95.5)	99,419 (93,3)	<0.001
≥T3	15,845 (3.7)	10,904 (3.3)	4,941 (4.6)	
cTX	5,839 (1.3)	3,657 (1.1)	2,182 (2)	
Gleason Grade Group, n (%)				
I	171,587 (39.6)	132,465 (40.6)	39,122 (36.7)	<0.001
II	114,141 (26.3)	86,602 (26.5)	27,539 (25.9)	
III	48,411 (11.2)	36,285 (11.1)	12,126 (11.4)	
IV	37,420 (8.6)	27,373 (8.4)	10,047 (9.4)	
V	32,401 (7.5)	22,667 (6.9)	9,734 (9.1)	
Unknown	29,237 (6.7)	21,272 (6.5)	7,965 (7.5)	
Lymph node status, n (%)				
N0	410,613 (94.8)	311,397 (95.3)	99,216 (93.1)	<0.001
N1	12,111 (2.8)	8,242 (2.5)	3,969 (3.6)	
NX	10,473 (2.4)	7,025 (2.2)	3,448 (3.2)	
Metastatic status				
M0	414,779 (95.7)	315,441 (96.6)	99,338 (93.2)	<0.001
M1	18,418 (4.3)	11,223 (3.4)	7,195 (6.8)	
Treatment, n (%)				
Radical prostatectomy (RP)	156,553 (36.1)	126,574 (38.7)	29,979 (28.1)	<0.001
External beam (EBRT)	99,732 (23)	72,674 (22.2)	27,058 (25.4)	
Brachytherapy (BT)	35,296 (8.1)	27,490 (8.4)	7,806 (7.3)	
BT + EBRT	18,940 (4.4)	14,790 (4.5)	4,150 (3.9)	
RP + EBRT	13,175 (3)	10,070 (3.1)	3,105 (2.9)	
No local treatment	100,705 (23.2)	68,796 (21.1)	31,909 (30)	
Unknown	8,796 (2)	6,270 (1.9)	2,526 (2.4)	

In the overall cohort, unmarried men (n = 106,533) were younger (65.1 vs. 65.5 years in married men), presented with higher PSA (7.3 vs. 6.3 ng/ml in married men), more frequently harbored biopsy GS 8-10 (18.6% vs. 15.3% in married men), and presented with cT3 or higher stage (4.6% vs. 3.3% in married men; all P < 0.001, Table 1). In all 5 subgroup analyses, which focused on the 3 D'Amico risk groups, the N1M0 patients, and the M1 patients, similar trends were seen, where biologically more aggressive disease was identified at a higher rate in unmarried individuals (Supplementary Table 1).

Temporal trends within the overall cohort demonstrated an increase in the rate of unmarried men from 23.0% in

2004 to 26.9% in 2015 (EAPC: 1.5, P < 0.001), while a decrease in the rate of married men from 77.0% in 2004 to 73.1% in 2015 (EAPC: −0.5%, P < 0.001) was recorded (Fig. 1). In all 5 subgroup analyses, which focused on the 3 D'Amico risk groups, the N1M0 patients, and the M1 patients, similar time trends were seen, where an increase in the rate of unmarried men was identified over time (data not shown).

CSM and OCM analyses

Cumulative incidence smoothed plots were generated and focused on CSM and OCM at 10 years. In the overall

Table 2
Multivariable competing risks regression models testing the effect of marital status (married vs. unmarried) on cancer-specific mortality in 433,197 prostate cancer patients within the Surveillance, Epidemiology, and End Results database (2004−2015), according to clinical characteristics, additionally adjusted for year of diagnosis and race

Variable	CSM		OCM	
	Multivariable HR (95% CI)	P value	Multivariable HR (95% CI)	P value
Age at diagnosis	1.02 (1.02−1.03)	P< 0.001	1.08 (1.08−1.09)	P< 0.001
Marital status				
Married	Ref.		Ref.	
Unmarried	1.19 (1.14−1.23)	P < 0.001	1.41 (1.38−1.45)	P < 0.001
Prostate-specific antigen	1.01 (1.01−1.01)	P < 0.001	1 (1−1)	P < 0.001
Gleason Grade Group (GGG)				
GGG I−III	Ref.		Ref.	
GGG IV−V	3.86 (3.70−4.02)	P < 0.001	1.12 (1.09−1.15)	P < 0.001
Clinical T-stage				
≤T2	Ref.		Ref.	
≥T3	1.41 (1.33−1.49)	P < 0.001	1.02 (0.96−1.08)	0.5
TX	1.17 (1.06−1.29)	0.002	1.01 (0.89−1.13)	0.9
Clinical N-stage				
N0	Ref.		Ref.	
N1	1.40 (1.31−1.49)	P < 0.001	0.91 (0.83-0.98)	0.02
NX	1.20 (1.12−1.29)	P < 0.001	0.97 (0.91-1.04)	0.4
Clinical M-stage				
M0	Ref.		Ref.	
M1	5.30 (4.99−5.62)	P < 0.001	0.56 (0.52−0.60)	P < 0.001
Treatment				
Local treatment	Ref.		Ref.	
No local treatment	1.67 (1.6−1.73)	P < 0.001	1.49 (1.46−1.53)	P < 0.001

CI = confidence interval; CSM = cancer-specific mortality; HR = hazard ratio; OCM = other-cause mortality.
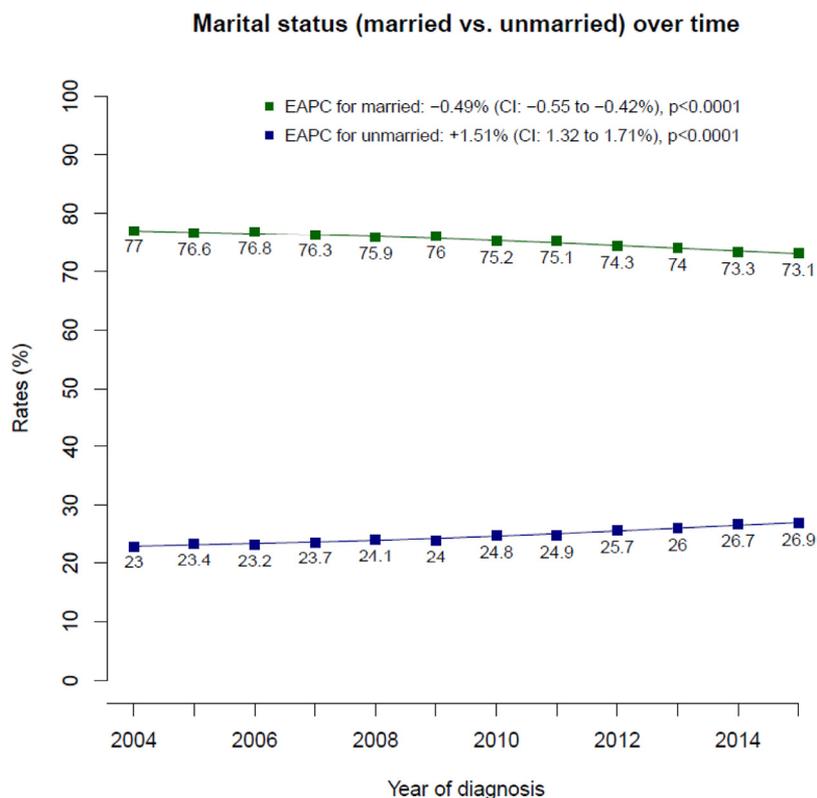

Fig. 1. Graphical presentation of temporal trends for marital status in 433,197 prostate cancer patients across all stages within the Surveillance, Epidemiology and End Results database from 2004 to 2015. CI = 95% confidence interval; EAPC = estimated annual percentage changes.
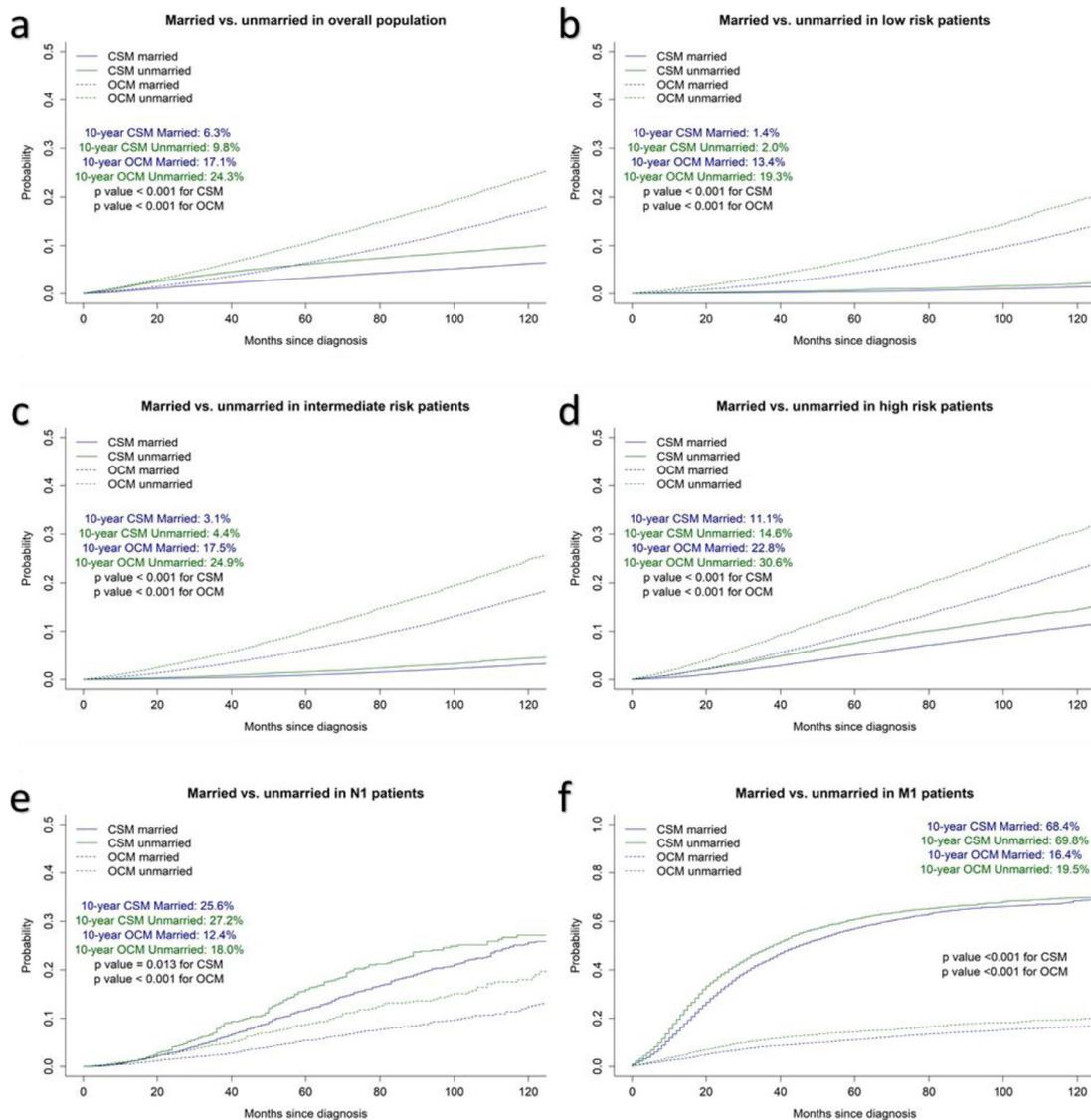
Fig. 2. Cumulative incidence plots depicting cancer-specific mortality (CSM) and other-cause mortality (OCM) over time (months since diagnosis) according to marital status (married vs. unmarried) in the overall cohort (A), the D'Amico low-risk patients (B), the D'Amico intermediate-risk patients (C), the D'Amico high-risk patients (D), the N1M0 patients (E), and the M1 patients (F). Additionally, 10-year CSM and OCM rates as well as statistical significance (Gray test) are shown for each separate analysis.

cohort, CSM rates were 9.8% vs. 6.3% and OCM rates were 24.3% vs. 17.1%, respectively, in unmarried vs. married men (both $P < 0.001$, Fig. 2A). In all 5 subgroup analyses that focused on the 3 D'Amico risk groups, the N1M0 patients, and the M1 patients, similar results were recorded (Fig. 2B−E).

In multivariable competing risks regression models focusing on the overall cohort, unmarried status represented an independent predictor of higher CSM (hazard ratio [HR]: 1.19, $P < 0.001$, Table 2). In subgroup analyses focusing on D'Amico low-risk patients (HR: 1.49, $P < 0.001$), D'Amico intermediate-risk patients (HR: 1.34, $P < 0.001$), D'Amico high-risk patients (HR: 1.15, $P < 0.001$), and M1 patients (HR: 1.08, $P = 0.002$), unmarried status predicted higher CSM. In the subgroup analysis focusing

on the N1M0 patients, marital status did not reach independent predictor status (HR: 1.10, $P = 0.21$, Table 3). Additionally, when substratified within the N1M0 subgroup according to the 3 most common treatment modalities, namely RP, RP combined with EBRT, and NLT, independent predictor status was not reached in either of the 3 examined subgroups (HR: 0.97, 1.40, and 1.10, respectively, all $P > 0.05$).

In multivariable competing risks regression models focusing on the overall cohort, unmarried status represented an independent predictor of higher OCM (HR: 1.41, $P < 0.001$, Table 2). Similarly, in subgroup analyses focusing on D'Amico low-risk patients (HR: 1.49, $P < 0.001$), D'Amico intermediate-risk patients (HR: 1.39, $P < 0.001$), D'Amico high-risk patients (HR: 1.29, $P < 0.001$), N1M0

Table 3
Multivariable competing risks regression models testing the effect of marital status (married vs. unmarried) on cancer-specific mortality in prostate cancer patients within the Surveillance, Epidemiology, and End Results database (2004−2015), stratified according to subgroups (D'Amico low-risk patients, D'Amico intermediate-risk patients, D'Amico high-risk patients, N1M0 patients, and M1 patients)

Patient subgroup	Variable	CSM		OCM	
		Multivariable HR (95% CI)	*P* value	Multivariable HR (95% CI)	*P* value
D'Amico low-risk patients	Marital status				
	Married	Ref.		Ref.	
	Unmarried	1.49 (1.29−1.73)	<0.001	1.49 (1.42−1.56)	<0.001
D'Amico intermediate-risk patients	Marital status				
	Married	Ref.		Ref.	
	Unmarried	1.34 (1.23−1.46)	<0.001	1.39 (1.34−1.44)	<0.001
D'Amico high-risk patients	Marital status				
	Married	Ref.		Ref.	
	Unmarried	1.15 (1.09−1.21)	<0.001	1.29 (1.24−1.34)	<0.001
N1M0 patients	Marital status				
	Married	Ref.		Ref.	
	Unmarried	1.10 (0.94−1.29)	0.2	1.60 (1.30−1.96)	<0.001
M1 patients	Marital status				
	Married	Ref.		Ref.	
	Unmarried	1.08 (1.03−1.14)	0.001	1.31 (1.19−1.45)	<0.001

CI = confidence interval; CSM = cancer-specific mortality; HR = hazard ratio.

Adjusted for baseline preoperative serum prostatic-specific antigen value, age at diagnosis, year of diagnosis, treatment, and race in all groups. Also adjusted for clinical tumor stage, and biopsy Gleason Grade Group in N1M0 and M1 patients.

patients (HR: 1.60, *P* < 0.001), and M1 patients (HR: 1.31, *P* < 0.001), unmarried status predicted higher OCM (Table 3).

In sensitivity analyses focusing on nonmetastatic RP patients, 10-year CSM rates were 2.6% vs. 1.9% and OCM rates were 11.1% vs. 7.3%, respectively, in unmarried vs. married men (both *P* < 0.001). In multivariable competing risks regression models, unmarried status represented an independent predictor of higher CSM (HR: 1.31, *P* < 0.001), as well as OCM (HR: 1.62, *P* < 0.001).

In sensitivity analyses focusing on the historical subgroup (2004−2009), 10-year CSM rates were 9.7% vs. 6.2% and OCM rates were 24.7% vs. 17.4%, respectively, in unmarried vs. married men (both *P* < 0.001). In multivariable competing risks regression models, unmarried status represented an independent predictor of higher CSM (HR: 1.16, *P* < 0.001), as well as OCM (HR: 1.38, *P* < 0.001). In sensitivity analyses focusing on the contemporary subgroup (2010−2015), 5-year CSM rates were 6.3% vs. 3.3% and OCM rates were 9.8% vs. 5.8%, respectively, in unmarried vs. married men (both *P* < 0.001). In multivariable competing risks regression models, unmarried status represented an independent predictor of higher CSM (HR: 1.25, *P* < 0.001), as well as OCM (HR: 1.54, *P* < 0.001).

Discussion

The survival of PC patients is strongly related to biological and pathological variables [9]. However, sociodemographics, such as marital status, may play an equally significant role [1]. The effect of marital status on overall mortality (OM) in cancer patients in general was confirmed in a number of studies, where unmarried individuals had a significantly higher risk of metastatic cancer at presentation, undertreatment and death from their cancer, as well as higher OM [1,10,11]. Likewise, in PC, an increased risk of higher CSM and OM was reported in unmarried men treated with either RP or radiation therapy, as well as with any treatment modality [4,5,12−14]. However, in one of the most contemporary studies by Schiffmann et al. addressing the effect of marital status, unmarried individuals no longer were exposed to an increased risk of CSM [6]. This effect may be related to changes in prevalence rates of married vs. unmarried men. Moreover, the study of Schiffmann et al. exclusively focused on RP patients, in whom a treatment-specific relationship between marital status and outcomes may exist. Last, but not least, it is possible that the vanishing of the protective effect of marital status may be related to very low mortality rates from PC in individuals selected for and treated with RP today. Based on these notions, we hypothesized that the reversal of this relationship observed in the most contemporary cohort of European men may also be applicable to North American patients [6]. We tested this hypothesis within the most contemporary SEER database (2004−2015) to ascertain, whether the marital status is an independent predictor of cancer-specific mortality in contemporary PC patients, across all disease stages, as well as in stage-specific subgroup analyses. Our analyses demonstrated several noteworthy observations.

First, within the overall population, the rate of unmarried men was 24.6%. Furthermore, the observed proportion of unmarried individuals was directly proportional to the risk

level in nonmetastatic patients, where it ranged from 21.7% to 27.1% from favorable to high-risk group. Additionally, we recorded the highest rate of unmarried individuals within the M1 subgroup (39.1%). Moreover, an important difference was recorded according to treatment type. Specifically, the rate of unmarried men was highest among NLT patients (30.2%) and lowest among RP patients (19.0%). These rates convincingly demonstrate a direct relationship, where higher proportion of unmarried men are recorded with increasing biological aggressiveness of PC. In consequence, these differences suggest that a larger proportion of unmarried men present with unfavorable PC risk level, grade, and stage. Finally, previously reported rates of unmarried men ranged from 22.0% to 23.3% in overall cohorts [4,5], from 8.9% to 18.4% in RP patients [6,12,14], and were 24.0% in EBRT patients [13]. To the best of our knowledge, we are the first reporting on contemporary differences across risk categories, disease grade, and stage. In consequence, direct comparisons with other studies are not possible.

Second, the rate of unmarried men increased over time in a meaningful and statistically significant fashion (EAPC: 23.0% in 2004 to 26.9% in 2015, $P < 0.001$). In all 5 subgroup analyses, a similar trend was recorded. Previously, Abdollah et al. also reported on temporal trends in marital status distribution [12]. However, their report exclusively focused on surgically treated PC patients within a historical cohort (SEER from 1988 to 2006). Despite these differences, a similar increasing trend in unmarried individuals was also reported (13.6% in 1988 to 17.7% in 2006).

Third, regarding CSM, our analyses demonstrated a disadvantage in unmarried individuals. It is noteworthy, that the protective effect on CSM recorded in married men persisted, even after specific adjustment for year of diagnosis. This relationship was recorded in the overall cohort, as well as in 4 out of 5 subgroups, namely D'Amico low-risk patients, D'Amico intermediate-risk patients, D'Amico high-risk patients, and M1 patients, but not in N1M0 patients. Moreover, this relationship was also recorded within the subgroup of nonmetastatic RP patients. Further sensitivity analyses that addressed potential changes in the effect of marital status over time corroborated the overall findings in both, the historical (2004−2009) and contemporary (2010−2015) cohorts. To the best of our knowledge, we are the first to perform a comprehensive analysis of marital status on CSM, across all PC stages. In consequence, our results refute our original hypothesis about potential disappearance of the protective effect that was previously recorded in married PC patients, when cancer control outcomes were examined [4,5,12−14]. However, our comprehensive analysis has revealed that this effect is not applicable to patients with N1M0 patients. Several arguments may be proposed to explain the difference in marital status effect relative to other patient subgroups. Possibly, a greater variety of treatment modalities that were offered to these patients, alone or in combination, may represent 1

such explanation. According to this premise, homogenous CSM rates that are predominantly and virtually exclusively determined by primary treatment may preclude the presence of a residual effect from marital status. Our attempts at explaining the differences by virtue of subgroup analyses within the 3 most common treatment modalities (RP, EBRT, and NLT) in the N1M0 group failed to provide a valid explanation. Since we are the first to perform a comprehensive analysis in all substages in addition to stage subgroup analyses, we cannot compare our findings with those of other investigators. Specifically, since none have reported on the relationship between marital status and CSM in N1M0 patients.

Fourth, regarding OCM, our analyses demonstrated a disadvantage in unmarried men in the overall group, as well as consistently within all 5 subgroups. The protective effect of marital status on overall survival is well known and has been demonstrated for a variety of urological as well as nonurological primaries [1−4]. However, to the best of our knowledge, only 2 studies described the effect of marital status on OCM. Specifically, the disadvantage of unmarried individuals regarding OCM was recently reported in nonsmall cell lung cancer and in head and neck cancer [15,16]. In consequence and to the best of our knowledge, we are the first to report a comprehensive analysis examining the effect of marital status on OCM for PC patients. Our findings add to the existing body of evidence that until now originates from outside of urologic oncology. It is of note, that like for CSM, the reported relationships achieved independent predictor status even after adjustment for year of diagnosis in OCM.

The rationale behind the protective effect of marital status for longevity is multifactorial. A benefit in social integration and socioemotional support as well as in socioeconomic resources was described [17]. Similarly, health behaviors and psycho-physical health status are important variables mediating the relation between marital status and mortality [18]. For example, better treatment adherence has been described for married patients [1]. In consequence, the clinical implications of our findings are that unmarried men may require closer follow-up, as well as other ancillary measures aimed at reducing the CSM and OCM disadvantages. Specifically, psychosocial and behavioral change interventions aiming at improving lifestyle, nutrition, or physical activity may be of value [19]. Similarly, support groups are known to improve quality of life of PC patients, potentially adding to improved survival [20,21]. Taken together, physicians treating unmarried patients with PC should be aware of poorer CSM and OCM outcomes in these individuals. In consequence, ongoing efforts aiming at improving treatment adherence and follow-up recommendations in these patients are warranted [1,17].

Our study has several strengths that distinguish it from previous reports. It relies on the most contemporary patient population that reflects modern diagnostics, staging, and

therapeutics. In consequence, it is the most generalizable study to illustrate contemporary management of PC patients. Moreover, it relies on the most stringent adjustment for potential selection biases that could distinguish married from unmarried patients. Unlike any previous study, it relies on multivariable competing risk regression models.

Several limitations of our study need to be mentioned. First, since SEER is an observational database, data are only retrospectively evaluated and determination of direct causal relationships of marital status on mortality and stage at presentation is not possible. Additionally, the SEER database does not provide more details about change of marital status over time. Similarly, the SEER database does not allow to ascertain whether unmarried men actually lived with their partners. Second, no further information regarding psychosocial risk factors or social support, as, for example, quality of life is accessible in the SEER database. Moreover, distance traveled, insurance status, education, or academic vs. nonacademic hospital status could not be addressed within the current analysis, which might represent potential factors associated with CSM [1,22]. The same accounts for comorbidities, which are not recorded. However, we focused on OCM and relied on competing risks regression to address this limitation. Also, only CSM was available for purpose of outcome analyses. None of potentially important earlier cancer-control outcomes such as biochemical recurrence, progression-free survival, and metastatic progression were available. Similarly, information regarding adjuvant or salvage treatment (i.e., RT, antiandrogen deprivation therapy, or chemotherapy) is not available within the SEER database. Moreover, standardized staging information was not available. Similarly, staging methods may have varied between patients or in some more detailed staging efforts were made. Finally, heterogeneity in treatment assignment that is applicable to all nonrandomized studies existed. However, these limitations apply to all observational studies that rely on either the SEER database or similar population-based databases [5,12,14].

Conclusions

Unmarried PC patients are at higher risk of CSM and OCM. This relationship applies to all stage subgroups, except for the N1M0 subgroup. Consequently, unmarried individuals should ideally benefit of improved counseling, closer follow-up, as well as of other measures aimed at reducing the CSM and OCM disadvantages.

Conflict of interest

There was no external financial support for this study. The authors declare that they have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.urolonc.2019.04.023.

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