Marital status and prostate cancer outcomes

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Introduction: *To evaluate the influence of marriage on the survival outcomes of men diagnosed with prostate cancer.*
Materials and methods: *We examined 115,922 prostate cancer cases reported to the Surveillance, Epidemiology, and End Results (SEER) database between 1988 and 2003. Multivariate Cox regression techniques were used to study the relationship of marital status and prostate cancer-specific and overall mortality.*
Results: *Married men comprised 78% of the cohort (n=91,490) while unmarried men (single, divorced, widowed, and separated) comprised 22% of the cohort (n = 24,432). Married men were younger (66.4 versus 67.8 years, p < 0.0001), more likely to be white (85% versus 76%, p < 0.0001), presented with lower tumor grades (68% are well or moderately differentiated versus 62%, p < 0.0001) and at earlier clinical stages (41% AJCC stage I/II versus 37%, p < 0.0001). Multivariate analysis revealed that unmarried men had a 40% increase in the relative risk of prostate cancer-specific mortality (HR 1.40; CI 1.35-1.44; p < 0.0001), and a 51% increase in overall mortality (HR 1.51; CI 1.48-1.54; p < 0.0001), even when controlling for age, AJCC stage, tumor grade, race and median household income. Furthermore, the 5 year disease-specific survival rates for married men was 89.1% compared to 80.5% for unmarried men (p < 0.0001).*
Conclusion: *Marital status is an independent predictor of prostate cancer-specific mortality and overall mortality in men with prostate cancer. Unmarried men have a higher risk of prostate cancer-specific mortality compared to married men of similar age, race, stage, and tumor grade.*

Key Words: prostate cancer, survival, marriage, competing risks regression

Introduction

The theory that marriage has beneficial effects for survival was first demonstrated by Durkheim's pioneering study on suicide in 1897.[1] Many population-based studies since this initial observation have further demonstrated the protective effects of marriage on survival, which has been validated across all major non-married categories (divorced/separated, widowed, and never-married).[2-4] Studies have also documented this effect in various types of cancer patient populations.[5-10]

The impact of marital status on long term prostate cancer survival was first explored in a study using Surveillance, Epidemiology, and End Results (SEER) data from 1973 to 1990.[11] These data illustrated the importance of marital status as an independent predictor of long term overall mortality and were corroborated in an analysis of a similar cohort of Norwegian prostate cancer patients from 1960 to 1991.[12] However, in the United States, the institution of marriage is constantly evolving. Households occupied by unmarried opposite sex partners, for example, have risen by 20% over the last decade. More married couples are electing to have fewer children or none at all. Same-sex households have likewise risen by 25% over the last decade.[13] In short, the United States has witnessed dramatic changes in what constitutes "marriage", with an evolving notion of the traditional nuclear family structure.

It is unknown, however, the extent to which the relationship between marital status and prostate cancer survival has changed, if at all, during the evolution of social normatives regarding marriage. In an effort to elucidate the relationship of an ever-evolving concept of marriage and long term prostate cancer survival metrics, we employ the use of a contemporary SEER dataset from 1988-2003. Through univariate and multivariate regression modeling, we explore the impact of marital status on long term prostate cancer-specific mortality and overall mortality in men diagnosed with prostate cancer.

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Materials and methods

Data

Data from the Surveillance, Epidemiology, and End Results (SEER) public-use database were used as the basis for this study. The SEER cancer registry is comprised of patients from 17 representative geographic regions within the United States which encompass approximately 26% of the general population and is made available by the National Cancer Institute.[14] The registry includes San Francisco-Oakland (SFO), Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, Atlanta, Alaska Native, San Jose-Monterey (SJM), Los Angeles (LA), rural Georgia, California (excluding SFO/SJM/LA), Kentucky, Louisiana, and New Jersey areas. The registry was queried using SEER*Stat software, version 7.0.4 in client-server mode (National Cancer Institute).

Patient population and variables

We identified 115,922 men diagnosed with adenocarcinoma of the prostate (C61.9-prostate gland and ICD-0-3 hist/behav = 8140/3: adenocarcinoma, NOS) from 1988 to 2003. These years were selected based on the tenure of the 3rd edition of the American Joint Committee on Cancer (AJCC) staging classification system. Patients were selected only if complete data regarding marital status, age, race, tumor grade, and clinical stage were available making the dataset perfectly complete. Marital status is categorized as single, married, separated, divorced, or widowed in the SEER registry. We combined the single, separated, divorced, and widowed categories to create a dichotomous variable indicating whether or not an individual was married at the time of diagnosis. Race data are entered into the SEER dataset as White, Black, and Other (which includes American Indian/Alaska Native, Asian/Pacific Islander, and Other Unspecified). Vital statistics are determined from local death certificates, voter registration records, and hospital medical records.

Statistical analysis

All statistical calculations were computed using Stata/SE v 11.0 (College Station, TX, USA) for Mac OS X. Univariate analysis using t-tests and χ^2 tests compared characteristics of patients separated by marital status. The normality of all continuous variables was examined using histograms and ladder-of-powers plots. Hazard ratios for the risk of prostate cancer-specific mortality and overall mortality were determined using multivariate Cox regression methods. Covariates were selected for inclusion in the final model based on a priori relationships with prostate cancer survival. The Breslow method was applied to handle tied failures. The proportional hazards of all variables were examined using "Log-Log" plots, scaled schoenfeld residuals, and by building time varying covariates into the model. In Cox regression survival analysis, competing events (e.g. death from other causes) impede the occurrence of the event of interest (prostate cancer-specific mortality). Competing risks regression models were therefore constructed to account for the effect of other causes of mortality. Log-rank tests were used to compare Kaplan-Meier estimates of survival.

Results

Cohort description

A total of 115,922 cases of prostate cancer were reported to the Surveillance, Epidemiology, and End Results (SEER 17) database between 1988 and 2003. Married men comprise 78% of the cohort (n = 91,490) while unmarried men (single, divorced, widowed, and separated) comprise 22% (n = 24,432). Table 1 shows the cohort characteristics stratified by marital status. Married men are younger (66.4 versus 67.8, $p < 0.0001$), more likely to be white (85% versus 76%, $p < 0.0001$), present with lower tumor grades (68% are well or moderately differentiated versus 62%, $p < 0.0001$) and at earlier clinical stages (41% AJCC stage I/II versus 37%, $p < 0.0001$). Married men also have higher median household incomes and had a longer duration of follow up during the study period.

Survival

The three leading causes of death by organ system were prostate (n = 20,050), heart (n = 8,921) and lung diseases (n = 2,163). Thirty-nine percent of married men (n = 36,032) died during the study period compared to 53% (n = 12,922) of unmarried men ($p < 0.0001$). With respect to prostate cancer-specific mortality, 17% (n = 15,835) of married men died of prostate cancer compared to 25% (n = 6,065) of unmarried patients ($p < 0.0001$). The 5 year overall survival rate of married men was 79.5% compared to 65.3% for unmarried men ($p < 0.0001$) while the prostate cancer specific 5 year survival rate was 89.1% and 80.5%, respectively ($p < 0.0001$), Figure 1.

Cox regression analysis

Unmarried men have an increased risk of overall mortality (HR 1.51; CI 1.48-1.54; $p < 0.0001$) and prostate cancer-specific mortality (HR 1.40; CI 1.35-1.44; $p < 0.0001$), even after controlling for age, AJCC stage, tumor grade, race, and median annual household income, Table 2. Several other variables also independently predicted mortality in this study as well. As expected, older age,

TABLE 1. **Cohort characteristics by marital status**

	Group 1 (Married) n = 91,490	Group 2 (Unmarried) n = 24,432	p value
Age at diagnosis (yr)	66.4	67.8	< 0.0001
Race			< 0.0001
White	77,987 (85%)	18,563 (76%)	
Black	8,464 (9%)	4,884 (20%)	
Other	5,039 (6%)	985 (4%)	
AJCC stage, 3rd Edition			< 0.0001
Stage I	5,925 (7%)	1,474 (6%)	
Stage II	31,017 (34%)	7,602 (31%)	
Stage III	30,580 (33%)	6,315 (26%)	
Stage IV	23,968 (26%)	9,041 (37%)	
Tumor grade			< 0.0001
Well differentiated	3,961 (4%)	1,000 (4%)	
Moderately differentiated	58,582 (64%)	14,133 (58%)	
Poorly differentiated	28,317 (31%)	9,067 (37%)	
Undifferentiated/anaplastic	630 (1%)	232 (1%)	
Region			< 0.0001
Pacific Coast	47,549 (52%)	13,312 (54%)	
East	19,383 (21%)	5,408 (22%)	
Northern Plains	16,307 (18%)	4,247 (17%)	
Southwest	8,211 (9%)	1,458 (6%)	
Alaska	40 (< 1%)	7 (< 1%)	
Duration of follow up (mo's)	93.9	75.2	< 0.0001
Median household income	$34,679	$34,489	0.0003

advanced AJCC stage, higher tumor grade, and black ethnicity were independently predictive of prostate cancer-specific mortality and overall mortality.

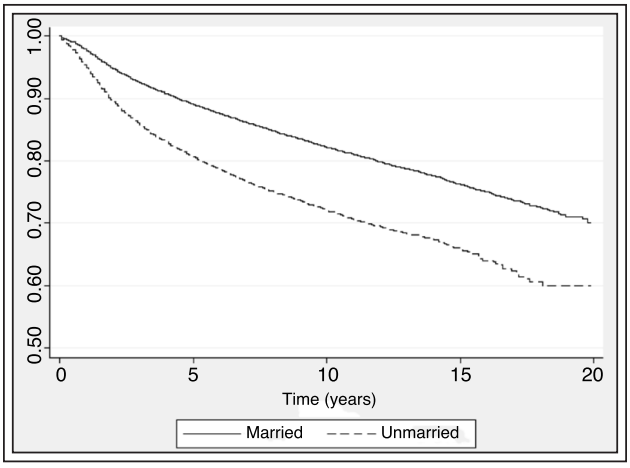

Figure 1. Kaplan-Meier estimates of prostate cancer-specific survival stratified by marital status (p < 0.0001).

Competing risks regression analysis

Since 28,904 patients died of some cause other than prostate cancer (59% of all deaths), efforts were made to adjust for these competing events. Using competing risks regression models (which account for non-prostate causes of death), marital status retained its significant explanatory power of prostate cancer-specific mortality, even after controlling for age, AJCC stage, tumor grade, median household income and race, Table 3. Patients who are unmarried at the time of diagnosis have a 16%-25% greater chance of dying from their disease (HR 1.20; CI 1.16-1.25; p < 0.0001) than married men even when taking into account competing causes of death, including cardiovascular and respiratory diseases, traumatic accidents and other primary cancers.

Discussion

Contemporary marriage at the time of diagnosis is a strong, independent predictor of prostate cancer-

TABLE 2. **Multivariate Cox regression analysis of variables associated with prostate cancer-specific and overall mortality**

	Prostate cancer specific mortality			Overall mortality		
	HR	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Age						
≤ 50	0.57	0.51-0.63	< 0.0001	0.28	0.26-0.31	< 0.0001
51-65	0.56	0.54-0.58	< 0.0001	0.40	0.39-0.41	< 0.0001
≥ 66	1.00	Referent		1.00	Referent	
AJCC stage, 3rd Edition						
Stage I	1.00	Referent		1.00	Referent	
Stage II	1.47	1.30-1.67	< 0.0001	0.93	0.89-0.97	< 0.0001
Stage III	1.63	1.45-1.84	< 0.0001	0.78	0.75-0.82	< 0.0001
Stage IV	12.9	11.5-14.6	< 0.0001	2.85	2.74-2.97	< 0.0001
Tumor grade						
Well differentiated	1.00	Referent		1.00	Referent	
Moderately differentiated	2.35	2.28-2.42	< 0.0001	1.64	1.61-1.68	< 0.0001
Poorly differentiated	3.35	3.03-3.69	< 0.0001	2.17	2.01-2.35	< 0.0001
Race						
Black	1.00	Referent		1.00	Referent	
White	0.65	0.61-0.70	< 0.0001	0.72	0.68-0.75	< 0.0001
Other	0.82	0.79-0.86	< 0.0001	0.83	0.81-0.85	< 0.0001
Marital status						
Married	1.00	Referent		1.00	Referent	
Unmarried	1.40	1.35-1.44	< 0.0001	1.51	1.48-1.54	< 0.0001
Median household income						
< $45,000	1.00	Referent		1.00	Referent	
≥ $45,000	0.94	0.90-0.98	0.008	0.91	0.89-0.94	0.0001

specific mortality and overall mortality, even when controlling for age, clinical stage, tumor grade, race, and other competing causes of mortality. Even after adjusting for competing causes of death, estimates from our model would indicate that unmarried men have a 16%-25% greater chance of dying from their disease than married men of similar age, clinical stage, tumor grade, and race.

This lower mortality rate observed for married patients may be secondary to stronger social supports.

TABLE 3. **Multivariate competing risks regression analysis of prostate cancer-specific mortality**

	HR	**95% CI**	**p value**
Marital status			
Married	1.00	Referent	
Unmarried	1.20	1.16-1.25	< 0.0001

*Grade, AJCC stage, age, race, and income included in model but not shown for brevity

Marriage is one of the most important types of social support, which has not only been linked to lower rates of morbidity and mortality, but also to more favorable "biologic profiles" with beneficial changes in cardiovascular, neuroendocrine, and immune function.[15] The spouse has been shown to be a positive influence in the care of the married patient as well as an important promoter of healthy behaviors.[16] Alternatively, lead-time bias may a contributor to the observed survival advantage as married patients are more likely to be diagnosed at earlier clinical stages; however, married men are also more likely to receive recommended therapies suggesting an important role for the spouse in the monitoring of the health of their spouse as well as encouraging healthy decisions.[5,6,17]

Krongrad and colleagues have previously shown the beneficial effects of the marital status on prostate cancer survival in an innovative study using a SEER dataset from 1973-1990.[11] In this analysis, marital status was a strong independent predictor of overall mortality and that unmarried men faced a 25%-31% increased risk

of death. However, our analysis is different in a few key respects. First, our dataset spans a more recent timeframe (1988-2003) in an effort to elucidate the contemporary relationship of marriage and prostate cancer survival. Second, we use a separate, more standardized staging classification system (American Joint Committee on Cancer, 3rd edition compared to SEER historic staging classifications). Lastly, in addition to age, clinical stage, tumor grade, race and marital status, we account for competing causes of deaths using competing risk regression techniques. This is may be an important control as 25% of the cohort died from causes other than prostate cancer, representing 59% of all deaths in the study period. Despite these methodological differences, however, the magnitude of the beneficial effect of marriage on cancer-specific and overall survival remains but is somewhat lower than predicted by previous published models.

Despite our findings, there are several important limitations to appreciate. First, these findings may have been an artifact of selection bias in that those who live longer simply have a more time to get married. Second, marital status is not a static entity, despite being treated as such in this study. That is, as time progresses, marriages dissolve and reform such that the marital status of many individuals may have changed during the study period. This is particularly true in a cohort of elderly men with prostate cancer who may have been "married" at the time of diagnosis, but "widowed" at the time of death. Unfortunately, "marital status" in SEER is merely a reflection of one's marital status at the time of diagnosis, making it difficult to treat marriage as a time-varying covariate. However, as previously pointed out, this likely led to an underestimation of the protective effect of marriage as the exclusion of "marital transitions" has actually been shown to diminish the protective effects of marriage on survival.[18] Furthermore, data on unmarried opposite sex partners, unmarried same-sex partners, and married same-sex partners is not presently available in the SEER public-use registry. Finally, this is a retrospective study design with all the inherent limitations of observational data. However, given the impracticality of randomization as well as the rigorous data quality control measures employed by the National Cancer Institute, this study design is a suitable approach for exploring the relationship of demographic variables and survival.

Conclusion

Marriage is a strong independent predictor of cancer-specific survival in men diagnosed with prostate cancer in recent decades. Even after adjusting for competing causes of death, married men have a higher risk of prostate cancer-specific mortality and overall mortality compared to married men of similar age, race, stage, and tumor grade. Further study may be required in the ensuing decades as traditional views of marriage are redefined in the context of evolving social mores. □

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