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Determinants of Prostate Cancer Survival in Arizona: Demographic and Clinical Characteristics

Gudeta D. Fufaa
Arizona Department of Health Services

In investigating the determinants of survival of prostate cancer cohorts, characterization of the cohort in terms of competing underlying causes of death would be appropriate. Atherosclerotic heart disease, bronchitis, acute myocardial infarction, chronic obstructive pulmonary disease, atherosclerotic cardiovascular disease, and stroke were found to be the major causes of death among prostate cancer cohorts aside from prostate cancer. A population-based assessment of the codeterminants of mortality and a demographic and clinical determinant of prostate cancer survival was undertaken. Average survival time and survival curves of the various age categories were significantly different. The average survival time and survival curves of the different levels of grade and SEER summary stage were significantly different. On average, the regression coefficients of age categories, the different levels of grade, and SEER summary stages were significant predictors of survival for the prostate cancer cohorts studied. Clinical management of prostate cancer patients should consider the risk factors for the identified codeterminants of mortality among prostate cancer cohorts.

Keywords: *age, grade, prostate cancer, SEER summary stage, survival*

Introduction

Prostate cancer is the most commonly diagnosed type of cancer among populations in the United States and is estimated to occur at 156.9 per 100,000 men (Centers for Disease Control and Prevention, 2010). The mean prostate-cancer-related death rate among all races/ethnicities in the United States from 2002 to 2006 is 25.6 per 100,000 persons (Edwards et al., 2010). The total healthcare budget associated with prostate cancer from 1998 to 2003 was estimated to vary from $2.6 to $4.3 billion (DeVol & Bedroussian, 2007). The mean prostate cancer incidence rate among men in Arizona between 1995 and 2007 varied between 112 and 137 per 100,000 persons (Indicator Based Information System [IBIS], 2010). IBIS is a system that allows the public to query cancer incidence and mortality estimated in Arizona by year. This public health data access tool is intended to support evidenced-based public health decision-making in the state of Arizona. The average prostate cancer mortality rate from 2000 to 2007 among men in Arizona varied from 8.32 to 11.52 per 100,000 persons (IBIS, 2010). The average prostate cancer mortality rate in Arizona is consistently lower than that of the U.S. rate (Stoll, 2000); however, assessments of the determinants of prostate cancer survival in Arizona are lacking.

Along with the age of the patient, the stage of prostate cancer at diagnosis and grade are hypothesized to determine survival in patients diagnosed with prostate cancer (Stattin et al., 2010). This is probably due to the influences of stage and grade on the choice of treatment options or due to the associated adverse effects of the kinds of therapeutic measures used (Lepor, 2002); moreover,

Please address queries to: Gudeta D. Fufaa, Ph.D., Arizona Department of Health Services, 150 N. 18th Avenue, Suite 300, Phoenix, AZ 85007-2602. Email: Gudeta.Fufaa@azdhs.gov

cardiovascular and other chronic diseases are associated with significant mortality among individuals diagnosed with prostate cancer (Ketchandji, Kuo, Shahinian, & Goodwin, 2009). This study was conducted with the objective of assessing the demographic and clinical determinants of prostate cancer survival and the impact of associated comorbidities associated with cardiovascular and other chronic diseases among prostate cancer subjects in the state of Arizona.

Materials and Methods

This study used population-based prostate cancer surveillance data in Arizona to investigate the effects of age at diagnosis, cancer stage, and grade on survival. Other causes of mortality among the population of subjects diagnosed with prostate cancer from 1995 to 2007 in the state of Arizona were also examined. Prostate cancer cases were identified from the Arizona Cancer Registry for the years 1995–2007. The Arizona Cancer Registry is a population-based surveillance system that collects, manages, and analyzes information on the incidence and mortality due to cancer, including prostate cancer. Cancer cases are abstracted by skilled abstractors at the hospital and then reported to the Central Registry, whereby the Registry staff undertakes the task of processing and quality-controlling the data. Hospitals with fewer than 50 beds are not required to abstract their own cancer cases; instead, Central Registry staff travel to those facilities to complete the abstracts. Age, sex, race/ethnicity, date of diagnosis, survival time, vital status, stage, and grade at diagnosis are some of the important demographic and clinical data that can be identified from the Registry database for each subject.

From 1995 to 2007, a total of 35,528 prostate cancer cases were identified from the Registry using The International Classification of Diseases for Oncology, ICD-O-2 (Percy, Van Holten, & Muir, 1990) and ICD-O-3 (Fritz et al., 2000). The underlying causes of death were identified using The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM; World Health Organization, 1992) and International Statistical Classification of Diseases and Related Health Problems, 10th Revision, (ICD-10; World Health Organization, 1999) codes for prostate cancer. Of these cases, other competing underlying causes of death were identified and their percentage contributions were described. Subjects who died of other causes of death were excluded from analysis. This resulted in total of 27,831 prostate cancer cases that were used for assessing survival. Descriptive statistics of age were generated for characterizing the cohort in terms of age groups. To examine the effect of age on survival, age groups were categorized. Mortality due to the comorbidities of cardiovascular and other chronic diseases among the cohorts was examined.

Surveillance, Epidemiology and End Results (SEER) staging (0, 1, 2, 3, 4, and 7; Beahrs, Henson, Hutter, & Kennedy, 1992) was used in characterizing and describing the effect of prostate cancer staging on survival time. The prostate cancer histological grading system of Beahrs et al. (1992) was used in describing the effect of grading on survival. Kaplan-Meier survival curves were used to compare survival time among the various categories of age and levels of stage and grade using IBM SPSS Statistics 19. Cox proportional hazards regression was used to investigate the predictive significance of age, grade, and stage on survival. The backward stepwise (likelihood ratio) method was used in fitting the Cox proportional hazards model. The hypothesis tested was that age, grade, and SEER summary stage are not significant predictors of survival.

Results

The proportions of nonprostate cancer related mortality are presented in Figure 1. After prostate cancer, the major causes of death among the cohort include atherosclerosic heart disease, bronchitis, acute myocardial infarction, chronic obstructive pulmonary disease, atherosclerotic cardiovascular disease, and stroke.

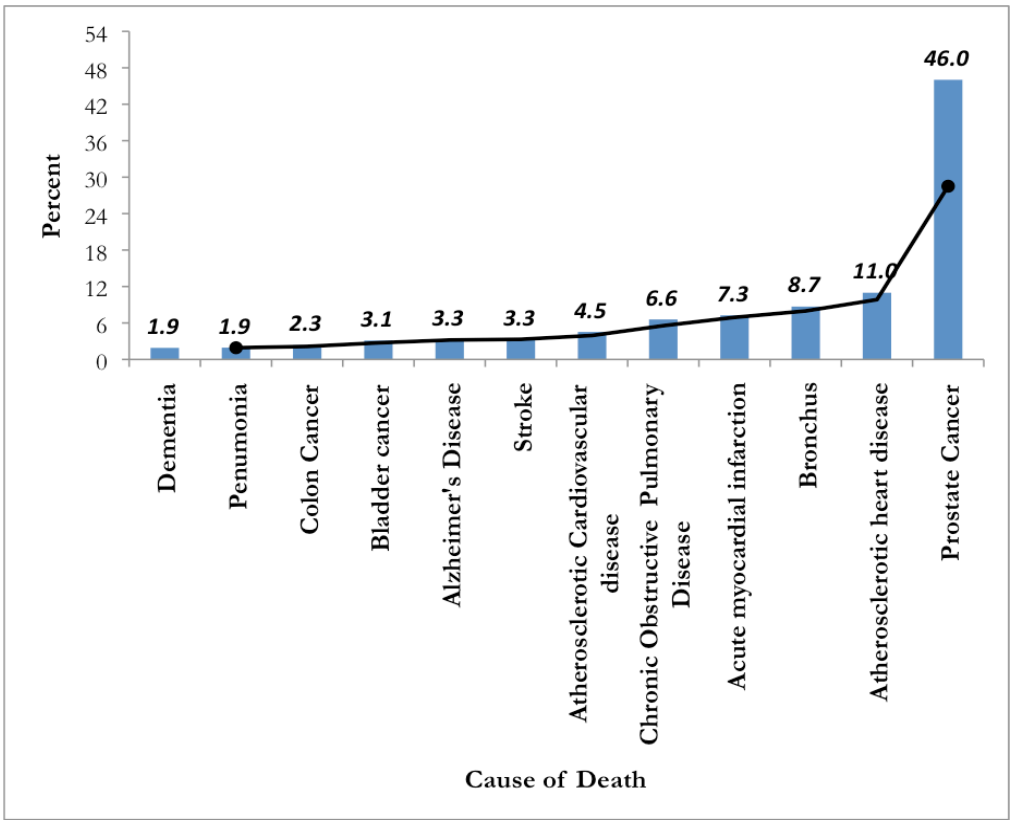

Figure 1. *Major Causes of Mortality in the Cohort*

The age distribution among the cohort by vital status in which all causes of mortality were considered is shown in Figure 2; the distribution in which only mortality due to prostate cancer was considered is shown in Figure 3. The average age among the cohorts in which all causes of mortality were considered was 66 for those who were alive and 73 for those who were deceased (Figure 2).

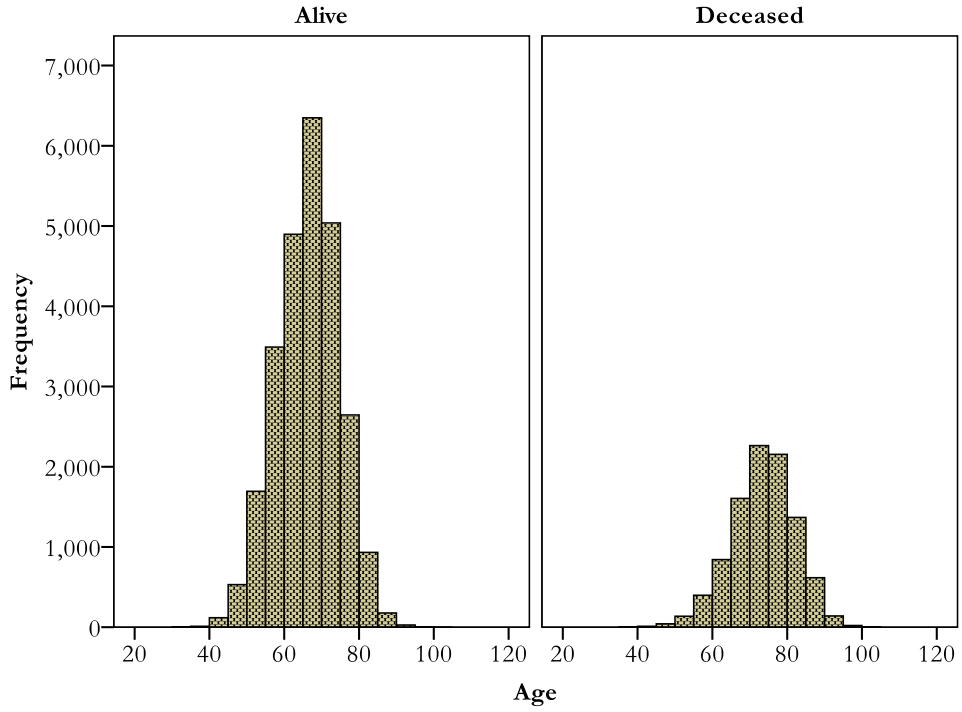

Figure 2. *The Distribution of Age Among the Cohort by Vital Status in Which Other Underlying Causes of Death Are Included*

The average age among the cohorts in which only mortality due to prostate cancer was considered was 66 for those who were alive and 72 for those who were deceased (Figure 3). This analysis indicated that the average age distribution is very similar when other underlying causes of death are considered aside from prostate cancer.

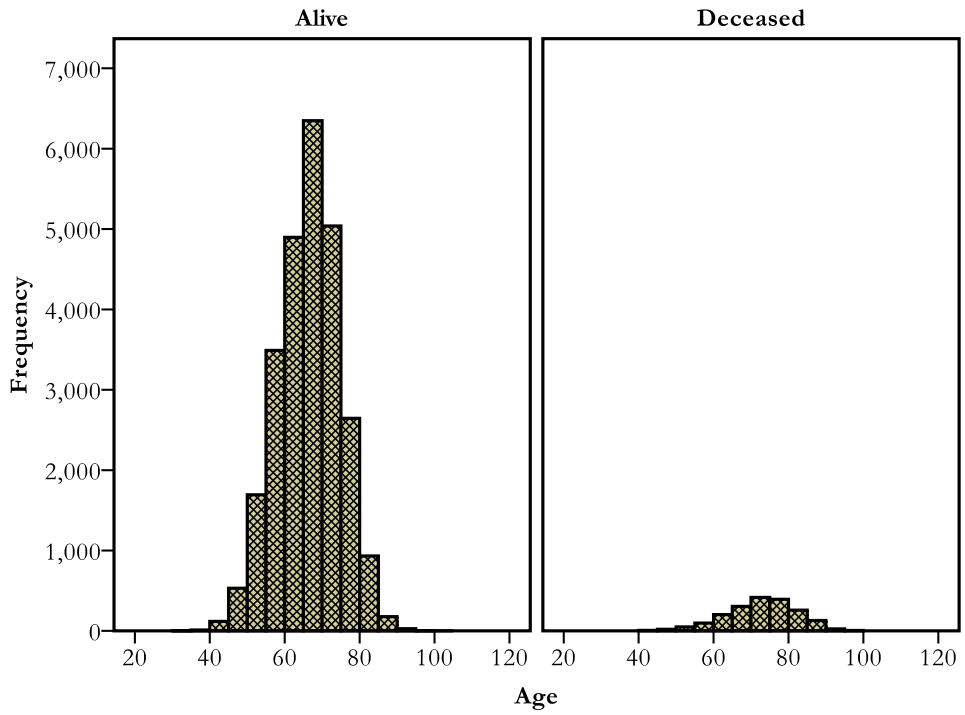

Figure 3. *The Distribution of Age Among the Cohort by Vital Status in Which Only Mortality Due to Prostate Cancer Cases Were Considered*

Comparisons of average survival time among the various categories of age, levels of grade, and SEER summary stage are given in Figures 4, 5, and 6, respectively. The log-rank test indicated that the average survival time is significantly different between the various age categories. The average survival time was shortest for the age group 81 and above, followed by the youngest age group (31–40; Figure 4).

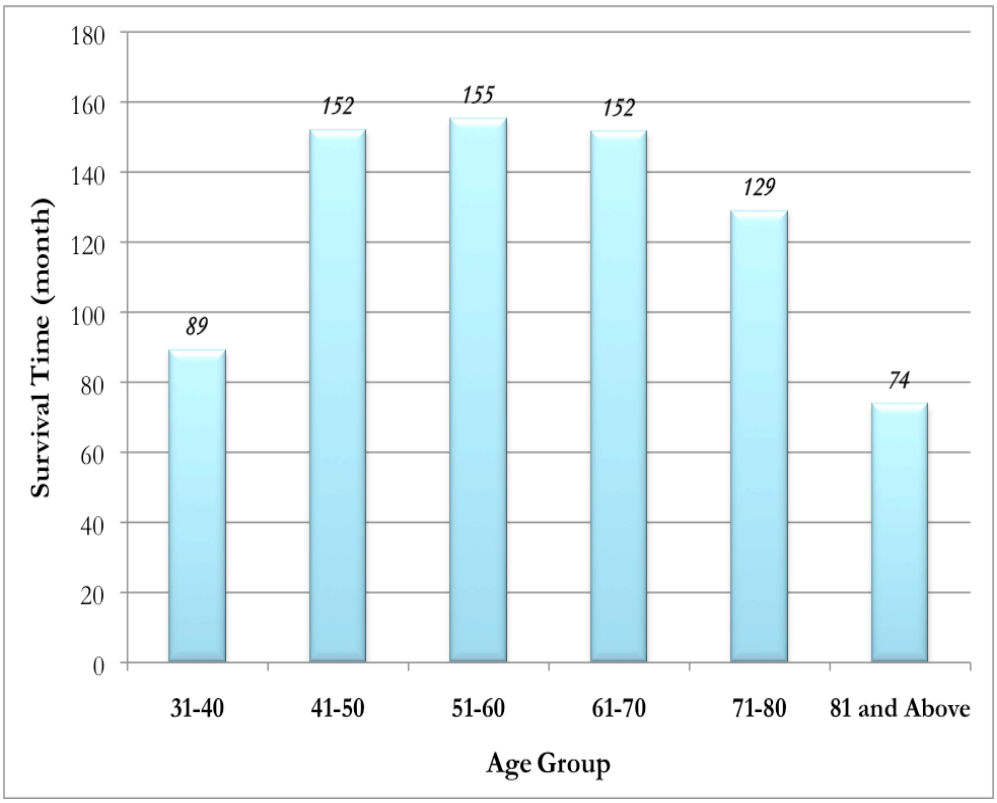

Figure 4. *Average Survival Time as Function of Age Group*

Similarly, the log-rank test showed that the average survival times of the various grades were significantly different from each other. The relationship between average survival time and grade was an inverse linear relationship. The lower the prostate cancer grade, the longer was the average survival time (Figure 5).

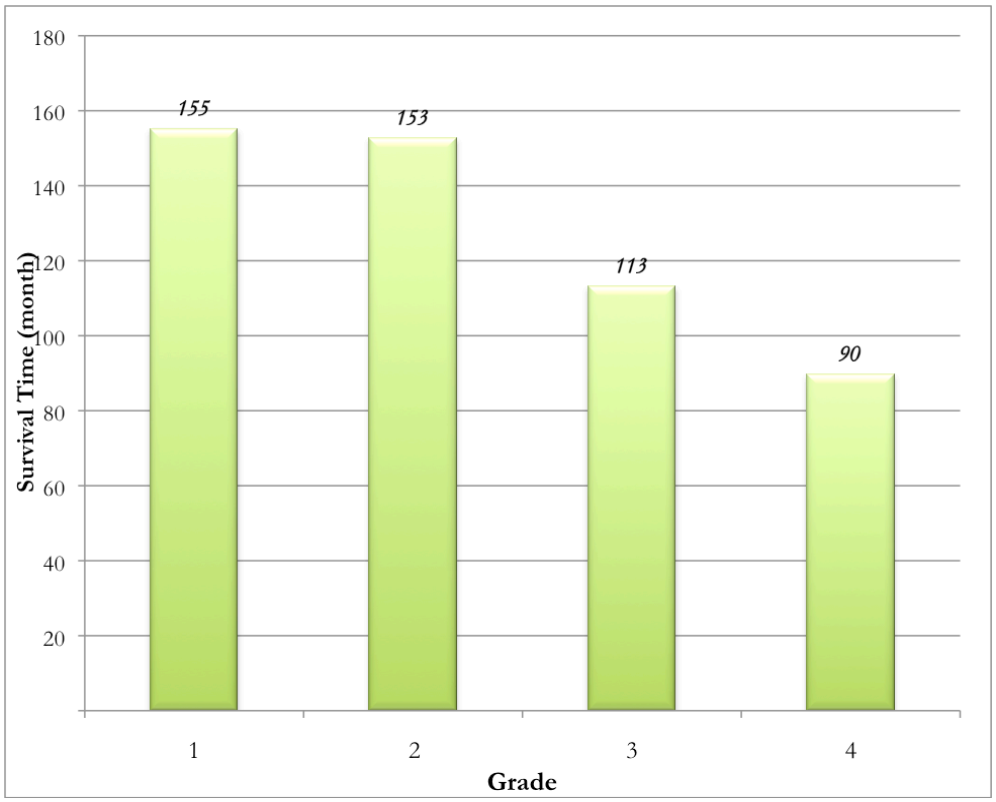

Figure 5. *Average Survival Time as Function of Grade*

Based on the log-rank test, the various stages had significantly different mean survival times. A similar trend was observed with regards to the association between the SEER summary stage and average survival time, although the average survival time for the SEER summary stage 0 was less than that of stage 1 (Figure 6). In particular, the average survival time for the highest SEER summary stage was strikingly the shortest among all of the SEER summary stage average survival times.

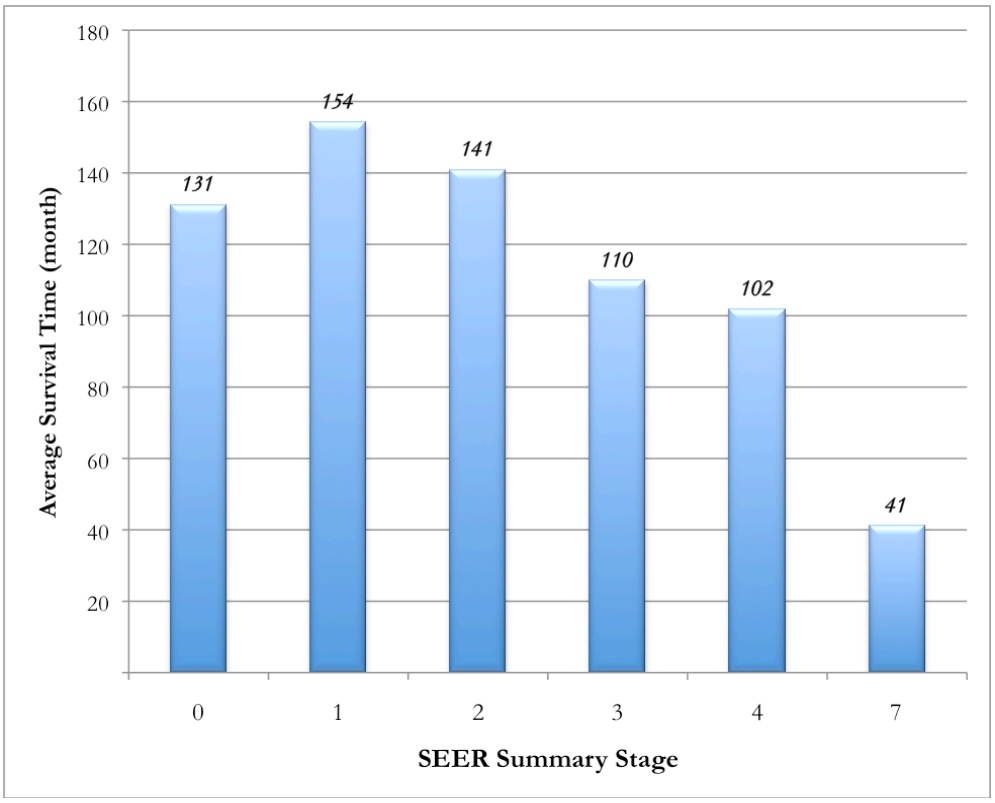

Figure 6. *Average Survival Time as Function of SEER Summary Stage*

Survival curves for the various categories of age, levels of grade, and SEER summary stages are presented in Figures 7, 8, and 9, respectively. Figure 7 shows that age group 81 and above has the lowest cumulative survival rate, followed by the age category 71–80. Age groups 41–50 and 51–60 have a very similar cumulative survival curve.

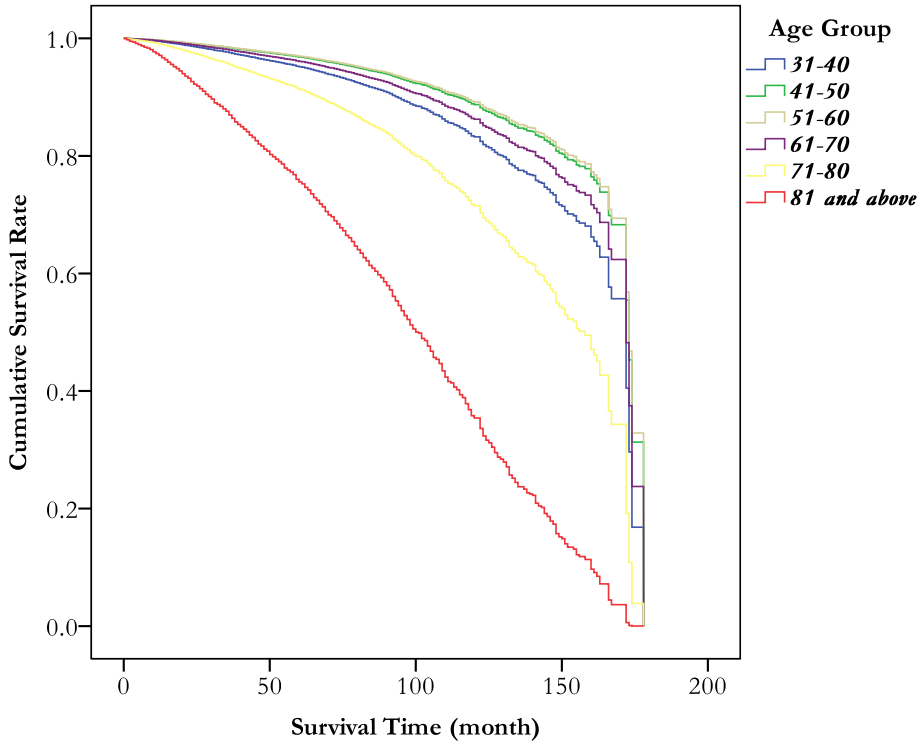

Figure 7. *Survival Curves for the Various Age Groups*

Figure 8 corroborates what is presented in Figure 5 in terms of average survival time. The cumulative survival rate for grade level 4 is the lowest among all grade levels described in the cohort. While the survival curves of grade levels 1 and 2 were very closely related, the survival curves for grades 4 and 5 were very similar.

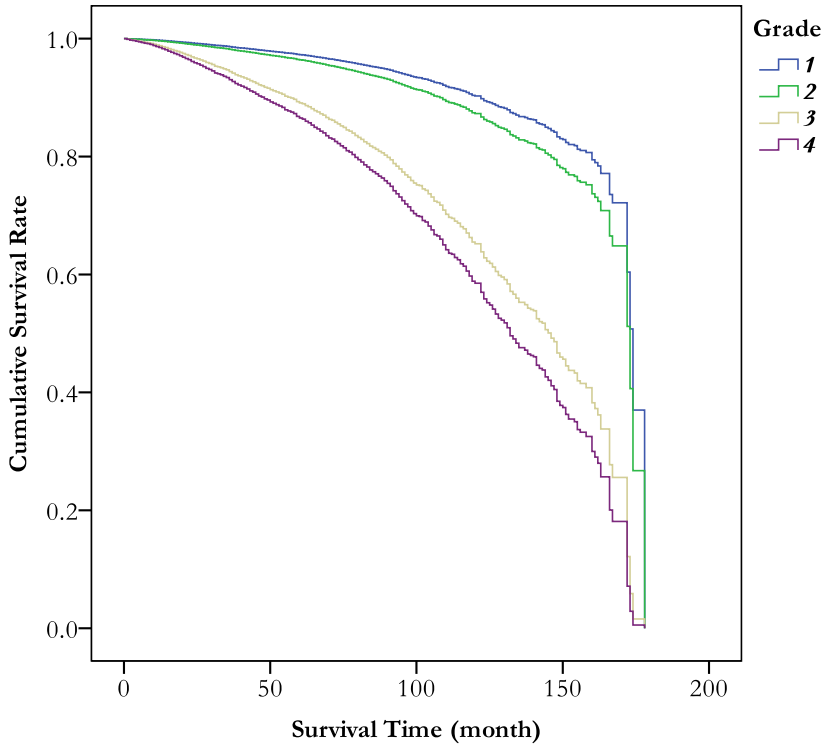

Figure 8. *Survival Curves for the Various Grades*

The cumulative survival rate for SEER summary stage 7 was the lowest among all stages described, while SEER summary stage 1 had the highest cumulative survival rate (Figure 9). This agrees with the result presented in Figure 5 regarding the distribution of average survival time for the various SEER summary stages.

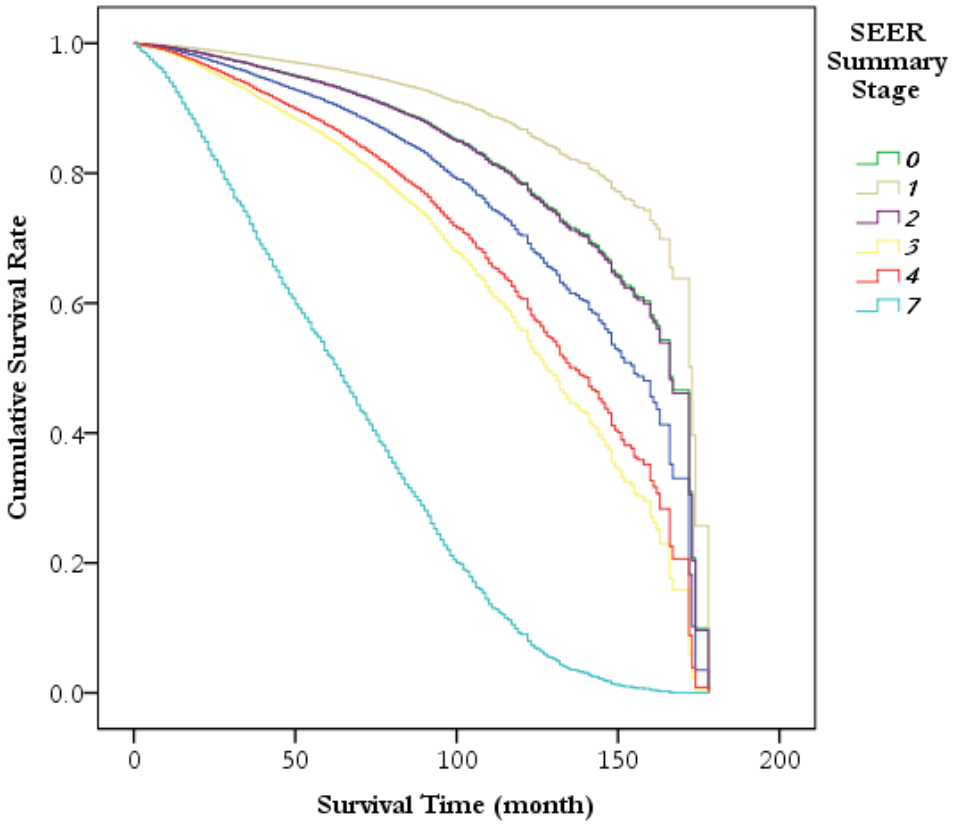

Figure 9. *Survival Curves for the Various SEER Summary Stages*

Table 1 presents the measures for overall model fitness (omnibus tests of model coefficients).

Table 1. *Omnibus Tests of Model Coefficients*

	Overall (Score)			Change From Previous Step			Change From Previous Block		
-2 Log Likelihood	Chi-Square	*df*	Sig.	Chi-Square	*df*	Sig.	Chi-Square	*df*	Sig.
22,744.048	9,407.485	13	.000	3,122.207	13	.000	3,122.207	13	.000

The overall mode fit is significant. Regression coefficients for the various variables and levels of variables included in the Cox regression model for predicting survival are presented in Table 2. Results presented in Table 2 show that on average, grade, stage, and age are significant predictors of survival, although grade 3 and SEER summary stages 0 and 1 were not significant predictors of survival compared to their respective reference groups.

Table 2. *Regression Coefficients for the Various Levels of the Variables Included in the Cox Regression Coefficients*

							95.0% CI for Exp(B)	
Variable	*B*	*SE*	Wald	*df*	Sig.	Exp(B)	Lower	Upper
Grade			*332.48*	*3*	*.000*			
1	-1.5	.203	53.41	1	.000	.23	.15	.34
2	-1.2	.154	63.34	1	.000	.29	.22	.40
3	-.2	.149	1.77	1	.183	.82	.61	1.10
Age Group			*782.96*	*5*	*.000*			
1	-1.6	.710	4.85	1	.028	.21	.05	.84
2	-2.3	.201	129.87	1	.000	.10	.07	.15
3	-2.4	.108	476.51	1	.000	.10	.08	.12
4	-2.1	.084	617.49	1	.000	.12	.10	.15
5	-1.2	.078	223.67	1	.000	.31	.27	.36
SEER Summary Stage			*1829.95*	*5*	*.000*			
1	-.3	.556	.34	1	.561	.72	.24	2.15
2	.4	.287	2.11	1	.147	1.52	.86	2.67
3	1.1	.253	20.59	1	.000	3.16	1.92	5.19
4	.7	.244	8.62	1	.003	2.04	1.27	3.30
5	2.1	.134	244.54	1	.000	8.18	6.29	10.64

Note: Wald = the Wald test (a test statistic used for testing whether the parameters associated with a group of explanatory variables are zero); Exp(B) = used to exponentiate the coefficients of the predictor variables included in the model to get a hazard ratio for a unit increase in the predictor variable.

Discussion

An elevated risk of cardiac and pulmonary dysfunction is observed among prostate cancer patients (Carver et al., 2007; Ketchandji et al., 2009). In the prostate cancer cohorts assessed in the current study, atherosclerotic heart disease was the second most important cause of death next to prostate cancer. Increased risk of death due to heart diseases among prostate cancer patients is attributed primarily to the impacts of prostate cancer therapy types, such as hormonal treatment (Tsai, D'Amico, Sadetsky, Chen, & Carroll, 2007). Hormonal treatment of prostate cancer is hypothesized to lead to pulmonary complications (Seigneur, Trechot, Hubert, & Lamy, 1988). On the other hand, the proportion of patients who died of atherosclerotic heart disease after using hormonal therapy was about 18%. The risk of treatment-related side effects in treating prostate cancer is likely related

to the stage of prostate cancer (metastatic versus nonmetastatic). Hormonal therapy is the primary treatment modality for patients with metastatic prostate cancer. Prostate cancer tumors are metastasized to the lungs and bones through the blood stream or the lymphatic system (Rusch, 2008).

Most of the chronic diseases identified as the major causes of death in the cohort have overlapping risk factors, and one health ailment is a risk factor for another. In this regard, chronic obstructive pulmonary disease is recognized as a risk factor for cardiovascular mortality among patients with ischemic heart disease (Nishiyama et al., 2010). The important risk factors for atherosclerotic heart disease are obesity, smoking, hypertension, high cholesterol, and type 2 diabetes (Saeed et al., 2009). In the current study, stroke was observed to be one of the underlying causes of death among the prostate cancer cohorts. This is probably due to the endocrine treatment effect of prostate cancer, in which it is found to increase the risk of stroke and ischemic heart disease (Robinson et al., 2011). Most of these risk factors are modifiable risk factors and need to be considered in the clinical management of prostate cancer patients.

Age is an important demographic determinant of prostate cancer survival, mainly because it affects the risk of prostate cancer and choice of therapeutic options. Bechis, Carroll, and Cooperberg (2010) found that patients diagnosed with advanced stages of prostate cancer have elevated risks of death because they have a lower chance of receiving local therapy, which negatively affects their survival. As observed among these cohorts, however, the youngest subjects could have low cumulative survival rate. Lin, Porter, and Montgomery (2009) found that younger men who have high-grade and advanced stages of prostate cancer could have a lower survival rate than older subjects. The etiological processes and factors that lead to lower survival rates among younger subjects warrant further investigation.

The effects of cancer stage and grade at time of diagnosis on prostate cancer survival have been well documented (Ketchandji et al., 2009). While older men with early stages of prostate cancer have a similar survival rate to those without prostate cancer (Keating, O'Malley, & Smith, 2006), younger men with high-grade and advanced stages of prostate cancer have a lower survival rate (Lin et al., 2009). Advanced stages and grades of prostate cancer are typically associated with lower survival rates because these clinical characteristics of prostate cancer are likely indicators of metastasized phases of that disease (Saad, 2009). Prostate cancer is known to metastasize preferentially to bone (Logothetis and Lin, 2005). Metastasized prostate cancer can lead to a significant increase in morbidity, owning to nerve compression that is likely caused by pathological fractures associated with the metastasis of the cancer; moreover, it increases the heath care cost (Lage, Barber, Harrison, & Jun, 2008) in addition to increasing morbidity, which eventually reduces survival.

Although population-based, this study has a number of limitations because it relied on registry data. Based on results from cancer-registry-based data analyses, it is very difficult to know whether longer survival is due to early diagnosis or more effective treatment modalities (Berrino, 2003). Case underreporting is also one of the limitations of registry-based studies. The Arizona Cancer Registry precludes cancer cases reported solely based on death certificate. This is typically due to the fact that death certificates do not indicate the date of diagnosis (Bullard et al., 2000).

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