Co-morbidities in a Retrospective Cohort of Prostate Cancer Patients

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Objective: To characterize rates of co-morbidity among prostate cancer patients treated with radical prostatectomy and to examine the association between co-morbidity status and race, clinical factors, and health behaviors for cancer control.

Design/Study Participants: Retrospective cohort study among prostate cancer patients treated with radical prostatectomy.

Setting: Academic medical center located in the southeastern region of the United States.

Main Outcome Measure: Patients with at least one of five co-morbid conditions considered were categorized as having a co-morbidity, and those without any were categorized as not having a co-morbid condition. Co-morbid conditions considered were hypertension, diabetes, heart problems, stroke, and high cholesterol, which had been recorded in the electronic medical record as part of their past medical history.

Results: Fifty-one percent of participants had a co-morbidity, with hypertension being the most common. The average number of co-morbidities among study participants was .87. In a multivariate logistic regression analysis, being diagnosed with prostate cancer within the past four years was associated with an increased likelihood of having a co-morbidity (OR=4.71, 95% CI=2.69, 8.25, P=.0001) compared with diagnosis five or more years ago. Age was also associated with an increased likelihood of having a co-morbidity (OR=1.30, 95% CI=1.005, 1.68, P=.05). In this study cohort, race, stage at diagnosis, and PSA level were not statistically associated with co-morbidity status.

Conclusion: Better chronic disease management is needed among prostate cancer survivors through more effective survivorship care planning and interventions that promote health behaviors. *Ethn Dis*. 2020;30(Suppl 1):185-192; doi:10.18865/ed.30.S1.185

Keywords: Co-morbidities, Retrospective Cohort, Prostate Cancer

Introduction

Prostate cancer is one of the leading causes of cancer among men in the United States.[1] In addition to African American race, established risk factors for prostate cancer include family history of prostate cancer and increasing age; the average age at prostate cancer diagnosis is sixty-six years.[1] Increasing age is also a risk factor for developing chronic conditions that include hypertension, diabetes, high cholesterol, and cardiovascular disease.[2] Thus, as men age, they are at risk for developing multiple acute and chronic conditions that increase their likelihood of morbidity and mortality. A substantial proportion of prostate cancer patients have at least one co-morbidity, or a chronic condition that is distinct from their primary prostate cancer diagnosis.[3] Previous research has shown that being diagnosed with prostate cancer and having a co-morbid condition (eg, diabetes, hypertension, cardiovascular disease) is associated with an increased risk of dying from causes other than prostate cancer. For example, prostate cancer patients in the Surveillance, Epidemiology, and Endpoints Registry (SEER) who had two or more chronic conditions had a 43% to 48% chance of dying from any cause within five years of their prostate cancer diagnosis.[4]

Because co-morbidities are common among men who have a personal history of prostate cancer and these other chronic conditions may

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be their cause of death, co-morbidity status should be integrated and considered as part of making decisions about prostate cancer treatment.[5-7] To do this, it is important to have an understanding of the distribution of co-morbidities among diverse patient populations. In population-based samples, for instance, African Americans are more likely to have hypertension and cardiovascular disease compared with Whites.[8,9] Characterizing the distribution of co-morbidities specifically among men who have a personal history of prostate cancer is also important for survivorship care planning. This is especially true given that it was estimated that 164,690 new prostate cancer cases would occur in 2018 with only 29,430 deaths.[10] Receiving quality care for co-morbidities during and after the acute treatment phase for cancer is necessary to reduce the likelihood of morbidity and mortality from chronic illnesses among cancer patients. Recent research has shown that having a greater number of co-morbidities and being African American are associated with wanting more information to help guide their follow-up care.[11]

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To extend previous research that examined co-morbidity in prostate cancer patients who were treated with all treatment modalities,[3] the purpose of this study was to characterize co-morbidities among prostate cancer patients treated with radical prostatectomy. Because of racial differences in the rates of chronic conditions (eg, hypertension, cardiovascular disease), we were also interested in determining if minority and non-minority prostate cancer patients differed in terms of having co-morbidities and the types of chronic conditions with which they have been diagnosed. We hypothesized that minority patients would be more likely to have at least one co-morbidity compared with non-minority patients. An additional objective of this study was to examine the association between co-morbidities and tumor characteristics (eg, stage of disease) to provide insight about how adverse prognostic factors for prostate cancer are associated with the potential risk of death from chronic conditions among prostate cancer survivors. Lastly, since dietary behaviors and physical activity are behavioral risk factors for chronic conditions,[12] we also examined the relationship between co-morbidity status and fruit/vegetable intake and physical activity.

Materials and Methods

Study Population

Participants in this study were men who had a personal history of prostate cancer and had provided a tissue sample as part of having a radical prostatectomy. Prostate cancer tissue samples were collected by the Biorepository and Tissue Analysis (BTA) Shared Resource at the Hollings Cancer Center (HCC) after patients provided written informed consent and privacy authorization using institutional guidelines at the Medical University of South Carolina (MUSC). As part of this informed consent process, men agreed for their tissue samples to be used as a part of cancer research and agreed to be contacted about participating in future studies. More than 90% of prostatectomy patients provided consent for their tissue sample to be stored in the BTA.

The HCC Biorepository was queried to identify men who had an ICD-10-CM code of C61 (malignant neoplasm of prostate) and CPT codes of 55810 (prostatectomy, perineal radical) and 55866 (laparoscopic procedures on the prostate) since 2011. The resulting study sample included 316 prostate cancer patients who had a tissue sample available in the HCC Biorepository when study recruitment was initiated in 2016. Of these 316, 83 (26%) completed a structured social determinants survey that provided the data to examine the association between health behaviors for cancer control and co-morbidity status.

Procedures

All study procedures were approved by the institutional review board at MUSC. First, information on sociodemographic characteristics (eg, race, age), prostate cancer variables, and co-morbidities was abstracted from the electronic health record (EHR) of eligible patients who were identified from the HCC Biorepository. Next, patients were contact-

ed by mailed invitation to complete a structured telephone interview that measured social determinants and health behaviors for cancer control. Patients could decline to participate in the social determinants survey by contacting the program manager at MUSC by telephone or email. Those who did not decline to complete the social determinants survey were contacted by a research assistant at MUSC to complete a 30-minute social determinants survey.

Measures

The following data elements were abstracted from the EHR for each study participant: year of birth; date of diagnosis; prostate specific antigen (PSA) levels at diagnosis; pathologic stage at diagnosis (T1a; T1c; T2a; T2b; T2c; T3a; T3b); Gleason score; race (White, African American); height; weight; and systolic and diastolic blood pressure at the time of the pre-surgical consultation visit. Co-morbidities were obtained from the patient's problem list as recorded in the EHR. Patients were categorized as having a history of hypertension (yes or no), diabetes (yes or no), heart problems (yes or no), stroke (yes or no), or high cholesterol (yes or no). We focused on these chronic conditions because they are among the leading causes of morbidity and mortality in the United States[13] and have been associated with an increased risk of all-cause mortality among prostate cancer patients.[4,14] Height and weight values were used to calculate body mass index using the Centers for Disease Control and Prevention BMI calculator.[15] Stage was recoded into a binary variable of early vs later stage disease (T1/T2 vs T3). The amount of time since diagnosis was calculated based on the date of diagnosis. We recoded time since diagnosis into a binary variable of within the past four years or five or more years from the date study recruitment was initiated.

The social determinants survey assessed self-reported race and ethnicity, self-report on the co-morbidities in the study, and fruit/vegetable intake and physical activity using items from the Health Information National Trends Survey (HINTS).[16] Specifically, men were asked how many cups of fruit and vegetables they eat each day (1=none/don't know, 2=½ cup or less, 3=½ to 1 cup, 4=1 to 2 cups, 5=2 to 3 cups, 6=3 to 4 cups, 7=more than four cups). Men who reported eating at least 2 to 3 cups were categorized as meeting recommended guidelines for each dietary behavior variable. Next, men were asked if they had participated in any physical activities or exercises during the past month (yes or no). Those who reported yes were asked how many days they were physically active or exercised of at least moderate intensity and on these days, how long they typically performed these behaviors. The total number of minutes for moderate intensity physical activity per week was calculated by multiplying the number of days by the minutes reported. Men who reported no physical activity during the past month, those who reported that they had been physically active during the past month, but had not been active during the past week, and those who reported physical activity, but did not meet the physical activity guidelines (eg, less than 150 minutes/week) were coded as not meeting guidelines.[17] The remaining participants were coded as having met the guidelines for physical activity.[17]

Data Analysis

Descriptive statistics were generated first to characterize the study patients (n=316). Next, frequencies were generated to identify the co-morbidities that were most and least common among participants. Chi square tests of association and t-tests were performed to examine the association between co-morbidity status, race, and clinical variables. Variables that had a bivariate association of P<.25 with co-morbidity status were included in the multivariate logistic regression analysis. Lastly, multivariate logistic regression analysis was used to identify factors having significant independent associations with co-morbidity status. Race was also included in the regression model regardless of the significance of the bivariate association with co-morbidity status because of disparities in chronic diseases. This same approach was used to examine the relationship between co-morbidity status and fruit/vegetable intake and physical activity in the sub-set of men who completed the social determinants survey.

Results

Table 1 shows the characteristics of the study patients. Thirty-two percent of patients were racial minorities (eg, African American) and 68% where non-minorities. The mean (SD) age was 65.2 (6.7). With respect to prostate cancer variables, the mean PSA was 9.2 (SD=10.9) and 77% of

Table 1. Study patient characteristics

Variable	Level	n (%)
Race	Minority	101 (32%)
	Non-minority	215 (68%)
Gleason score	4+3/4+4/4+5/5+3/5+5	79 (28%)
	3+3/3+4	201 (72%)
Stage	T3	69 (23%)
	T2	229 (77%)
Time since diagnosis	Within past four years	217 (69%)
	Five or more year	99 (31%)
Age	Mean (SD)	65.2 (6.7)
PSA	Mean (SD)	9.2 (10.9)
BMI	Mean (SD)	29.4 (5.0)

men had been diagnosed with stage T2 disease and 23% had been diagnosed with stage T3 disease. In addition, 72% of men had a Gleason score of 3+4 or 3+3. Sixty-nine percent of men were diagnosed within the past four years and 31% were diagnosed more than five years ago. In the subset of men who completed the social determinants survey, 31% met guidelines for fruit intake, 25% met guidelines for vegetable intake, and 30% met guidelines for physical activity.

With respect to co-morbidity status, 51% of men had at least one co-morbid condition; men were most likely to have high blood pressure (42%), high cholesterol (24%), diabetes (12%), heart problems (9%), and stroke (.63%). Among those who had at least one co-morbidity, the mean (SD) number was .87 (1.02).

Table 2 shows the results of the bivariate analyses of co-morbidity. Time since diagnosis had significant bivariate association with co-morbidity status. Men who were diagnosed within the past four years were more likely to have a co-morbidity compared with those who were diagnosed more than four years ago (61% vs 30%, chi square=25.4, P=.0001). The mean PSA was also higher among men who had a co-morbidity (mean=10.2, SD=13.6) compared with those who did not have a co-morbidity (mean=8.2, SD=6.6) (t=-1.70, P=.09). Sixty-one percent of men who had stage T3 disease had a co-morbidity compared with 49% of men who were diagnosed with stage T2 disease (chi square=3.04, P=.08). There were also small mean differences in age based on co-morbidity status. For instance, the average (SD) age was 65.7 (6.5) among men who had a co-morbidity compared with 64.8 (7.0) among those without any co-morbidities (t=-1.20, P=.23). Fifty-five percent of men from racial minority groups had a co-morbidity compared with 49% of non-minority men (chi square=1.04, P=.31). BMI was similar between men who had at least one co-morbid condition (mean=29.5, SD=5.6) and those who did not have any co-morbidities (Mean=29.4, SD=4.4) (t-value=-.20, P=.84). Among the sub-set of men who completed the social determinants survey, none of the behavioral risk factors (fruit/vegetable intake or physical activity) were associated significantly with having a co-morbidity.

The results of the multivariate logistic regression model of co-morbidity status are provided in Table 3. Only time since diagnosis had significant independent association with having a co-morbid condition. Men who were diagnosed within the past four years had a greater likelihood of having a co-morbid condition compared with those who were diagnosed more than four years ago (OR=4.71, 95% CI=2.69, 8.25, P=.0001). The likelihood of having a co-morbid condition increased with older age (OR=1.30, 95% CI=1.005, 1.68, P=.05).

Discussion

The purpose of this study was to examine co-morbidity rates among prostate cancer survivors who were treated with radical prostatectomy. Overall, 51% of men had one co-morbidity, the average number of co-morbidities was .87, and high blood pressure was the most common co-morbid condition. Forty-two percent of men had high blood pressure, but less than 1% had a history of stroke. Chronic disease management among cancer patients and survivors is an important priority[18]; our findings underscore the need for greater chronic disease management among prostate cancer patients, regardless of their racial background, especially when they are within the first four years of being diagnosed.

The overall rates for co-morbidities in our sample were higher than those reported in previous research,[3] but there was some consistency in the

Table 2. Bivariate analysis of comorbidity status

Variable	Level	% Comorbidity	Chi Square	P
Race	Minority	55%	1.04	.31
	Non-minority	49%		
Gleason score	4+3/4+4/4+5/5+3/5+5	52%	.03	.86
	3+3/3+4	51%		
Stage	T3	61%	3.04	.08
	T2	49%		
Time since diagnosis	Within past four years	61%	25.4	.0001
	Five or more year	30%		
	Co-Morbidity Mean (SD)	**No-Comorbidity Mean (SD)**	**T-Value**	**P**
Age	65.7 (6.5)	64.8 (7.0)	-1.20	.23
BMI	29.5 (5.6)	29.4 (4.4)	-.20	.84
PSA	10.2 (13.6)	8.2 (6.6)	-1.70	.09

rates for individual co-morbidities in our sample and other studies. For instance, Edwards et al[3] found that 13% of prostate cancer patients in a national sample had a history of diabetes whereas 11% of patients in our study had a history of this disease. Further, 56% of prostate cancer patients who had a radical prostatectomy reported a history of hypertension[18] and 42% patients in our sample had hypertension. However, 30.5% of prostate cancer patients in a national sample had at least one co-morbidity.[3] Our higher overall rates of co-morbidity may be due to our including hypertension, whereas other studies, including the study by Edwards and colleagues, based co-morbidity on conditions included in the Charlson Co-Morbidity Index, which does not include hypertension.[3,19,20] Together with the findings from previous studies demonstrating that hypertension is associated with an increased risk of biochemical recurrence among men treated with radical prostatectomy,[21,22] the exclusion of hypertension in studies that examine prostate cancer outcomes may be a significant omission.

In addition to being a risk factor for all-cause mortality and death from cardiovascular disease,[9] hypertension was associated with an increased risk of biochemical recurrence among prostate cancer patients.[21,22] There continues to be significant racial disparities in prostate cancer incidence and mortality.[1] African American men have the greatest incidence of prostate cancer among men in the United States and are about twice as likely as White men to die from this disease.[1] Previous research has shown that African Americans are more likely than Whites to have high blood pressure.[9] Specifically, hypertension was associated with a two-fold increase in biochemical recurrence among African American and White men who were treated with radical prostatectomy.[22] While Post and colleagues[22] found that African American prostate cancer patients were significantly more likely to have hypertension compared with White patients, there were non-significant racial differences in overall rates of hypertension in our study and mean levels of systolic and diastolic blood pressure did not differ between

Table 3. Logistic regression model of comorbidity

Variable	Level	Odds ratio	95% CI	P
Race	Minority	1.56	.90, 2.69	.11
	Non-minority			
Age	[a]	1.30	1.005, 1.68	.05
Stage	T3	1.20	.65, 2.21	.56
	T2			
Time since diagnosis	Within past four years	4.71	2.69, 8.25	.0001
	Five or more years			
PSA	[a]	1.17	.85, 1.61	.33

a. ORs for continuous variables reflect the OR for a 1-SD unit change in the covariate.

minorities and non-minorities in our sample (data not shown). However, our sample showed higher blood pressures and higher BMI measures overall. The average (SD) systolic and diastolic blood pressures were 142.1 (17.5) and 82.3 (9.3), respectively, the average (SD) BMI was high (29.4, 5.0), and 37% of men in our sample were obese. This may explain why there were no racial differences in co-morbidity status in our study.

We found that men who had been diagnosed with prostate cancer within the past four years had a significantly increased likelihood of having a co-morbid condition compared with those who had been diagnosed five or more years ago. This may be due to temporal changes in the extent to which co-morbidities are recorded in electronic medical records. All health care providers and systems were required to implement and demonstrate meaningful use of electronic medical records in January 2014[23]; there may be greater documentation of co-morbidities in electronic medical records as information systems were introduced and expanded to meet federal requirements. However, recent research has shown high agreement between patient self-reported co-morbidities and documentation of these conditions in the medical record.[24] Further, a similar proportion of men had specific co-morbidities based on self-report and electronic medical record. For instance, 44% of men self-reported hypertension and 44% of men had hypertension according to the electronic health record. Similarly, 8% of men self-reported a personal history of diabetes. Additional research is needed to determine why men who have a shorter time from prostate cancer diagnosis are more likely than longer-term survivors to have a co-morbidity.

Interestingly, none of the behavioral risk factors (eg, diet, physical activity) for co-morbidities were associated significantly with having a chronic disease among men who completed the social determinants survey. This may be due to the small number of men who were included in this analysis; however, it is important to note that a minority of these participants met recommended guidelines for fruit/vegetable intake and physical activity. Recommendations for physical activity cancer survivors include 150 minutes of moderate intensity exercise weekly[25]; however, only 30% of men in our study met this recommendation. Similarly, only 31% and 25% met recommended guidelines for fruit and vegetable intake, respectively. Diet behaviors and physical activity are important strategies for cancer control among prostate cancer survivors and are also recommended for chronic disease management[25]; and our findings emphasize the importance of developing behavioral interventions to enhance these behaviors in prostate cancer survivors, especially those who have a co-morbidity.

Overall, 51% of men had one co-morbidity, the average number of co-morbidities was .87, and high blood pressure was the most common co-morbid condition.

Study Limitations

In considering the results of this study, some limitations should be noted. First, co-morbidities were examined among men who were treated with radical prostatectomy at one academic health center, and men who have several comorbid conditions do not receive surgery as their primary treatment. Therefore, our study may reflect the lowest percentage of co-morbidity for prostate cancer diagnosis. Co-morbidities should be examined among men who have been treated with different modalities at diverse academic and community oncology clinical settings. Secondly, co-morbidity was determined based on the presence of the leading causes of death in the United States (eg, cardiovascular disease, stroke, hypertension, diabetes) at the time of medical abstraction in a retrospective cohort of prostate cancer patients. Other co-morbidity indices include a more extensive list of conditions[20]; however, these measures may not ask about chronic diseases that are common in minority populations. Notably, the inclusion of hypertension in our measure of co-morbidity may be a better reflection of the chronic disease burden in diverse samples of prostate cancer patients. Lastly, it is also important to determine co-morbidity status prospectively at the time of diagnosis to be able to examine the association between chronic condi-

tions and prostate cancer outcomes. Detailed information on when prostate cancer patients were diagnosed with chronic diseases should be captured as part of prospective studies to understand the trajectory of co-morbidity in these patients.

Study Implications

Despite these potential limitations, the results of our study have important implications for prostate cancer survivorship. First, our findings demonstrate that chronic disease management is needed among prostate cancer patients. Survivorship care plans are now being implemented at the conclusion of cancer treatment to facilitate the patient's transition back to primary care by summarizing their cancer diagnosis, treatment, and follow-up care[26,27]; however, our findings suggest that efforts may also be needed to manage diseases such as hypertension and to promote cancer control behaviors at all phases of cancer survivorship. A little more than 50% of the patients in our study had at least one co-morbidity, 37% were obese, and only about one third of men met recommended guidelines for diet and physical activity. Although we were not able to determine the specific age and date at which men were diagnosed with co-morbid conditions such as diabetes and hypertension because this information was not recorded in the electronic medical record, blood pressure and obesity were measured at the time of the pre-surgical consultation visit. Further, the mean levels for systolic and diastolic blood pressure were above normal ranges and 87% and 57% of participants in our study had values that were above 120 mm Hg and 80 mm Hg, respectively, regardless of hypertension status. Blood pressure may have been elevated due to anxiety at the time of the pre-surgical consultation visit. However, national data show that only about 50% of individuals who have hypertension have this condition under control, men were less likely than women to have controlled hypertension, and there are racial differences in the rates of controlled disease in national samples.[28]

Research in breast cancer patients has shown that adherence to noncancer medications for chronic conditions decreases during the first year after treatment; potential reasons for reduced adherence to noncancer medications include greater prioritization of cancer treatment and financial toxicity.[29] To our knowledge, financial toxicity and adherence to noncancer medications has not been examined specifically among prostate cancer patients and these are important areas for future research. Because of the high burden of chronic disease and the potential for cancer patients to reduce their adherence to noncancer medications following their diagnosis and treatment,[29] primary care services may need to be integrated into oncology care. Primary care oncology is emerging as a cancer care service in which providers focus on the medical and psychological impact of cancer treatment, with the management of co-morbidities as one component of this specialty.[30,31] Primary care oncologists could play an important role in managing co-morbidities at diagnosis, through treatment, and during short- and long-term survivorship among prostate cancer patients. Future studies are needed to evaluate the impact of primary care oncology on the management of co-morbidities and prostate cancer outcomes in diverse patient populations.

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Conflict of Interest

No conflicts of interest to report.

Author Contributions

Research concept and design: Jefferson, Drake, Savage; Acquisition of data: Jefferson, Lilly, Savage; Data analysis and interpretation: Jefferson, Lilly, Savage, Tucker Price; Manuscript draft: Jefferson, Drake, Lilly, Tucker Price; Acquisition of funding: Drake; Administrative: Jefferson, Lilly, Savage, Tucker Price; Supervision: Jefferson, Savage

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