ASSOCIATION BETWEEN CANCER AND THE DETECTION AND MANAGEMENT OF COMORBID HEALTH CONDITIONS AMONG ELDERLY MEN WITH PROSTATE CANCER IN THE UNITED STATES

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ABSTRACT

Association between Cancer and the Detection and Management of Comorbid Health Conditions among Elderly Men with Prostate Cancer in the United States
(Under the direction of Andrea K. Biddle)

Using the data from the Surveillance, Epidemiology, and End Results registry (SEER)-Medicare Program, this dissertation analyzed the longitudinal relationship between prostate cancer and comorbid conditions. This study examined the detection and use of care for comorbidities among patients who were diagnosed with prostate cancer in 2000. The study also assessed racial disparity in survival among the survivors after controlling for use of care for non-cancer comorbidities, which have never been controlled for in previous cancer survival analyses.

Prostate cancer survivors not only were more likely to be diagnosed with comorbidities, but also received more necessary care for non-cancer conditions after 2000. The prevalence rates of chronic obstructive pulmonary disease, diabetes, depression, hypercholesterolemia, and hypertension and the overall severity of comorbidities increased more among the prostate cancer group than the non-cancer comparison group across time. After 2000, prostate cancer survivors were more likely to receive necessary care, especially clinical assessment and management of chronic conditions, than individuals without cancer. Although these findings did not differ by race, the magnitudes of changes after cancer diagnosis were larger among black survivors.

Black prostate cancer survivors had higher overall, cancer-specific, and non-cancer mortality rates than white survivors. Although racial disparities in survival were largely explained by racial differences in socioeconomic status and cancer disease information, the

disparities were no longer statistically significant after controlling for comorbidities and use of care for non-cancer conditions.

In conclusion, cancer diagnosis may represent an important opportunity for prostate cancer survivors, especially black survivors, to be more aware of their health and to receive more necessary care. Efforts to increase early diagnosis, appropriate treatment, and post-diagnosis use of care among black survivors may be necessary to improve their survival and to further eliminate racial disparities in prostate cancer survival.

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LIST OF ABBREVIATIONS

ACE-PRO	Access to Care for the Elderly Project
CAD	Coronary Artery Disease
CCI	Charlson Comorbidity Index
CHF	Congestive Heart Failure
CI	Confidence Interval
CMS	Centers for Medicaid and Medicare Services
COPD	Chronic Obstructive Pulmonary Disease
CPT	Current Procedural Terminology
GEE	Generalized Estimating Equation
HCPCS	Healthcare Common Procedure Coding System
HMO	Health Maintenance Organization
HR	Hazard Ratio
ICD-9	International Classification of Diseases, 9th Revision
MedPAC	Medicare Payment Advisory Commission
MMA	Medicare Prescription Drug, Improvement, and Modernization Act
NCI	National Cancer Institute
NCICI	National Cancer Institute Combined Index
PCP	Primary Care Physician
PH	Proportional Hazard
PR	Prevalence Ratio
PSA	Prostate Specific Antigen
SEER	Surveillance, Epidemiology, and End Results registry
SES	Socioeconomic Status

TIA	Transient Ischemic Attack
XRT	Radiation Therapy

CHAPTER 1. INTRODUCTION

Cancer is a prevalent disease affecting the elderly population in the United States. With early detection and effective treatment, cancer is no longer considered a fatal disease. Since many cancer survivors eventually die from causes other than cancer, issues related to other health conditions also are very important for this population. Comorbidities are commonly observed in cancer survivors, especially among elderly survivors (1). The presence of other comorbidities not only complicates cancer management decisions, it also affects a cancer survivor's health-related quality of life and survival (2-6). However, previous studies have focused on the association between comorbidities at cancer diagnosis and patients' cancer-related outcomes (3-6). The longitudinal effect of cancer on comorbidities remains unclear.

This study analyzed the longitudinal relationship between cancer and comorbidities. Specifically, we focused on prostate cancer survivors who comprise the second largest cancer population in the United States. Since the majority of prostate cancer patients are at least 65 years of age, the co-occurrence of chronic conditions represents an important health issue for this population because the majority of them die from causes other than cancer (7). The following sections first describe prostate cancer in the United States, racial disparity among prostate cancer survivors, and then describe the policy significance, followed by the purpose and structure of this dissertation.

1.1 Prostate Cancer in the United States

Prostate cancer is the most frequently diagnosed cancer among men in the United States. It is estimated that more than two million American men have a history of prostate cancer (8, 9). A man has an one-in-six chance to develop prostate cancer during his lifetime (8). Previous epidemiological studies have concluded that age, race, and a positive family disease history are the strongest risk factors for prostate cancer (8, 10-12). Evidence about the influence of other factors including hormone level, diary habit, obesity, and physical exercise is inconclusive (12). Currently, more than 80 percent of prostate cancer survivors are at least 65 years of age (8). Although prostate cancer is the second leading cause of cancer-related death (only after lung cancer), the overall 5-year relative survival rate (as compared with non-cancer population) is approximately 99 percent (9).

The prostate specific antigen (PSA) blood test is the most commonly used method to detect prostate cancer. The American Cancer Society suggests that PSA test should be offered annually beginning at age 50 years to men who have a life expectancy of at least ten years (13). The incidence of prostate cancer has increased dramatically as a result of PSA testing, the use of which has substantially increased since the mid-1990s (14). However, the use of the PSA screening is controversial and equivocal (15-17). At present, more than 90% of prostate cancer patients are diagnosed with localized or regional stage cancer, which are highly survivable (9). Results from the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial demonstrated that the mortality rates from prostate cancer did not differ between patients who received annual PSA screening or usual care (18). Also, the benefits of prostate cancer treatments for localized or regional prostate cancer are controversial. At present, radiation therapy or surgery has not resulted in an overall survival benefit over watchful waiting (16, 19, 20). However, previous studies found potential psychological harms by prostate screening (15, 21) and adverse effects, such as

incontinence and erectile dysfunction, caused by cancer treatments (15, 22, 23). Therefore, researchers have questioned whether it is necessary to diagnose and treat patients with early stage prostate cancer (15-17).

Since prostate cancer is predominantly survivable, the majority of its survivors die from causes other than cancer (9). For many survivors, prostate cancer and its treatment may constitute only a fraction of medical history. Other comorbid conditions may play a more important role in a survivor's health, longevity, and physical function. However, the comorbidities among prostate cancer survivors have not been the focus of previous cancer survivorship research. It is unclear whether comorbidities are more likely to be diagnosis after prostate cancer diagnosis. It also is unclear whether survivors receive more necessary care for their comorbidities after their prostate cancer diagnosis.

1.2 Racial Disparity among Prostate Cancer Survivors

Racial disparity in health outcomes of prostate cancer survivors has been observed in many previous studies (8, 9, 24-33). Prostate cancer incidence and mortality rates for black men are approximately twice the rates for white men (9). In addition, black men are more likely to be diagnosed with advanced prostate cancer than white men and to have worse prognosis (31). In North Carolina, one recent study surveyed black and white patients within six months of prostate cancer diagnosis to investigate potential explanatory factors that might be associated with racial disparity (28). Compared with white patients, black patients indicated that they have less access to appropriate care and expressed less trust in physicians, both of which may create barriers to timely diagnosis of prostate cancer.

Racial disparity in survival among prostate cancer survivors has consistently been reported in current literature (26, 27, 29-33). Various studies have tried to identify the factors that may explain the racial differences in overall and cancer mortality rates. A previous study

found that the difference in survival between black and white patients is associated with pre-existing comorbidities (32). However, another study found that even after controlling for treatment options and comorbidities, black patients diagnosed with localized prostate cancer still have worse overall and prostate cancer-specific survival rates than those rates observed in white men (27). A study using California cancer registry data found that racial disparity in survival was completely explained by treatment option, stage, grade, year of diagnosis, and socioeconomic status (SES) (30). However, other studies using data from national registries found that even after controlling for SES, treatment options, and pre-existing comorbidities, black survivors diagnosed with localized prostate cancer still had worse overall and prostate cancer survival rates than those observed in white men (27, 29). A meta-analysis found that black survivors had higher cancer recurrence, prostate cancer mortality and overall mortality than white survivors (33). After controlling for comorbidity, type of prostate cancer screening, and access to health care, racial differences diminished for overall mortality but remained for cancer recurrence and prostate cancer mortality.

1.3 Policy Significance

Chronic diseases are prevalent in elderly cancer survivors in the United States. The existence of comorbidities may not only influence the choice of cancer treatment, but also may affect the health-related quality of life and mortality of cancer survivors. The issues related to comorbidities become more important for elderly cancer survivors because the majority of them die from causes other than cancer. Understanding the longitudinal relationship between comorbidities and cancer is crucial to providing appropriate care for cancer survivors. However, although the number of elderly cancer survivors has been increasing over time, few longitudinal studies have focused on comorbidities among this population.

This dissertation first attempted to assess the influence of prostate cancer on the diagnosis of manageable chronic conditions. The results can inform policy makers and health care providers about whether cancer diagnosis provides an opportunity for previously underdiagnosed comorbidities to be found. In addition, we compared the number of office visits by physician specialty and examined whether the new comorbidities are more likely to be diagnosed by certain physician specialties. These findings provide information about which physician specialty tend to be the main health care provider for prostate cancer survivors.

In the next step, this study examined the use of necessary care for non-cancer comorbidities among prostate cancer survivors. We identified the type of necessary care that cancer survivors tend to underuse for their non-cancer comorbid conditions. We also evaluated the risk factors that are associated with less use of necessary care. The results of our analyses can provide policy makers and health care providers information about vulnerable cancer survivors who tend to underuse appropriate medical services. By examining the relationship between type of health provider and use of care, we may identify more effective ways to deliver care to cancer survivors, thus representing the first step to figuring out what care is needed and how best to provide it. Our findings provide a reference for other researchers to develop prospective studies that examine more effective ways to deliver care for cancer survivors.

Black patients are traditionally a vulnerable population experiencing poor quality of care (34-36). Effective control of comorbidity in black cancer patients may help improve life expectancy and lead to a reduction in survival disparities (37). However, the use of necessary care for non-cancer comorbidities has never been controlled for in previous cancer survivorship studies. In this dissertation, we examined not only whether use of necessary care is associated with longer survival but also whether racial disparity decreased

after controlling for use of necessary care. Since use of necessary care is a potentially modifiable factor, the results of this study inform policy makers and health care providers whether increasing use of necessary care is an effective way to improve survival and further eliminate racial disparity among prostate cancer survivors.

1.4 Purpose of this Dissertation

The purpose of this dissertation was to examine the longitudinal relationship between prostate cancer and comorbidities. We first analyzed whether comorbidities are more likely to be diagnosed after prostate cancer diagnosis. We then evaluated the relationship between cancer and the proportion of necessary care that is received across time. We also conducted subgroup analyses to evaluate whether the findings from these analyses differ by race. Finally, we examined whether racial disparity in mortality remains after controlling for time-varying comorbidities, use of necessary care, and other relevant factors. The data were obtained from Surveillance, Epidemiology, and End Results registry (SEER)-Medicare program. The specific aims of this study were:

Aim 1: To evaluate whether the comorbidities are more likely to be diagnosed after prostate cancer diagnosis and whether the finding is different by race

The prevalence of chronic obstructive pulmonary disease (COPD), diabetes, depression, hypercholesterolemia, and hypertension was compared before and after the cancer diagnosis. Early detection of these comorbidities may lead to better disease control by appropriate medical treatments. In addition, we used the Charlson Comorbidity Index (CCI) (38, 39) and National Cancer Institute Combined Index (NCICI) (40) to assess the severity of comorbidities at different time points. To indentify the main health care provider for prostate cancer survivors, we examined the number of office visits by physician specialty. We further examined whether the new chronic conditions (i.e., those conditions diagnosed

after the cancer diagnosis) tend to be identified by prostate cancer specialists or by primary care physicians (PCPs). Finally, we conducted subgroup analyses to examine whether the findings from above analyses are different by race.

Aim 2: To evaluate the longitudinal relationship between prostate cancer and use of necessary care and to evaluate whether the finding is different by race

After cancer diagnosis, survivors may receive more medical services because cancer follow-up may provide regular contact with the health care system, increasing the chance of receiving appropriate medical care (35). We used the refined Access to Care for the Elderly Project (ACE-PRO) indicators to examine the receipt of care for non-cancer comorbidities for a maximum of ten years. The use of necessary care for each indicator was measured in every two years. We also calculated a composite score that indicates the overall use of necessary care during each time period. We examined whether prostate cancer survivors used more necessary care after cancer diagnosis. Subgroup analyses were conducted to examine whether the findings differ by race. Finally, we used regression analyses to identify the risk factors for less use of necessary care. Specifically, we examined the relationship between type of care provider (i.e., oncologist or primary care physician) and use of necessary care.

Aim 3: To investigate whether racial disparity in mortality remains after controlling for time-varying comorbidities and use of necessary care

Racial disparity in survival has been observed among prostate cancer survivors. We conducted a survival analysis to examine whether racial disparity in mortality rate remains after controlling for time-varying comorbidities (from Aim 1) and use of necessary care (from Aim 2), neither of which have been controlled in previous studies. A Cox proportional hazards (PH) model was used to evaluate whether black survivors have a higher overall mortality rate than the white survivors after controlling for other factors. Since prostate

cancer and other causes are competing risks for death, competing-risk models were conducted to examine racial disparity in cancer and non-cancer mortality.

1.5 Structure of this Dissertation

Chapter 2 first reviews current literature defining cancer survivorship. It also reviews approaches to measure comorbidity and use of care for non-cancer health conditions. A literature review of behavioral changes after cancer diagnosis and comorbidities among cancer survivors also is presented in Chapter 2. These sections are intended to provide background on and justification for this dissertation. Finally, a comparison of previous studies and the current study is provided at the end of Chapter 2. Chapter 3 describes the data source, study sample, and variable definitions of this dissertation. This chapter also contains a detailed description of study hypotheses and the analysis plans. Chapters 4-6 are individual manuscripts, each of them accomplishing one of the three study aims of this dissertation described in Section 1.4. These manuscripts take the place of a single results chapter, and each is intended for submission for independent publication. The references for the manuscript are combined with other general references in a single bibliography. Chapter 7 summarizes the findings and limitations of this dissertation and provides recommendations for future research and policy implications.

CHAPTER 2. LITERATURE REVIEW

2.1 Cancer and American Seniors

Cancer is a prevalent disease affecting the elderly population. At present, persons older than 65 account for approximately two-thirds of newly diagnosed malignancies in the United States (9). The availability of effective treatment has significantly extended the life expectancy among cancer patients, with approximately 66% of cancer patients surviving more than five years beyond the initial cancer diagnosis (9). It is estimated that there are more than 10 million cancer survivors in the United States, which represents 3.5% of the entire population (9). The number of cancer survivors is expected to continue to grow with more early detection, effective treatments, and the aging of the population. From 2000 to 2050, the absolute number of patients aged 65 and older diagnosed with cancer is expected to double (41).

2.2 Cancer Survivorship

2.2.1 Survivors

With early detection and effective treatments, cancer survival has improved dramatically over the past three decades (9, 23). As a result, the definition of cancer survivor has evolved over time. Before 1986, the general medical definition of a cancer survivor was a patient who remains disease free for a minimum of five years (23, 42, 43). At present, the NCI Office of Cancer Survivorship gives a very broad definition of cancer survivor: “An individual is considered a cancer survivor from the time of cancer diagnosis, through the balance of his or her life. Family members, friends and caregivers are also impacted by the survivorship experience and are therefore included in this definition (44).” In the current study, we define patients as cancer survivors from the time of cancer diagnosis. For those who survive for more than five years, we measure their health outcomes separately because they are considered long-term survivors by the old definition (23).

2.2.2 Survivorship

Dr. Fitzhugh Mullan, a physician who was diagnosed with cancer at 32, described the survivorship experience as the seasons of the year (45). He depicted three seasons of cancer survival: acute, extended, and permanent survival. The acute phase of survival proceeds from cancer diagnosis through the completion of primary treatment. The primary issues of this phase are cancer treatment and its side effects. The extended phase of survival of cancer survivorship begins at the completion of primary cancer treatment, and is dominated by watchful waiting, regular follow-up examinations, and intermittent therapy. The permanent phase of survival does not represent a single moment but evolves from extended disease-free survival when the likelihood of recurrence is sufficiently low.

2.2.3 Survivorship Research

The NCI Office of Cancer Survivorship provides the following definitions for cancer survivorship research:

> Survivorship research encompasses the physical, psychosocial, and economic sequelae of cancer diagnosis and its treatment among both pediatric and adult survivors of cancer. It also includes within its domain, issues related to health care delivery, access, and follow up care, as they relate to survivors. Survivorship research focuses on the health and life of a person with a history of cancer beyond the acute diagnosis and treatment phase. It seeks to both prevent and control adverse cancer diagnosis and treatment-related outcomes such as late effects of treatment, second cancers, and poor quality of life, to provide a knowledge base regarding optimal follow-up care and surveillance of cancers, and to optimize health after cancer treatment (44).

Dr. Noreen Aziz, the Senior Program Director of NCI Office of Cancer Survivorship, recently reviewed the studies investigating adverse medical outcomes and post-treatment follow-up care among long-term cancer survivors (22). She also examined definitional issues, research paradigms, and methodological concerns about cancer survivorship research. Dr. Aziz found that long-term or late adverse treatment effects commonly are observed in pediatric survivors. However, the issues remain relatively understudied among those who were diagnosed as adults. She also found that follow-up care relevant to survivorship outcomes is neither standardized nor guideline- or evidence-based for most adult cancers, and optimal practices have yet to be defined. To date, few studies have compared survivors' health outcomes pre- and post- cancer diagnosis (22). Most of the current literature relevant

to this domain is derived from cross-sectional studies and it remains unclear whether the adverse symptoms began during treatment or immediately after treatment (22, 43). Dr. Aziz recommends that more prospective research be conducted to provide more knowledge about symptoms that persist after cancer treatment or arise as late effects and interventions that are effective in preventing or controlling them (22). She also emphasizes the importance of conducting studies of vulnerable population including older or long-term survivors.

2.3 Comorbidities among Cancer Survivors

The co-occurrence of comorbidities is an important health issue for cancer survivors, especially for the elderly population. At present, most patients who are diagnosed with cancer will not die from it (9). Previous studies have found that cancer survivors are at a greater risk for other comorbidities than the non-cancer population (6, 46, 47). These increased risks may be the results of the side effects or late effects of cancer treatment, genetic predisposition, or common lifestyle factors. A population-based study found that 69% of cancer patients aged 40 to 84 have at least one chronic condition other than cancer (1). Several studies also indicated that the presence of other chronic health conditions may not only complicate treatment management, but may negatively affect prognosis and post-treatment health-related quality of life (3-6). Another study reported that prostate cancer patients are more likely to die from non-cancer causes than from cancer itself (32), demonstrating the influence of comorbidities and other factors on overall mortality rate and cancer-related death. However, the authors did not report the risk factors for death due to causes other than cancer (32).

2.4 Behavioral Changes after Cancer Diagnosis

A cancer diagnosis has the potential to have mixed effects on the diagnosis or management of other comorbidities. On the one hand, cancer diagnosis may represent “a teachable moment” for risk factor reduction because patients tend to be more aware of their other health problems after cancer diagnosis (48-50). To prevent cancer recurrence and to increase the likelihood of survival, cancer survivors often attempt to quit smoking, to eat healthier, and to engage in regular exercise (48-56). Previous studies have found a positive effect of these lifestyle changes on health-related outcomes (51, 57, 58). In addition, patients may receive more medical services after diagnosis because cancer follow-up may provide regular contact with the health care system, increasing the chance of receiving appropriate medical care (35). Health care providers also may identify some chronic conditions that were underdiagnosed prior to the cancer diagnosis. Therefore, it is possible that comorbidities would be better controlled after cancer diagnosis.

On the other hand, comorbidities may worsen after cancer diagnosis. Long-term and late effects of cancer treatments are commonly observed among cancer survivors. For example, chemotherapy and radiation therapy may have negative effects on erectile function, cardiovascular disease, or mental health (22, 23, 59). In addition, cancer patients may not think that the continued management of other comorbidities is as important after their cancer diagnosis. Survivors may receive less care for comorbidities because their care may consist primarily of specialty care provided by specialist physicians, with little attention to primary care needs (36). Insufficient primary care may lead to development of other comorbidities or the worsening of existing comorbidities.

2.5 Risk Adjustment for Comorbidities in Cancer Patients

The Charlson Comorbidity Index (CCI) is a commonly used measure of comorbidity in epidemiologic and outcomes research (38, 39). The measure was originally developed in

1987 using 1-year mortality data from internal medicine patients admitted to a single New York hospital. The index provides an overall score based on a composite of values assigned to 19 medical conditions. Each condition is assigned a score of 1, 2, 3 or 6 depending on the risk of dying associated with this condition, and the total score ranges from 0 to 37 with higher scores representing increased risk of death. The CCI estimates 1-year risk of mortality from specific medical conditions among hospitalized patients and has been validated in an evaluation of breast cancer patients (38, 60). The original CCI was designed for use with medical records rather than medical claims. Deyo and colleagues adapted the index for use with administrative databases by matching the conditions in the CCI to their corresponding International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes (39). The authors validated the performance of the CCI (Deyo modification) in predicting health outcomes in Medicare beneficiaries who underwent lumbar spine surgery.

One of the limitations of the original CCI is that the calculation of index score depends solely on the codes obtained from inpatient claims. Therefore, cancer patients who have chronic conditions but have not been hospitalized for them during the study period may be mistakenly classified as having no comorbidities. To incorporate the medical diagnoses from outpatient visits, Klabunde and colleagues developed a new measure (NCI Index) to estimate mortality risk of comorbidities specifically using SEER-Medicare data (61). The NCI Index adapts the chronic conditions identified by Charlson and colleagues (38) and calculates two separate comorbidity scores from inpatient and physician (Medicare Part B) claims. Klabunde and her colleagues demonstrated that the NCI Index has better performance than the CCI in predicting 2-year, non-cancer mortality among elderly prostate and breast cancer patients (61). In addition, the NCI Index weights comorbid conditions differently than the CCI, and the conditions weights vary by cancer site. In a subsequent study, Baldwin and colleagues demonstrated that the NCI Index has predictive ability similar

or equivalent to receipt of chemotherapy and non-cancer mortality for colorectal cancer patients when compared to other comorbidity measures (62).

Based on their previous work, the researchers at the NCI recently developed a new measure of comorbidity severity (40). Unlike the NCI Index, which results in two separate scores, the NCICI combines comorbid conditions identified from Medicare inpatient and physician claims into a single comorbidity index. Researchers can sum the weighted conditions to establish a single index and to compare the severity of comorbidities across patients. A higher comorbidity score represents a more severe health problem. Klabunde and her colleagues compared the performance of the new weighted and un-weighted indices with the estimated comorbidity measures in predicting non-cancer mortality (40). Compared with the Charlson and un-weighted NCI Combined indices, the NCI Index and weighted NCICI showed the best model fits in predicting non-cancer mortality. The NCICI is easier to implement and statistically more efficient than the NCI Index because only a single comorbidity score is calculated. Different chronic condition weights are estimated for breast, colorectal, lung, and prostate cancer patients. To date, most previous studies used the CCI to adjust the risk for non-cancer mortality for their cancer survivors (27, 32, 63). To our knowledge, none of the published studies has used the NCICI to control for the comorbidity severity for cancer survivors.

2.6 Quality of Care for Comorbidities of Cancer Patients

Asch and colleagues (34) from the RAND Corporation have developed a comprehensive system for measuring underuse of necessary care among elderly patients using inpatient and outpatient Medicare claims. A multi-specialty physician panel developed 46 indicators of necessary care and avoidable outcomes for 15 medical conditions: 1) with a high prevalence or incidence among the elderly population, 2) for which effective treatment is available, and 3) are identifiable from diagnoses coded on claim data. Medical conditions

include acute myocardial infarction, anemia, angina, breast cancer, cerebrovascular accident, cholelithiasis, chronic obstructive pulmonary disease, congestive heart failure, depression, diabetes, gastrointestinal bleeding, hip fracture, hypertension, pneumonia, and transient ischemic attack. Necessary care is defined as care for which: 1) the benefits of the care outweigh the risks, 2) the benefits to the patients are likely and substantial, and 3) physicians have judged that not recommending the care would be inappropriate. Asch and colleagues found that among 16 of 40 necessary indicators, Medicare beneficiaries received indicated care less than two-thirds of the time. In addition, blacks were less likely to receive adequate necessary care as indicated by 16 of the indicators.

The ACE-PRO indicators were updated in 2006 to reflect changes in performance measurement and clinical practice. The refined ACE-PRO indicators have been tested and validated on Medicare claims by Medicare Payment Advisory Commission (MedPAC) (64). The refined ACE-PRO consists of 40 indicators for medical conditions covering anemia, angina, breast cancer, colorectal cancer, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, depression, diabetes, gastrointestinal bleeding, hypertension, and stroke or transient ischemic attack. Based on the type of care, these indicators can be grouped into clinical assessment in chronic condition, management of chronic condition, follow-up after hospitalization, possible adverse outcomes avoided, and work-up at initial diagnosis.

Earle and colleagues evaluated the quality of health care of Medicare beneficiaries and found that elderly breast cancer survivors received more preventive care than the non-cancer controls (35), suggesting that breast cancer patients' enhanced participation in the health care system may explain better quality of care. The study used the SEER-Medicare data and followed 5-year breast cancer survivors for two years. Compared with matched controls, breast cancer survivors were more likely to receive influenza vaccination, lipid

testing, cervical and colon screening, and bone densitometry. Elder age, black race, lower socioeconomic status, and residing in a rural area were cited as risk factors for underuse of preventive care. In addition, seeing both oncology specialists and primary care physicians was associated with the use of more preventive care.

Different findings were reported in colorectal cancer patients. Despite the higher prevalence of comorbidities, colorectal cancer survivors tended to underuse adequate treatment for their chronic conditions. Earle and Neville adopted the method developed by Asch and colleagues to evaluate underuse of necessary care among colorectal cancer survivors (36). This study followed 5-year colorectal cancer survivors for two years and found that colorectal cancer survivors were less likely to receive preventive care and acute interventions for their comorbidities than the non-cancer controls. The study also examined other factors that are associated with underuse of care. Patients who received care from both oncologists and primary care providers are more likely to use adequate care. Black race also was a strong predictor for underuse of care. However, the findings of this study may not apply to other types of cancer survivors, such as those with prostate cancer. As well, the study only focuses on the use of care for a 2-year period after patients have survived their invasive colorectal cancers for five years and colorectal cancer survivors generally do not have severe long-term consequences from the cancer or its treatment. Despite this research, little is known about whether patients receive adequate care before a cancer diagnosis and right after the cancer treatment, or whether underuse of necessary care is associated with poor health outcomes in cancer survivors.

2.7 Comparison between Previous Studies and the Current Study

The dissertation can expand our knowledge of comorbidities among elderly cancer survivors. Our study design has several advantages over previous studies. A comparison

between previous studies and the current study is listed in Table 1. Previous studies usually measure the prevalence or severity of comorbidities cross-sectionally, either at the time of cancer diagnosis or at a certain time point after cancer diagnosis. Our study measured and compared the prevalence and severity of comorbidities pre- and post-cancer diagnosis. The longitudinal follow-up allowed us to evaluate the influence of cancer diagnosis on comorbidities. Other studies typically use the CCI to control for the severity of comorbidities for cancer survivors. Our study measured comorbidity severity using the NCICI, which was developed specifically for use with Medicare claims. As well, by including a non-cancer comparison group, we were able to control for the effect of aging on comorbidities.

Table 1. Comparison between previous studies and current study

Topic	Previous studies	Current study
Comorbidities	• Cross-sectional - At cancer diagnosis - A time-point after cancer diagnosis • Use CCI • Examine only cancer survivors	• Longitudinal - Pre- and post-cancer diagnosis - Long-term follow-up • Use both CCI and NCICI • Also includes individuals without cancer
Use of care	• Cross-sectional • Breast or colorectal cancer survivors • Use the original ACE-PRO indicators • Include matched non-cancer controls	• Longitudinal • Prostate cancer survivors • Use the refined ACE-PRO indicators • Include individuals without cancer
Racial disparity	• Focus on overall and cancer mortality • Use Cox proportional hazards model only • Control comorbidity severity at the index date with CCI • Use of care is not controlled	• Also focus on non-cancer mortality • Use both Cox proportional hazards and competing-risk survival models • Control time-varying comorbidity severity with NCICI • Control for use of necessary care

CCI: Charlson Comorbidity Index; NCICI: National Cancer Institute Combined Index

Previous studies have investigated the level of adequate care among long-term breast and colorectal cancer survivors cross-sectionally (i.e., for a 2-year time period) but did not analyze the association between use of necessary care and a survivor's health outcomes (35, 36). The original ACE-PRO indicators were used in one of the previous

cancer survivorship study (36). In our study, we used the refined ACE-PRO indicators to evaluate the receipt of adequate care among prostate cancer survivors and follow them longitudinally for a maximum of ten years. We also investigated the risk factors for less use of necessary care among prostate cancer patients. Specifically, we examined the longitudinal influence of types of care provider on use of care.

Previous studies, using cross-sectional study design, have observed racial differences in prostate cancer patients' initial comorbidities, access to care, and survival rates (27, 31, 32, 65, 66). Our study examined these racial differences in all of our longitudinal analyses. We first evaluated the changes in comorbidity severity pre- and post-cancer diagnoses and estimate the differences by race. We then examined the racial difference in use of necessary care and analyzed whether the difference changed after prostate cancer diagnosis. Finally, we investigated whether racial disparity in survival rate remains after controlling for time-varying comorbidity severity, use of necessary care, and other confounders.

CHAPTER 3. RESEARCH DESIGN AND METHODS

3.1 Overview

This dissertation employed data from the SEER-Medicare Program to investigate the longitudinal relationship between prostate cancer and comorbidities among elderly prostate cancer survivors. We examined the data of prostate cancer survivor and individuals without cancer for up to ten years, beginning from 1998 through 2007. Table 2 provides a summary of methods used to address the three aims in this dissertation. In Aim 1, we first analyzed the unadjusted change in prevalence and severity of comorbidities pre- and post-cancer diagnosis. We then conducted Poisson regressions and GEE models to examine the changes controlling for other confounders. In Aim 2, we examined how prostate cancer survivors use necessary care for their comorbidities and whether this pattern of use precedes the cancer diagnosis. Similar to Aim 1, we first evaluated unadjusted use of necessary care and then adjusted for other confounders by GEE models. In Aim 3, we examined the potential racial disparity in survival among prostate cancer survivors. We first compared unadjusted Kaplan Meier survival curves by race. We then evaluated racial difference in overall, cancer, and non-cancer mortality after controlling for time-varying comorbidities, use of necessary care, and other confounders.

Table 2. Summary of study designs, methods, and analytical models by study aim

Study	Sample & Questions	Analytic Model	Outcomes of Interest	Key Independent Variables
Diagnosis of comorbidities	Cancer and non-cancer groups - Is the **prevalence** of chronic conditions higher after cancer diagnosis? - Is the **severity** of comorbidities greater after cancer diagnosis? - Do cancer survivors make more visits to health care providers after diagnosis? - Are the new chronic conditions diagnosed by prostate cancer specialists or primary care physician? - Are the findings from the above analyses different between black and white men?	• Unadjusted - Chi square test - Student's t test • Adjusted - Poisson regression - GEE model	• Crude prevalence of manageable chronic conditions • CCI • NCICI • Number of office visit	• Cancer • Cancer*time • Race • Race*time
Use of care for comorbidities	Cancer and non-cancer groups - Are cancer survivors more likely to receive **necessary care** for their comorbidities? - What is the effect of prostate cancer on the proportion of necessary care that is received? - Does the above relationship vary by race?	• Unadjusted - Chi square test - Student's t test • Adjusted - GEE model	• Proportion of patients receiving each type of necessary care • A composite score combining similar type of care • A composite score indicating the overall use of care	• Cancer • Cancer*time • Race • Race*time
Racial disparity in survival	Cancer group only - Do **racial differences** in mortality remain after controlling for severity of comorbidities (from Aim 1) and underuse of care (from Aim 2)? - What are other risk factors for mortality among prostate cancer survivors?	• Unadjusted - Kaplan-Meier survival curves - Log rank test • Adjusted - Cox proportional hazards model - Competing-risk model	• Overall mortality • Cancer mortality • Non-cancer mortality	• Race • Comorbidity • Use of care

GEE: General generalized estimating equations; NCICI: National Cancer Institute Combined Index; CCI: Charlson Comorbidity Index

3.2 Research Hypotheses

In Aim 1, we examined the longitudinal relationship between prostate cancer and diagnosis of other comorbidities. We first examined whether the prevalence and severity of comorbidities change differently between cancer and comparison groups after 2000. Since patients tend to have more contact with the health care system after cancer diagnosis (35), we expected some previously underdiagnosed chronic conditions to be identified. We then conducted subgroup analyses to examine whether the findings from these analyses were different by race. Previous studies reported that black patients generally have more comorbidities (32) but the comorbid conditions are more likely to be underdiagnosed than white patients (67). Therefore, we expected the increases in diagnosis comorbid conditions were more in black survivors. Finally, we compared the number of office visits by specialty among cancer survivors. We expected prostate cancer specialists to become the main health care providers for survivors after cancer diagnosis and to provide some primary care. In Aim 1, our hypotheses were:

H_1: After 2000, the prevalence and severity of comorbidities increase more among cancer survivors than among individuals without cancer
H_2: After cancer diagnosis, the prevalence and severity of comorbidities increase more among black survivors than among white survivors
H_3: Survivors make more visits to prostate cancer specialists but fewer visits to PCPs after cancer diagnosis
H_4: New comorbidities identified after cancer diagnosis are more likely to be diagnosed by prostate cancer specialists than by PCPs.

In Aim 2, we examined the longitudinal relationship between prostate cancer and use of necessary care for other comorbid conditions. We compared the proportion of necessary care that was received by cancer and non-cancer comparison groups. We expected prostate cancer survivors to receive more necessary care because they may have more contact with the health care system (35). In subgroup analysis, we expected the black survivors to use less necessary care than the white survivors based on the findings from

previous literature (34-36). However, we expected the racial difference in use of necessary care among cancer survivors decreases after prostate cancer diagnosis. Finally, we examined the relationship between type of care provider and use of necessary care. Based on the findings from previous literature (35, 36), we expected survivors seeking care from both prostate cancer specialists and PCPs to receive more necessary care than those who visit prostate cancer specialists only, PCPs only, and neither of them. Our hypotheses were:

H_1: Before 2000, the use of necessary care is not different between cancer and non-cancer comparison groups.
H_2: After 2000, cancer group uses more necessary care more than the non-cancer comparison group does.
H_3: Black survivors consistently use less necessary care than white survivors
H_4: Racial difference in use of necessary care decreases after cancer diagnosis
H_5: Survivors who visit both prostate cancer specialists and PCPs after cancer diagnosis receive more necessary care than those who visit either or neither of them.

In Aim 3, we examined the racial disparity in survival among prostate cancer survivors after controlling for time-varying comorbidity (from Aim 1) and use of necessary care (from Aim 2). We expected that racial differences in overall and cancer mortality would remain, but the racial difference in non-cancer mortality would disappear after we control for other variables. The hypotheses of Aim 3 were:

H_1: The magnitude of racial disparity in overall mortality decreases after controlling for time-varying comorbidities and use of necessary care. However, the disparity is still statistically significant.
H_2: The magnitude of racial disparity in cancer mortality decreases after controlling for time-varying comorbidities and use of necessary care. However, the disparity is still statistically significant.
H_3: No racial disparity is observed in non-cancer mortality after controlling for time-varying comorbidities and underuse of care.

3.3 Conceptual Framework

Figure 1. Conceptual model

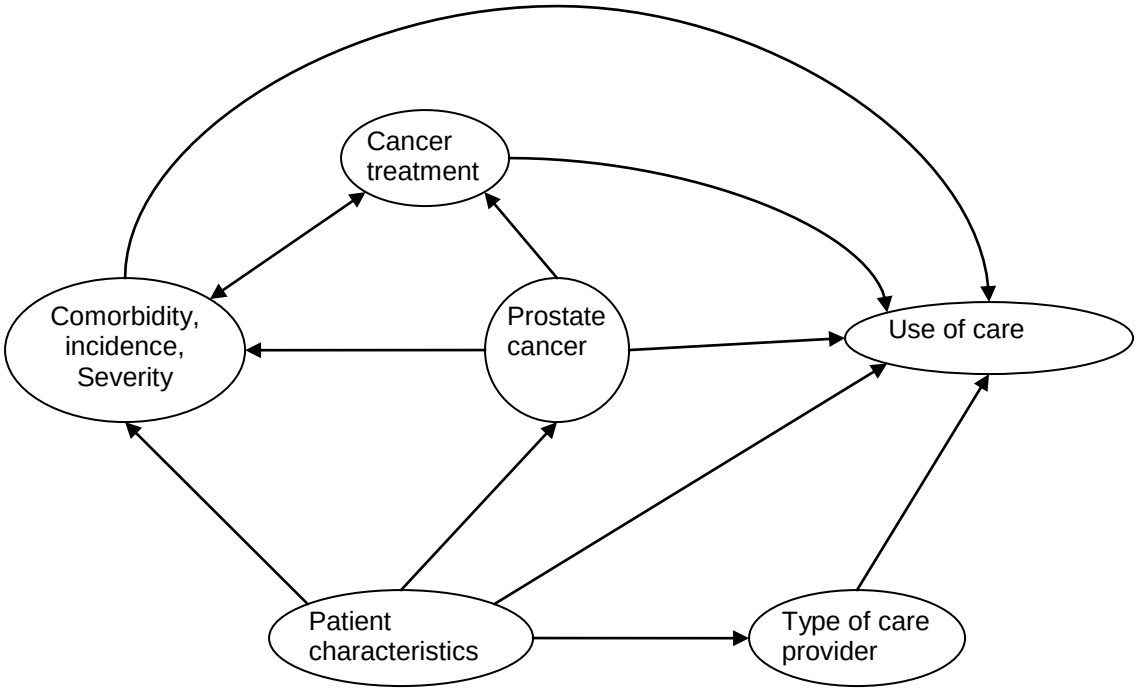


Figure 1 represents a conceptual model describing the relationship between prostate cancer, comorbidities, and use of care. Based on previous literature, patients' characteristics including age, black race, and family disease history are the primary risk factors for prostate cancer and also are associated with the prevalence of other comorbidities (8, 10, 11). In addition, socioeconomic status (SES), insurance status, and marital status are associated with time until diagnosis and the use of care for other comorbidities (25, 28, 31). The correlation between cancer treatment and comorbidities are bidirectional. The existence of comorbidities will influence the choice of cancer treatment, and the side effects of cancer treatment will affect the prevalence and severity of comorbidities (3-6).

The relationship between cancer and use of necessary care for comorbidities remains unclear. Researchers have found that breast cancer survivors are more likely to

receive preventive medical care whereas colorectal cancer survivors tend to receive less medical services (35, 36). However, the relationship between prostate cancer and the use of necessary care remains unstudied. In addition, patients' age, race, SES, and comorbidities have all been shown to be correlated with the underuse of care among cancer survivors (36). In previous studies, the type of care provider is shown to be associated with use of necessary care (35, 36).

3.4 Data Source

3.4.1 SEER Registry

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) is an authoritative program collecting information on cancer incidence and survival statistics, serving as the only comprehensive source of population-based cancer information in the United States (68). After the most recent expansion in 2000, the SEER Program reports cancer incidence and survival data from 17 population-based cancer registries covering approximately 26 percent of the population. Residents in current SEER regions include 23 percent of whites, 23 percent of blacks, 40 percent of Hispanics, 42 percent of American Indians and Alaska Natives, 53 percent of Asians, and 70 percent of Hawaiian/Pacific Islanders in the United States. The SEER Program is considered the standard for quality among cancer registries around the world. It routinely collects data on patient demographics, primary tumor site, stage at diagnosis, primary course of treatment, and cause of death. The SEER Program collects SES information including median household economic and educational status (69, 70). These SES variables are aggregate measures from the US Census Bureau that reflect the characteristics of census tracts and zip codes in which patients resided during the year of their first diagnosis (69).

This dissertation used the data from the SEER-17 registries, which cover Arizona native Americans, Alaska Natives, nine states (California, Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah), and seven regions (Atlanta, Detroit, rural Georgia, Los Angeles, San Francisco, San Jose, and Seattle). Data are available for all cases diagnosed from 2000 through 2005.

3.4.2 Medicare Enrollment and Claims Files

Medicare is the primary health insurer for 97% of the US population ages 65 years and older (70). All Medicare beneficiaries receive Part A benefits, which are generally paid for by payroll taxes for workers. Approximately 99 percent of Medicare beneficiaries pay no premium for Part A services because they have at least 40 quarters of Medicare-covered employment (71). Medicare Part A benefits cover inpatient care in hospitals, including critical access hospitals, and skilled nursing facilities (but not custodial or long-term care), hospice care and some home health care services. Among Medicare Part A beneficiaries, 95% of them also pay a monthly premium for the Part B benefits (70). Medicare beneficiaries pay premiums for Part B benefits, which cover physician services, outpatient care, durable medical equipment, some of the services of physical and occupational therapists, and home health in some cases. Medicare claims provide information about comorbidities and use of medical services that are the outcomes of interests in this study.

3.4.3 SEER-Medicare Data

The SEER-Medicare data are population-based data that combine SEER cancer registry information with Medicare enrollment and claims files (70, 72). The linkage of SEER program data and Medicare claims was initially completed in 1991 as the result of collaboration between the National Cancer Institute, the SEER registries, and Centers of Medicare and Medicaid Services (CMS). The current SEER-Medicare data include all Medicare-eligible beneficiaries appearing in the SEER registry through December 31, 2005,

and their Medicare claims through December 31, 2007 (72). The linkage of SEER and Medicare data is relatively complete, with 93% of elderly SEER registrants linked to the Medicare enrollment file (70). A beneficiary's disease diagnoses, treatments, and services received are available in the Medicare claims. However, data are missing for health maintenance organization (HMO) enrollees, services not covered by Medicare (i.e., outpatient prescription drugs and long term care), services provided by Veterans Affairs or Medicaid, or by Medicare supplement programs (i.e., Medigap) (70).

At present, the SEER-Medicare data include more than 3.3 million individuals with cancer; of whom, approximately 40,000 were diagnosed with prostate cancer in 2000 (72). In addition to beneficiaries with cancer, the SEER-Medicare data also include a sample of Medicare beneficiaries who do not have cancer. The non-cancer group is drawn from a random, 5-percent sample of Medicare beneficiaries living in the SEER regions and comprises approximately 400,000 cancer-free individuals. Compared with the overall elderly population, elderly adults living in the SEER regions are less likely to be white, to live in poverty, and to reside in rural areas (70). In addition, elderly persons in the SEER regions also have higher rates of HMO enrollment and lower rates of cancer mortality.

3.5 Study Sample

The same study sample was used for both Aims 1 and 2. We included only patients who were diagnosed with localized or regional prostate cancer (i.e., Stage I, II, and III) in 2000 to evaluate the long-term effect of prostate cancer on comorbidities. These patients are not likely to die from prostate cancer because their five-year relative survival rate is approximately 100% as compared with the non-cancer population (73). Approximately 5% prostate cancer patients were excluded from our analysis because of distant prostate cancer, which has a five-year relative survival rate of only 32% (73) and because the presence of

some comorbidities (e.g., cardiovascular diseases) may be associated with hormonal treatment for distant prostate cancer (59). Another 5% of patients were excluded because their prostate cancer stage was either missing or unknown. The data of each cancer patient were examined for up to ten years, beginning from January 1, 1998, through December 31, 2007. To be eligible for inclusion in the study, patients must have been enrolled continuously in Medicare Part A and Part B during the study period. To observe the presence of comorbidities before cancer diagnosis, we included only patients who were diagnosed with prostate cancer at age 67 or older as of January 1, 2000, thus allowing for two years of observation prior to diagnosis. Medicare beneficiaries who are eligible for Medicare because of disability or the presence of end-stage renal disease before age 65 were excluded from the analyses. HMO enrollees also were excluded, as services provided by HMOs are not included in the SEER–Medicare data. Other exclusion criteria included: prior cancer history, diagnosis with a second cancer within six months, noninvasive tumors (i.e., carcinoma in situ), unstaged prostate cancer, diagnosis after age 84, diagnosis at death or via autopsy, and missing income and education information. Finally, patients of races other than black and white were excluded from the analyses because of the small sample size and unreliable classification of the race groups (69).

To adjust for the potential effect of aging, we also included a non-cancer comparison group from the 5-percent random sample of individuals without cancer included in the SEER-Medicare data. Inclusion criteria for the non-cancer comparison group were: male gender, black or white race, qualified for Medicare benefit because of age, continuously enrolled in Medicare Part A and Part B and never enrolled in the HMO program during the study period, and living in the SEER-17 regions.

Table 3 compares the variables available for the cancer and comparison groups. Demographic information, including age, race, SEER region, median income and education

level in residential areas, is available for both groups. We were able to assess the severity of comorbidities and the use of necessary care from the Medicare claims for both groups. However, some variables such as marital status, cancer stage, tumor grade, primary cancer treatment, and type of care provider were available only for the cancer cases in our study. Therefore, when we identified the factors associated with higher comorbidity scores and more use of necessary care, we focused only on the prostate cancer group.

Table 3. Comparison of available variables for cancer cases and non-cancer controls

Variables	Cancer-cases	Non-cancer controls
Age	Yes	Yes
Race	Yes	Yes
SEER registry site	Yes	Yes
Median income in residential area	Yes	Yes
Median education level in residential area	Yes	Yes
Comorbidity severity	Yes	Yes
Use of care for comorbidities	Yes	Yes
Marital status	Yes	No
Cancer stage	Yes	N/A
Tumor grade	Yes	N/A
Cancer treatment	Yes	N/A
Type of care provider	Yes	N/A

N/A: not applicable

Similar inclusion and exclusion criteria were adopted for the study sample in Aim 3. However, we also included survivors who were diagnosed with distant prostate cancer in the survival analyses. Individuals without cancer were excluded because we only focused on racial disparity in survival among prostate cancer survivors. In addition, we only included survivors from registries with at least 11 black prostate cancer cases in 2000. Survivors from

Hawaii, Iowa, New Mexico, Utah, rural Georgia, San Jose, and Seattle were excluded because black race only consists of a very small proportion of their populations.

3.6 Variable Definitions

3.6.1 Socio-demographic information

A cancer patient's age, race, and date of death are available from both SEER and Medicare data. Demographic information from these two sources is highly consistent (69). Since the demographic data for the comparison group are available only in the Medicare enrollment file, we employed Medicare's Enrollment Database as our primary source to identify age, race, and vital status for both groups. Empirically, data aggregated at the census tract level are more likely to reflect a patient's SES than are zip code level data (69). However, the SES information for the comparison group is available only at the zip code level; hence, we controlled for median household income and percentage of residents with less than a high school degree at zip code level from the 2000 Census for both cancer and comparison group in Aims 1 and 2.

In Aim 3, since the non-cancer comparison group was excluded, we adopted median household income, percentage of residents living below poverty level, percentage of residents with less than a high school degree at census tract level in the analyses.

3.6.2 The date and cause of death

The date of death is available in both Medicare and SEER data, but is derived from different sources covering different time periods. The Medicare death date was obtained from Medicare Enrollment Database, which is updated nightly by the Social Security Administration, and includes death data through December, 2007. The SEER death date is primarily derived from state death certificates, but it is sometimes acquired from the Medicare Enrollment Database when state data are unavailable, whereas SEER Program

has this information only until December, 2005. We used Medicare as the primary source to identify time of death for overall mortality because it allows us to have a longer follow-up timeframe (i.e., up to eight years). For analyses disaggregating mortality by causes, we employed data from the SEER Program which has information for cause of death. These analyses were limited to deaths prior to 2005.

3.6.3 Primary cancer treatment

We used definitions similar to those used in previous studies examining racial differences in the outcomes of localized prostate cancer patients (27, 63). The type of primary treatment for prostate cancer was identified from the SEER data and Medicare claims within six months of cancer diagnosis. Surgery is defined as procedures performed with curative intent or in anticipation of a subsequent curative procedure (27). To identify radical prostatectomy and procedures performed on regional lymph nodes, we used: (1) the SEER indicator for whether a cancer-directed surgery was performed; (2) procedure codes from Medicare claims (International Classification of Diseases, 9th Revision, [ICD-9] 60.5 and 60.6; Current Procedural Terminology [CPT] codes 55810, 55812, 55815, 55840, 55842, 55845, 55866); and (3) site-specific surgery codes 30–90 from the SEER data. Radiation therapy (XRT) is defined as external beam therapy, brachytherapy, or therapeutic isotope radiation therapy as listed in the SEER data (63). Specifically, we used: (1) the SEER indicator for whether a cancer-directed XRT was performed; (2) ICD-9 procedure codes 92.2x, V58.0, V66.1, V67.1, CPT codes 77301, 77400–77499; revenue center codes 0330–0339 from Medicare claims; and (3) site-specific radiation codes 1–5 from the SEER data to identify XRT. Men who receive both surgery and XRT will be classified as having surgery because some patients may receive XRT after an incomplete or unsuccessful surgery (27, 63).

3.6.4 Type of care provider

The type of care provider was classified based on the specialty information in the Medicare Carrier Claims (36). Prostate cancer specialists were defined as sub-specialists in urology (code 34), hematology oncology (code 83), medical oncology (code 90), surgical oncology (code 91), or radiation oncology (code 92). Primary care physician (PCPs) were defined as physicians in general practice (code 01), family practice (code 08), internal medicine (code 11), geriatric medicine (code 38), or multi-specialty group practices (code 70).

3.7 Risk Adjustments for Comorbidities

We used the CCI and the NCICI to assess the severity of comorbidities at different time points. The CCI is a commonly used measure of comorbidity in epidemiologic and outcomes research (27, 38, 39, 63, 74). Researchers can accumulate the weighted comorbidities to establish a single index and to compare the severity of comorbidities across patients. A higher comorbidity score represents more severe health problems. The NCICI was developed specifically for the use with SEER-Medicare data to adjust for the risk of dying from causes other than cancer (40). The NCICI adapts the comorbid conditions from the CCI but weights them differently, and allows the comorbidity weights vary by cancer site. Compared with the CCI, the NCICI performed better in predicting non-cancer mortality among cancer survivors (40). The CCI and NCICI are described in detail in Section 2.5. The comorbidities and their ICD-9 codes and weights for CCI and NCICI are listed in Table 4.

Table 4. Chronic conditions and their weights in NCICI and CCI index

Chronic conditions	ICD-9 Codes	NCICI	CCI
AIDS	042-044.9	N/A	6
Cerebrovascular disease	430-438	0.266	1
Chronic pulmonary disease	490-496, 500-505, 506.4	0.725	1
Congestive heart failure	428-428.9	0.874	1
Dementia	290-290.9	0.777	1
Diabetes	250-250.3, 250.7	0.239	1
Diabetes with complications	250.4-250.6	0.44	2
Moderate/severe liver disease	572.2-572.8	N/A	3
Moderate/severe renal disease	582-582.9, 583-583.7, 585, 586, 588-588.9	0.678	2
Myocardial infarction (acute)	410-410.9	0.242	1
Myocardial infarction (history)	412	0.054	1
Paralysis	344.1, 342-342.9	0.393	2
Peptic ulcer disease	531-534.9, 531.4-531.7, 532.4-532.7, 533.4-533.7, 534.4-534.7	-0.247	1
Peripheral vascular disease	443.9, 441, 441.9, 785.4, V43.4, Procedure 38.48	0.359	1
Rheumatologic disease	710.0, 710.1, 710.4,714.0-714.2, 714.81, 725	0.091	1
Various cirrhosis	571.2, 571.5, 571.6, 571.4-571.49	N/A	1

Source: Klabunde et al. 2007 (40), Deyo et al. 1992 (39)
ICD-9: International Classification of Diseases, 9th Revision
NCICI: National Cancer Institute Combined Index; CCI: Charlson Comorbidity Index

3.8 Quality of Care Measures

We used the refined Access to Care for the Elderly Project (ACE-PRO) indicators from the Medicare Payment Advisory Commission (MedPAC) to assess use of necessary ambulatory care among elderly Medicare beneficiaries (64). The MedPAC, an independent Congressional agency, advises the US Congress on issues affecting the Medicare program. The ACE-PRO indicators were originally developed for MedPAC by researchers from the RAND Corporation in 2000 (34). MedPAC has used the ACE-PRO indicators to study the access to and quality of care associated with various geographic and socioeconomic factors,

and has used the results of these analyses in their reports to Congress (64). The ACE-PRO indicators were updated in 2006 to reflect changes in performance measurement and clinical practice. The refined ACE-PRO indicators have been tested and validated on Medicare claims by MedPAC (64).

The refined ACE-PRO indicators consist of 40 items for medical conditions covering anemia, angina, breast cancer, colorectal cancer, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, depression, diabetes, gastrointestinal bleeding, hypertension, and stroke or transient ischemic attack. Six indicators were excluded from our analysis because they were developed specifically either for women or for other cancers. Based on the suggestion of MedPAC, the remaining 34 indicators (Table 5) were categorized into five groups by their type of care (i.e., Clinical Assessment in Chronic Conditions, Management of Chronic Conditions, Follow-up after Hospitalization, Avoidable Adverse Outcomes, and Work-up at Initial Diagnosis) (64).

Table 5. Indicators for the Refined Access to Care for the Elderly Project

Clinical Assessment for Chronic Conditions
Two outpatient visits every year for patients with diabetes mellitus
Two outpatient visits every year for patients with coronary artery disease
Two outpatient visits every year for patients with stroke or transient ischemic attack
Two outpatient visits every year for patients with chronic obstructive pulmonary disease
Two outpatient visits every year for patients with heart failure
One outpatient visit every year for all elderly Medicare beneficiaries
Management of Chronic Conditions
Comprehensive eye exam every two year for patients with diabetes mellitus
Hemoglobin A1C test every year for patients with diabetes mellitus
Lipid profile every year for patients with diabetes mellitus
Lipid profile every year for patients with coronary artery disease
Measurement of electrolytes and renal function every year for patients with heart failure
Follow-up after Hospitalization
At least one non-emergent ambulatory visit within 4 weeks following discharge of patients hospitalized for diabetes mellitus
At least one non-emergent ambulatory visit within 4 weeks following discharge of patients hospitalized for acute myocardial infarction
At least one non-emergent ambulatory visit within 4 weeks following discharge of patients hospitalized for stroke or transient ischemic attack
At least one non-emergent ambulatory visit within 4 weeks following discharge of patients hospitalized for heart failure
At least one ambulatory visit within 4 weeks following discharge of patients hospitalized for gastrointestinal bleeding
At least one hemoglobin or hematocrit test within 4 weeks following discharge of patients hospitalized for gastrointestinal bleeding
At least one ambulatory visit within 2 weeks following discharge of patients hospitalized for depression

Table 5. Indicators for the Refined Access to Care for the Elderly Project (continued)

Avoidable Adverse Outcomes
Hospitalization for diabetic, hyperosmolar, ketotic coma, and uncontrolled diabetes mellitus among patients with a history of diabetes mellitus
Hospitalization for renal, ophthalmologic, neurologic, and circulatory complications of diabetes mellitus and non-traumatic lower extremity amputation in patient with a history of diabetes mellitus
Three or more emergency department visits for coronary artery disease in patients with a history of coronary artery disease
Hospitalization for heart failure in patients with a history of heart failure
Hospitalization for chronic obstructive pulmonary disease in patients with a history of chronic obstructive pulmonary disease
Hospitalization for malignant hypertension in patients with a history of hypertension
Work-up at Initial Diagnosis
Electrocardiography or Holter monitor within 2 days of initial diagnosis of transient ischemic attack
Carotid angiogram or non-invasive carotid imaging procedure within 2 weeks of initial diagnosis in patients hospitalized for carotid artery stroke
Carotid imaging to carotid endarterectomy interval less than 2 months, in patients with a hospitalization for stroke or transient ischemic attack prior to the carotid endarterectomy
Diagnostic ultrasound, radionuclide ventriculography, or left ventriculogram within 3 months, before or after, initial diagnosis of heart failure
Diagnostic ultrasound, radionuclide ventriculography, or left ventriculogram within 3 months, before or after, hospitalization for heart failure
Electrocardiography within one month before or three months after initial diagnosis of heart failure
Chest X-ray within one month before or three months after initial diagnosis of heart failure
At least one inpatient or outpatient visit, within four weeks following initial diagnosis of gastrointestinal bleeding in an outpatient setting
Colonoscopy or barium enema within one month before or three months after initial diagnosis of iron deficiency anemia
Hemoglobin or hematocrit test within one to six months after initial diagnosis or anemia

Source: MedPAC Report (64); publicly-available at: http://www.medpac.gov/publications/contractor_reports/MACIEFeb1206Final.pdf

The ACE-PRO indicators were originally developed for analysis using two years of data (64). Many indicators use the first year of observation to determine individuals who are qualified to be part of denominators and use the second year of observation to identify numerators. In this study, we made some adjustments to the ACE-PRO method for our ten-year study timeframe. For indicators of clinical assessment, management of chronic conditions, and avoidable adverse outcomes, an individual became qualified for the denominator after the year when he was first diagnosed with a chronic condition. For indicators of follow-up after hospitalization, we used the first event in each time period without another event within four weeks following the discharge of the previous event. For the indicators of work-up at initial diagnosis, we examined the care at the first diagnosis in the entire time frame, rather than the first diagnosis in each time period. Our ten years of follow-up allows us to identify the initial diagnosis more precisely than the conventional ACE-PRO method using only two years of data.

We estimated use of necessary care in each two-year time period (64). For each indicator, we first used the ICD-9 codes to identify the number of individuals who were qualified for it (i.e., the denominator). We then used the CPT codes to identify the number of qualified individuals who met the requirement of the indicator (i.e., the numerator). The ratio of numerator to denominator represents the proportion of individuals who used the necessary care. For example, we assessed the eye care indicator by calculating the proportion of individuals with a history of diabetes mellitus who had comprehensive eye exam.

$$eye\ care\ indicator_t = \frac{number\ of\ \ diabetic\ patients\ who\ had\ eye\ exam_t}{number\ of\ \ patients\ with\ a\ \ prior\ history\ of\ \ diabetes_t}$$

For each person, we also calculated composite scores for (1) clinical assessment for chronic condition, (2) management of chronic condition, (3) follow-up after hospitalization, (4)

possible adverse outcomes avoided, and (5) work-up at initial diagnosis. Finally, we calculated an overall composite score by dividing the sum of numerators by the sum of denominators to measure the proportion of eligible care that was received by each person during each time period.

$$overall\,use\,of\ necessary\,care_{it} = \frac{\sum_{j=1}^{34} care\ received_{ijt}}{\sum_{j=1}^{34} qualified\ for\ care_{ijt}}$$

3.9 Competing-risk Survival Analysis

Prostate cancer and other causes are competing risks for cancer patients' mortality because a patient who dies from one of these causes cannot die from the other. Typically, cancer survivorship studies use Cox proportional hazard (PH) model (75) when cancer-specific mortality is the outcome of interest (26, 27, 29-31). Patients who die from causes other than cancer are treated as censored cases, which implicitly assumes that the risks of dying from cancer and other causes are independent. At present, there is no valid mathematic method to examine whether the competing risks are indeed independent (76). However, these risks are very likely dependent because the presence of prostate cancer (i.e., the risk of dying from cancer) may change the risk of dying from other comorbidities. For example, prostate cancer treatments may have negative effects on survivors' cardiovascular disease and mental health (22, 23, 59). In addition, the presence of comorbidities also may complicate treatment management and further affect the risk of dying from cancer. If the competing-risk relationship just described differs by race, the hazard ratio of race directly obtained from a PH model would be biased.

To account for the competing risks in our survival analysis, we use the cumulative incidence curve method developed by Fine and Gray (77). Their competing-risk model

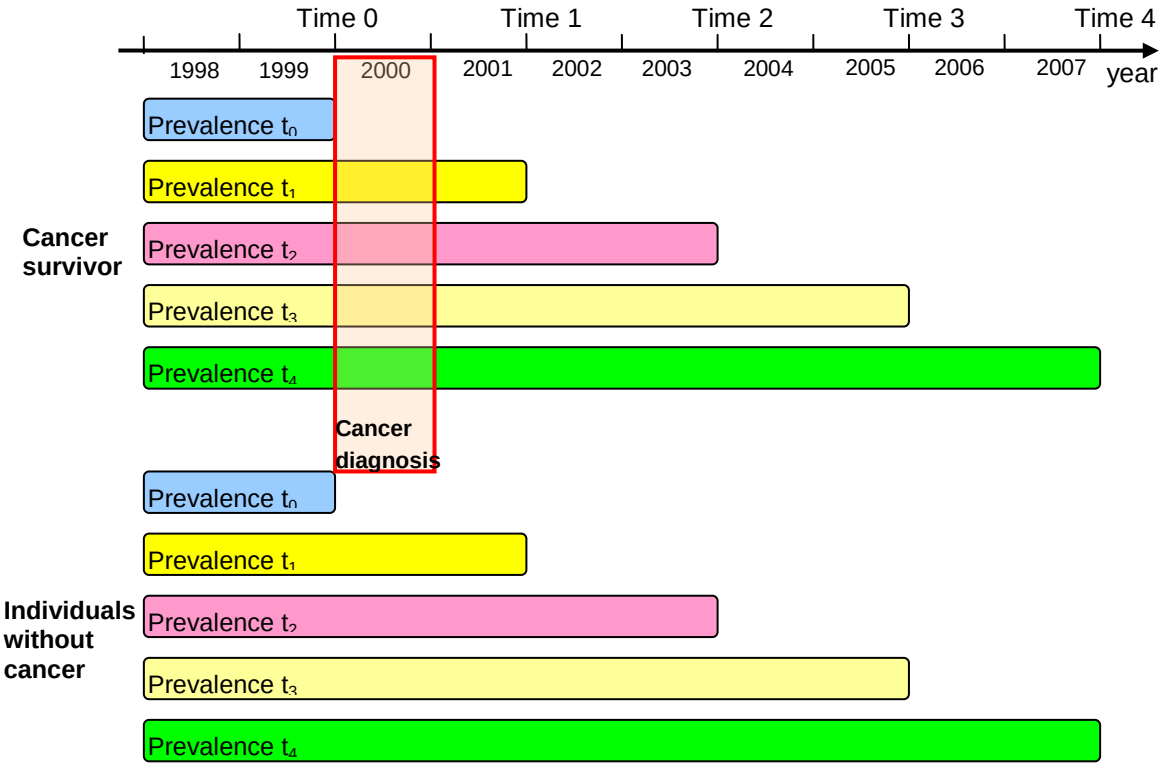
allows the dependence of competing risks in the Cox PH model and estimates hazard ratios of independent variables for competing risks (i.e., cancer and non-cancer deaths) separately. We compared the hazard ratios of black race obtained from the Cox PH and competing-risk models to evaluate whether we have consistent findings for racial disparity.

3.10 Analysis Plans

3.10.1 Aim 1

The cumulative prevalence rates were measured as of December 31st in 1999, 2001, 2003, 2005, and 2007 (Figure 2). At each time point, we calculated the proportion of patients alive with a disease history of COPD, diabetes, depression, hypercholesterolemia, or hypertension. To confirm a comorbid condition, we required a patient to have at least one inpatient or two outpatient visits with the disease diagnosis codes within 12 months (See Table 4). Chi-squared tests were conducted to compare the crude prevalence rates between the cancer and comparison groups (78). We also used modified Poisson regression analysis to compare comorbidity prevalence rates between cancer and comparison groups adjusting for age, race, registry site, income, and education (79).

Figure 2. Analytic plan to compare comorbidity prevalence pre- and post-cancer diagnosis



We measured the changes over time in individual patient's overall comorbidity severity by CCI (38, 39). At each time point, crude comorbidity scores for both cancer and non-cancer groups were compared using Student's t tests (78). To account for repeated measures, we also estimated a generalized estimating equations (GEE) model (80, 81). The effects of cancer on CCI at various time points were of primary interest. The sum of coefficients between cancer indicator and its interaction term with time was tested by Wald test at each time point (80, 81). Other factors, including age, race, registry site, education, and income, which might be associated with comorbidities and prostate cancer, were controlled for in the model. For prostate cancer survivors, we used the NCICI to measure their comorbidity severity. At each time point, we compared the NCICI scores between black and white survivors using Student's t test (78). A GEE model was conducted to investigate

the longitudinal relationship between race and comorbidity severity (80, 81). Wald tests were conducted to further examine the relationship between race and NCICI at various time points. Age, race, registry site, education, income, marital status, and cancer treatment also were controlled for in the GEE model.

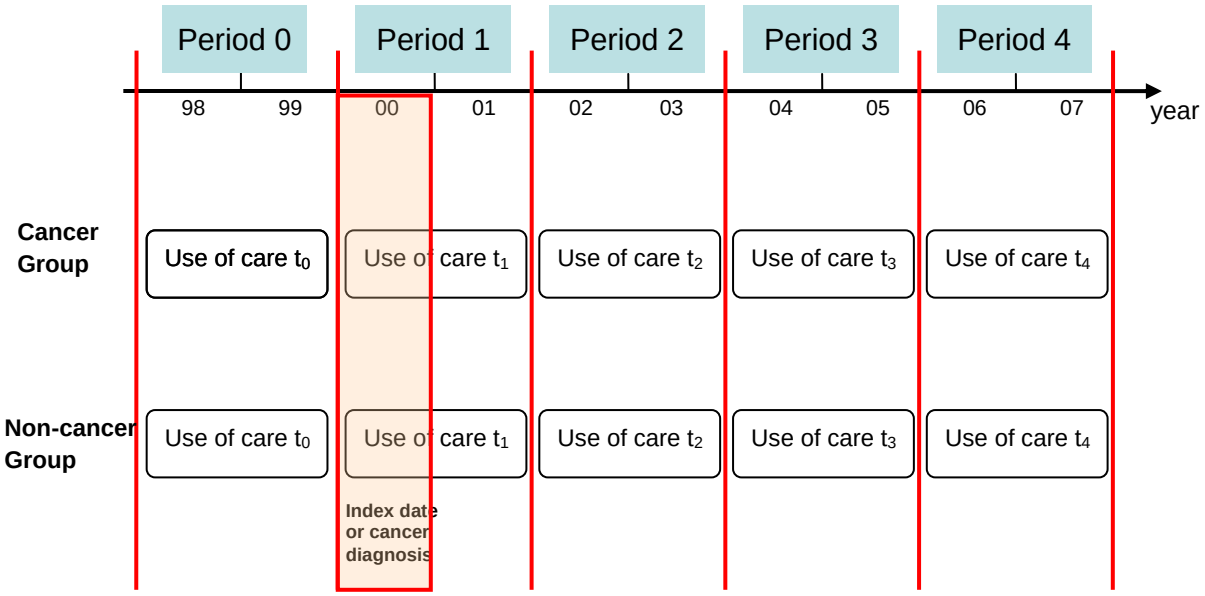
In addition, we examined the number of physician visits over time. The average number of office visit to PCPs, prostate cancer specialists, and other specialists were calculated in each two-year period. Student's t tests were conducted to analyze whether cancer survivors made more visits to prostate cancer specialists and fewer visits to PCPs than they did before cancer diagnosis (78). We further examined the relationship between types of provider and newly diagnosed comorbidities. Specifically, we focused on newly diagnosed diabetes and hypertension, which are prevalent conditions among the elderly. The first diagnosis code of a new condition after cancer was linked to the diagnosing health care provider. Cases of newly diagnosed diabetes or hypertension between 2000 and 2001 were stratified by the type of health care provider. We used a Chi-square test (78) to examine whether the new conditions were more likely to be diagnosed by prostate cancer specialists than by PCPs.

3.10.2 Aim 2

The use of necessary care for each ACE-PRO indicator was measured during five time periods (Figure 3). Period 0 measured the baseline use of care in 1998 and 1999 (i.e., two years before the index date (i.e., cancer diagnosis or 2000). Data from Period 1 evaluate whether patients received necessary care for their comorbidities right after cancer diagnosis (i.e., between 2000 and 2001). Periods 2 and 3 focused on the use of care between 2002 and 2003 and between 2004 and 2005, respectively. Data in the last period, Period 4 (between 2006 and 2007), measured the use of care after patients had survived prostate cancer for more than five years. The result from this final period can be directly

compared with the findings from previous studies evaluating the use of care in other types of cancer (35, 36).

Figure 3. Analytic plan to compare the use of care pre-and post-cancer



For each indicator, we first compared the ratios of numerators to denominators between cancer and non-cancer groups during different time periods. Chi-square tests (78) were conducted to examine whether prostate cancer survivors received the same level of care for their comorbid conditions as the comparison group did. For different types of care, we conducted Student's t tests to compare composite scores between cancer and comparison groups in different time periods.

Multivariate GEE regression models (80, 81) were conducted to analyze the association between prostate cancer diagnosis and overall use of necessary care. The effects of cancer on use of necessary care during various time periods were of primary interest. The sum of coefficients between cancer indicator and its interaction term with time was tested by Wald test in each time period (80, 81). Other factors, including age, race, registry site, education, income, and comorbidities, which might be associated with use of

care and prostate cancer diagnosis, were controlled for in the models. We also conducted a subgroup GEE analysis for cancer survivors only to examine whether racial differences in use of care changed after cancer diagnosis. Wald tests were conducted to assess the relationship between race and use of necessary care during various time periods. In addition to the independent variables in the previous GEE model, we also controlled for marital status, primary cancer treatment, tumor grade, and type of care provider, which were available only for the cancer group.

3.10.3 Aim 3

This aim examined racial disparity in survival among prostate cancer survivors. Kaplan-Meier survival curves (82) were used to compare the unadjusted survival (measured in months) by race and cancer stage. Log-rank tests were conducted to evaluate whether black patients have different survival rates as compared with white patients. We then assessed adjusted racial disparity in overall mortality using Cox PH models (75). We also examined the racial disparity in cancer or non-cancer mortality using the competing-risk models (77), which allow for the dependence of competing risks in the PH model and estimates hazard ratios (HRs) of independent variables for competing risks (i.e., cancer and non-cancer deaths) separately. We compared the HRs of black race after controlling for factors which have been shown to be potentially responsible for racial disparity, such as a patient's age, registry site, marital status, SES, and cancer disease information (i.e., stage, grade, and treatment). Subsequently, we evaluated the effect of additional adjustment for time-varying NCICI score and use of care on racial disparity in overall survival.

Finally, we identified the risk factors for overall, cancer, and non-cancer mortality among men with prostate cancer. A patient's demographic information, cancer disease information, SES, comorbidity, and use of care were examined in the regression models. We first compared the results of Cox PH models controlling for static or time-varying comorbidity

scores. The PH assumption was tested by both graphical and goodness-of-fit approaches for each variable (83). Finally, we compared the models using the Cox PH (i.e., the approach commonly used in the current literature) or competing-risk methods to identify risk factors for dying from cancer or other causes.

CHAPTER 4. ASSOCIATION BETWEEN CANCER AND THE DETECTION OF COMORBID HEALTH CONDITIONS AMONG ELDERLY MEN WITH PROSTATE CANCER IN THE UNITED STATES

4.1 Abstract

Background: Prostate cancer is a highly survivable disease, but coexisting comorbidities are the major threat to life for its survivors. This study examined whether more comorbidities were detected after cancer diagnosis.

Methods: Patients diagnosed with localized/regional prostate cancer at ages 67-84 in 2000 (n=9,053) were identified from the Surveillance, Epidemiology, and End Results-Medicare Program. A comparison group of Medicare beneficiaries with no history of cancer was also included (n=43,926). Patients' claims from 1998 through 2007 were examined. The prevalence rates of chronic obstructive pulmonary disease (COPD), diabetes, depression, hypercholesterolemia, and hypertension and overall comorbidity score as measured by Charlson Comorbidity Index (CCI) and National Cancer Institute Combined Index (NCICI) were calculated in two-year intervals. We also compared the number of office visits by specialty across time. Poisson regression and generalized estimating equations models were used to assess longitudinal change in comorbidity prevalence and severity, respectively.

Results: Comorbidities were more likely to be diagnosed after prostate cancer. The prevalence rate of COPD in the cancer group was significantly lower than non-cancer group before cancer diagnosis (prevalence ratio [PR]=0.94, 95% confidence interval [95%CI]:0.89-0.99, p=0.05). However, COPD was marginally more prevalent among cancer group after diagnosis (PR=1.08, 95%CI: 1.04-1.13, p<0.001). Similar trends were observed in other comorbidities. In addition, the overall comorbidity score of cancer group increased significantly more than control group across time. Survivors made more visits to both prostate cancer specialists and primary care physicians after cancer diagnosis, especially among black survivors.

Conclusions: Survivors visit health care providers more frequently after cancer diagnosis, which may lead to discovery of previously underdiagnosed chronic conditions.

Keywords: prostate cancer, comorbidities, SEER-Medicare, prevalence, outpatient visit

4.2 Introduction

Cancer is a prevalent disease affecting the elderly population in the United States, with approximately two-thirds of new malignancies diagnosed among patients at least 65 years of age (73). It is estimated that more than 10 million Americans currently live with a history of cancer diagnosis, and the number of survivors is expected to continue to grow with more early detection, effective treatments, and the aging of the population (73). From 2000 to 2050, the absolute number of patients aged 65 and older diagnosed with cancer is expected to double (41). Since the majority of elderly cancer survivors eventually die from

causes other than cancer (73), health problems related to non-cancer conditions also have become very important for this population.

Comorbidities (i.e., additional coexisting health conditions) are commonly observed in cancer survivors, especially among the elderly population (1, 6, 46, 47). Previous studies have found that cancer survivors are at a higher risk for other comorbidities than the non-cancer population (6, 46, 47). These increased risks may be the result of the side effects or late effects of cancer treatment, genetic predisposition, diet, or common lifestyle factors. A population-based study found that 69% of cancer patients aged 40 to 84 have at least one chronic condition other than cancer (1). The presence of comorbidities may not only complicate treatment management, but may negatively affect prognosis and post-treatment health-related quality of life (3-6). Previous studies also reported that prostate cancer patients are more likely to die from causes other than cancer (7, 32), demonstrating the potential influence of comorbidities and other factors on mortality. However, these previous studies primarily focused on the effect of comorbidities at cancer diagnosis on patients' cancer-related outcomes (3-6, 32). The longitudinal association between cancer and comorbidities has yet to be fully investigated.

A cancer diagnosis has the potential to have mixed effects on the diagnosis or management of other comorbidities. On one hand, cancer diagnosis may represent "a teachable moment" for risk factor reduction because patients tend to be more aware of their other health problems after cancer diagnosis (48-50). To prevent cancer recurrence and to increase the likelihood of survival, cancer survivors often attempt to quit smoking, to eat healthier, and to engage in regular exercise (48-56). Previous studies have found a positive effect of these lifestyle changes on health-related outcomes (51, 57, 58). In addition, patients may receive more medical services after diagnosis because cancer follow-up may provide regular contact with the health care system, increasing the chance of receiving

appropriate medical care (35). Health care providers also may identify some chronic conditions that were underdiagnosed prior to the cancer diagnosis. Therefore, it is possible that comorbidities would be better controlled after cancer diagnosis.

On the other hand, comorbidities may worsen after cancer diagnosis. Long-term and late effects of cancer treatments are commonly observed among cancer survivors. For example, chemotherapy and radiation therapy may have negative effects on erectile function, cardiovascular disease, or mental health (22, 23, 59). In addition, cancer patients may not think that the continued management of other comorbidities is as important after their cancer diagnosis. Survivors may receive less care for comorbidities because their care may consist primarily of specialty care provided by specialist physicians, with little attention to primary care needs (36). Insufficient primary care may lead to development of other comorbidities or the worsening of existing comorbidities.

The purpose of this study is to investigate whether diagnosis of prostate cancer creates an opportunity to detect other comorbid conditions. We selected prostate cancer survivors as our study sample for several reasons. First, prostate cancer is the most prevalent cancer in men, and patients with a history of prostate cancer comprise approximately one-fifth of total cancer survivors (second only to breast cancer survivors) (73). Second, prostate cancer is predominantly survivable and the majority of its survivors are aged 65 and older (73). The majority of elderly prostate cancer survivors die from causes other than cancer (7, 32), implicating the importance of comorbidities for this population. Finally, to our knowledge there has been no published study examining the prevalence and severity of comorbidities longitudinally among prostate cancer patients.

We first estimated the prevalence of chronic obstructive pulmonary disease (COPD), depression, diabetes, hypercholesterolemia, and hypertension before and after the prostate cancer diagnosis. These comorbid conditions were selected because they are both common

and associated with non-cancer mortality but often are underdiagnosed among the elderly population (84-90). These occult diseases may remain undetected for many years, and some patients are first identified at an advanced stage during emergency room visit or hospitalization (90). Early detection of these comorbidities may lead to better disease control by appropriate medical treatments. In addition, we used the Deyo modification of the Charlson Comorbidity Index (CCI) (38, 39) and National Cancer Institute Combined Index (NCICI) (40) to assess the severity of comorbidities longitudinally. Since a cancer diagnosis may create a chance for survivors to have more contact with the health care system (35), we expected to observe increases in the prevalence and severity of comorbidities after cancer. To indentify the main health care provider for prostate cancer survivors, we examined the number of office visits by physician specialty. After cancer diagnosis, we expected the number of office visits to prostate cancer specialists and primary care physicians (PCPs) would increase and decrease, respectively. We further examined whether the new chronic conditions (i.e., those conditions diagnosed after the cancer diagnosis) tend to be identified by prostate cancer specialists or by PCPs. We hypothesized that new chronic conditions are more likely to be diagnosed by prostate cancer specialists, who tend to be the main providers of care to patients after a cancer diagnosis. Finally, we conducted subgroup analyses to examine whether the findings are different by race. Previous studies reported that black patients generally have more comorbidities than white patients (32, 91, 92), but that comorbid conditions are more likely to be underdiagnosed among black patients (67). Thus, we expected the changes in prevalence and severity of comorbidities to be greater in black patients.

4.3 Methods

Data Sources

This study used the data from the Surveillance, Epidemiology, and End Results registry (SEER)-Medicare Program. The SEER-Medicare data are population-based data that combine SEER cancer registry information with Medicare enrollment and claims files (70, 72). The SEER Program of the National Cancer Institute (NCI) is an authoritative program collecting information on cancer incidence and survival statistics, serving as one of very few comprehensive sources of population-based cancer information in the United States (68). The SEER Program is considered the standard for quality among cancer registries around the world. It routinely collects data on patient demographics, primary tumor site, stage at diagnosis, primary course of treatment, and cause of death. The SEER Program also collects socioeconomic status (SES) information including median household economic and educational status (69, 70). These SES variables are aggregate measures from the US Census Bureau that reflect the characteristics of the census tracts and zip codes in which patients resided during the year of their first diagnosis (69). We used the data from the SEER-17 registries, which cover Arizona native Americans, Alaska Natives, nine states (California, Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah), and seven regions (Atlanta, Detroit, rural Georgia, Los Angeles, San Francisco, San Jose, and Seattle).

Medicare is the primary health insurer for 97% of the US population aged 65 years and older (70). All Medicare beneficiaries receive Part A benefits, which are generally paid for by payroll taxes collected from workers. Approximately 99% of Medicare beneficiaries pay no premium for Part A services because they have at least 40 quarters of Medicare-covered employment (71). Medicare Part A benefits cover inpatient care in hospitals, including critical access hospitals, and skilled nursing facilities (but not custodial or long-term care), hospice care and some home health care services. Among Medicare Part A beneficiaries, 95% of them also pays a monthly premium for the Part B benefits (70).

Medicare beneficiaries pay premiums for Part B benefits which cover physician services, outpatient care, durable medical equipment, some of the services of physical and occupational therapists, and home health in some cases. A beneficiary's disease diagnoses, treatments, and services received are available in the Medicare claims. However, data are missing for health maintenance organization (HMO) enrollees, services not covered by Medicare (i.e., outpatient prescription drugs and long term care), and services provided by Veterans Affairs or Medicaid, or by Medicare supplement programs (i.e., Medigap policies) (70).

Cohort Selection

Patients diagnosed with localized or regional prostate cancer (i.e., Stage I, II, and III) in 2000 were included in this study. These patients are not likely to die from prostate cancer because their five-year relative overall survival rate is approximately 100% as compared with the non-cancer population (73). Patients diagnosed with distant prostate cancer were excluded because their five-year relative survival rate is only 32% (73) and the presence of some comorbidities (e.g., cardiovascular diseases) may be associated with hormonal treatment for distant prostate cancer (59). A patient's claims were examined for up to ten years, beginning from January 1, 1998 through December 31, 2007. To be eligible for inclusion in the study, patients must have been continuously enrolled in Medicare Part A and Part B during the study period. To observe the presence of comorbidities for at least two years before cancer diagnosis, we included only patients who were diagnosed with prostate cancer at age 67 or older as of January 1, 2000, thus allowing for two years of observation prior to diagnosis following their enrollment in Medicare at age 65. Medicare beneficiaries who are eligible for Medicare because of disability or the presence of end-stage renal disease before age 65 were excluded from the analyses. HMO enrollees also were excluded, as services provided by HMOs are not included in the SEER–Medicare data. Other

exclusion criteria included: prior cancer history, diagnosis with a second cancer within six months, noninvasive tumors (i.e., carcinoma in situ), unstaged prostate cancer, diagnosis after age 84, diagnosis at death or via autopsy, and missing income and education information. Finally, patients of races other than black and white were excluded from the analyses because of the small sample size and unreliable classification of the race groups (69).

We also included a comparison group from the 5-percent random sample of individuals without cancer in the SEER-Medicare data. Inclusion criteria for the comparison group were: male gender; qualified for Medicare benefit because of age; age between 67 and 84 years as of January 1, 2000; continuously enrolled in Medicare Part A and Part B and never enrolled in the HMO program during the study period; and living in areas covered by the SEER-17 registry.

Variable Definitions

Covariates

A cancer patient's age, race, and date of death are available from both SEER and Medicare data. Demographic information from these two sources is highly consistent.(69) Since the demographic data for the comparison group are available only in the Medicare enrollment file, we employed Medicare's Enrollment Database as our primary source to identify age, race, and vital status for both groups. We controlled for median household income and percentage of residents with less than a high school degree at zip code level from the 2000 Census for both groups in our analyses.

The type of care provider was classified based on the specialty information in the Medicare Carrier Claims (36). Prostate cancer specialists were defined as sub-specialists in urology (code 34), hematology oncology (code 83), medical oncology (code 90), surgical

oncology (code 91), or radiation oncology (code 92). Primary care physicians were defined as physicians in general practice (code 01), family practice (code 08), internal medicine (code 11), geriatric medicine (code 38), or multi-specialty group practices (code 70).

Primary cancer treatment

The type of primary treatment for prostate cancer was identified from the SEER data and Medicare claims within six months of cancer diagnosis. Previous studies suggested that surgery and radiation therapy (XRT) are consistently reported in SEER and Medicare claims data (>90% agreement) (93, 94). Surgery was defined as procedures performed with curative intent or in anticipation of a subsequent curative procedure (27). We used: (1) the SEER indicator for whether a cancer-directed surgery was performed; and (2) International Classification of Diseases, 9th Revision, (ICD-9) procedure codes 60.5 and 60.6; Healthcare Common Procedure Coding System (HCPCS) codes 55810, 55812, 55815, 55840, 55842, 55845, and 55866 from Medicare claims to identify radical prostatectomy and procedures performed on regional lymph nodes. XRT is defined as external beam therapy, brachytherapy, or therapeutic isotope radiation therapy as listed in the SEER data (63). We used: (1) the SEER indicator for whether a cancer-directed XRT was performed; and (2) ICD-9 procedure codes 92.2x, V58.0, V66.1, V67.1, HCPCS codes 77301, 77400–77499, and 77750-77799 from Medicare claims to identify XRT. Men who receive both surgery and XRT were be classified as having surgery because some patients may receive XRT after an incomplete or unsuccessful surgery (27, 63).

Comorbidities

We measured comorbidity prevalence within the prostate cancer and non-cancer groups using ICD-9 diagnosis codes from the Medicare inpatient, outpatient, and physician claims. The codes to identify COPD, diabetes, hypertension, depression, and hypercholesterolemia are listed in Table 4. In addition, we used the CCI and the NCICI to

assess the severity of comorbidities at different time points. The CCI is a commonly used measure of comorbidity in epidemiologic and outcomes research (27, 38, 39, 63, 74). Researchers can accumulate the weighted comorbidities to establish a single index and to compare the severity of comorbidities across patients. A higher comorbidity score represents more severe health problems. The NCICI was developed specifically for the use with SEER-Medicare data to adjust for the risk of dying from causes other than cancer (40). The NCICI adapts the comorbid conditions from CCI but weights them differently and the comorbidity weights vary by cancer site. Compared with the CCI, the NCICI performed better in predicting non-cancer mortality among cancer survivors (40). The comorbidities and their ICD-9 codes and weights for CCI and NCICI are listed in Table 4.

Statistical Analyses

The cumulative comorbidity prevalence rates were measured as of December 31st in 1999, 2001, 2003, 2005, and 2007 (Figure 2). At each time point, we calculated the proportion of patients alive with a disease history of COPD, diabetes, depression, hypercholesterolemia, or hypertension. To confirm a comorbid condition, we required a patient to have at least one inpatient or two outpatient visits with the relevant disease diagnosis codes within 12 months. Chi-squared tests were conducted to compare the crude prevalence rates between cancer and non-cancer groups (78). We also conducted Poisson regressions with robust error variances to compare the prevalence ratios between cancer and non-cancer groups adjusting for age, race, registry site, income, and education (79).

We measured the changes over time in individual patient's overall comorbidity severity by CCI (38, 39). At each time point, crude comorbidity scores for both cancer and non-cancer groups were compared using Student's t tests (78). To account for repeated measures, we used a generalized estimating equations (GEE) model (80, 81). The effects of cancer on CCI at various time points were of primary interest. The sum of coefficients of

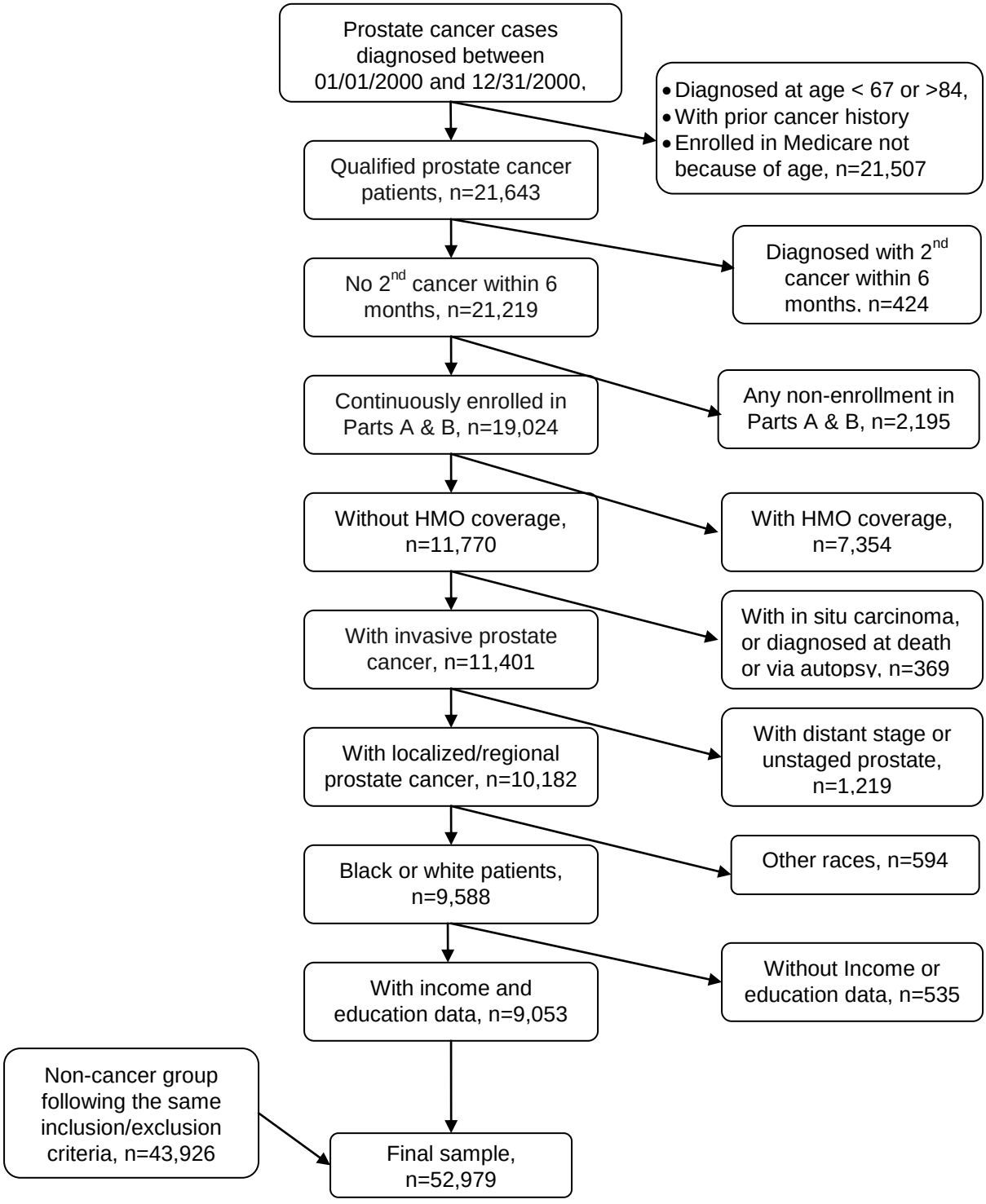
cancer indicator and its interaction term with time was examined by Wald test at each time point (80, 81). Other factors, including age, race, registry site, education, and income, which might be associated with comorbidities and prostate cancer, were controlled for in the model. For prostate cancer patients, we also used the NCICI to measure their comorbidity severity. We conducted subgroup analysis by race. In addition, we examined the number of physician visits over time. We further examined the relationship between types of provider and newly diagnosed comorbidities. Specifically, we focused on newly diagnosed diabetes and hypertension, which are prevalent conditions among the elderly.

4.4 Results

Study Sample

A total of 43,150 prostate cancer cases were initially identified in 2000 from the SEER-Medicare data (Figure 4). Employing the inclusion and exclusion criteria described earlier, 9,053 prostate cancer patients and 43,926 individuals without cancer comprised our study sample.

Figure 4. Procedures to generate the study sample of prostate cancer patients



HMO: health maintenance organization

Table 6 presents the baseline characteristics of the study sample. Compared with individuals without cancer, prostate cancer survivors were generally younger and had longer follow-up ($p<0.001$). Individuals with prostate cancer tend to live in areas with higher median household income and lower proportions of residents with less than a high school degree. Compared with individuals without cancer, cancer survivors are more likely to be black (9.0% vs. 5.6%, $p<0.001$). Among white men, cancer survivors were more likely to be younger and to have longer follow-up ($p<0.001$). Compared with the white comparison group, members of the white cancer group were less likely to live in areas in which fewer people have a high school degree ($p<0.001$), and with higher median household income ($p<0.001$). Similar findings were observed among black patients. However, except for the length of follow-up ($p<0.01$) and registry site ($p<0.001$), none of the differences in baseline characteristics between the black cancer and non-cancer groups was statistically significant. At the time of cancer diagnosis, black survivors were less likely to be married than white survivors (74.0% vs. 82.5%, $p<0.001$) (Table 7). In addition, prostate cancer grades were not significantly different between black and white survivors. Compared with white survivors, black survivors were less likely to receive surgery or XRT as their primary treatment ($p<0.001$).

Table 6. Comparison of baseline characteristics between cancer & non-cancer groups

Sociodemographic Characteristics	Both			Black			White		
	Cancer (n=9,053)	Non-cancer (n=43,926)	p value	Cancer (n=811)	Non-cancer (n=2,466)	p value	Cancer (n=8,242)	Non-cancer (n=41,460)	p value
Age (years) on 01/01/2000, %									
67-69	19.1	19.2	<0.001	22.1	20.4	0.52	18.8	19.1	<0.001
70-74	37.5	33.2		35.9	35.4		37.7	33.1	
75-79	29.6	29.6		27.9	28.1		29.8	29.7	
80-84	13.8	18.0		14.2	16.1		13.8	18.1	
Mean age, year	74.0	74.4	<0.001	73.7	74.1	0.08	74.0	74.5	<0.001
Mean follow-up time, month	105.7	102.8	<0.001	100.6	97.3	<0.01	106.2	103.1	<0.001
Alive as of 12/31/2007, %	65.7	64.1	<0.01	56.0	54.6	0.49	66.6	64.7	<0.001
Registry site, %									
San Francisco	3.0	2.9	<0.001	2.7	3.3	<0.001	3.1	2.9	<0.001
Connecticut	7.6	6.9		3.2	3.6		8.0	7.1	
Detroit	11.7	8.2		33.1	20.4		9.7	7.5	
Hawaii	0.4	0.4		0.1	0.1		0.5	0.5	
Iowa	8.7	8.3		0.9	0.9		9.5	8.7	
New Mexico	2.1	2.6		0.3	0.7		2.3	2.7	
Seattle	5.9	5.3		1.1	1.3		6.4	5.6	
Utah	3.7	3.1		0.4	0.3		4.0	3.2	
Atlanta	3.1	3.1		6.7	7.7		2.7	2.8	
San Jose	1.9	2.1		0.9	0.6		2.0	2.2	
Los Angeles	6.0	6.4		8.0	8.6		5.8	6.3	
Rural Georgia	0.2	0.3		0.5	1.1		0.2	0.2	
Greater California	14.7	17.3		4.1	6.5		15.7	17.9	
Kentucky	5.8	9.0		2.8	5.8		6.1	9.2	
Louisiana	7.0	7.0		17.1	19.6		6.0	6.3	
New Jersey	18.3	17.2		18.3	19.4		18.3	17.1	
Percent persons age 25+ of same race with less than a high school education									
Mean, %	16.2	16.5	0.02	28.2	28.9	0.17	15.0	15.8	<0.001
Annual household income									
Mean, $	51,281	49,140	<0.001	35,544	35,465	0.89	52,829	49,954	<0.001

Table 7. Baseline characteristics of black and white cancer survivors

	Black	White	p-value
Marital status at cancer diagnosis (%)			
Ever married	74.0	82.5	<0.001
Never married	13.7	5.2	
Unknown or missing	12.3	12.3	
Prostate cancer grade (%)			
1 (well differentiated)	3.2	4.8	0.053
2 (Moderately differentiated)	68.4	69.0	
3 (Poorly differentiated)	22.8	22.0	
4 (Undifferentiated)	0.7	0.3	
Unknown or missing	4.8	3.9	
Primary cancer treatment (%)			
Radiation therapy	43.7	51.2	<0.001
Surgery	24.0	25.8	
Watchful waiting	32.3	23.0	

Comorbidity Prevalence

As expected, more comorbid conditions were diagnosed among cancer survivors than among individuals without cancer after 2000 (i.e., the year when prostate cancer was diagnosed among survivors) (Table 8). On December 31st, 1999, the prevalence rate of COPD was significantly lower in cancer group than in non-cancer group. After 2000, the COPD prevalence rate became significantly higher among cancer group than among non-cancer group. A similar time trend of prevalence rate was observed in diabetes. Compared with individuals without cancer, prostate cancer patients were less likely to be diagnosed with diabetes before cancer (15.3% vs. 17.6%, $p<0.001$). However, the prevalence rates of diabetes were significantly higher in the cancer group after 2000. Although hypercholesterolemia and hypertension were always more prevalent among cancer patients than among individuals without cancer, the differences in prevalence increased over time.

Finally, we conducted subgroup analyses by race. For both black and white patients, the prevalence rate of each condition increased more in the cancer group than in non-cancer group after 2000.

Table 8. Unadjusted comorbidity prevalence rate (%)

			Prevalence time point				
			Pre-diagnosis	Post-diagnosis			
Race	Condition	Group	12/31/99	12/31/01	12/31/03	12/31/05	12/31/07
Both	Hypertension	Cancer	51.8†	69.1¶	76.9¶	83.4¶	85.3¶
		Non-cancer	50.4	63.3	71.4	77.1	79.9
	Hypercholesterolemia	Cancer	18.9‡	29.9¶	38.9¶	48.4¶	52.7¶
		Non-cancer	17.5	27.2	35.2	43.2	47.7
	COPD	Cancer	16.4¶	24.8‡	28.8‡	32.9¶	33.4¶
		Non-cancer	17.9	23.4	27.1	29.9	30.8
	Diabetes	Cancer	15.3¶	20.9	24.7	33.4¶	34.5¶
		Non-cancer	17.6	21.2	24.1	27.6	29.5
	Depression	Cancer	2.2¶	4.7	6.6	8.2	8.5
		Non-cancer	3.0	4.9	6.7	7.9	8.5
Black	Hypertension	Cancer	61.0†	79.2¶	84.8¶	88.8¶	90.7¶
		Non-cancer	56.4	69.4	75.6	80.4	81.4
	Hypercholesterolemia	Cancer	13.3‡	22.5‡	31.0‡	40.4‡	44.1†
		Non-cancer	9.5	17.6	24.9	32.7	37.3
	COPD	Cancer	18.6	28.8‡	34.4¶	38.6¶	40.7¶
		Non-cancer	17.8	23.7	26.5	29.4	29.8
	Diabetes	Cancer	21.8	30.2	35.5	45.0¶	48.0¶
		Non-cancer	24.4	28.8	32.2	36.6	39.1
	Depression	Cancer	1.7	3.6	5.7	5.8	6.2
		Non-cancer	2.3	4.3	4.8	5.3	6.2
White	Hypertension	Cancer	50.9	68.1¶	76.2¶	83.0¶	84.9¶
		Non-cancer	50.0	63.0	71.2	77.0	79.8
	Hypercholesterolemia	Cancer	19.4‡	30.6¶	39.6¶	49.1¶	53.4¶
		Non-cancer	17.9	27.8	35.8	43.8	48.2
	COPD	Cancer	16.2¶	24.4†	28.3	32.5¶	32.8‡
		Non-cancer	17.9	23.4	27.2	29.9	30.9
	Diabetes	Cancer	14.6¶	20.0	23.7	32.4¶	33.4¶
		Non-cancer	17.2	20.8	23.7	27.2	29.0
	Depression	Cancer	2.3¶	4.8	6.7	8.4	8.7
		Non-cancer	3.1	5.0	6.8	8.0	8.6

COPD: Chronic pulmonary disease

Chi-squared tests were conducted between cancer and non-cancer groups: Significance denoted as: †: $p<0.05$; ‡: $p<0.01$; ¶: $p<0.001$

Consistent with the previous analyses, Poisson regression models indicated that the prevalence rates of COPD, diabetes, and depression were lower among cancer survivors than among individuals without cancer before 2000 (Table 9). However, COPD and diabetes were more prevalent among the cancer group after 2000. Individuals with diagnosis of cancer were more likely to be diagnosed with hypercholesterolemia or hypertension at each time point and the magnitude of the prevalence ratios (PR) was higher after 2000, suggesting that some of the previously underdiagnosed conditions might be found after prostate cancer diagnosis. The racial subgroup analysis suggested that the magnitude of increase in PR was larger among black men.

Table 9. Adjusted disease prevalence ratios in cancer vs. non-cancer groups

Race	Condition	Prevalence time point				
		12/31/99	12/31/01	12/31/03	12/31/05	12/31/07
Both	Hypertension	1.03 † (1.00 – 1.05)	1.09 ¶ (1.07 – 1.11)	1.07 ¶ (1.06 – 1.09)	1.08 ¶ (1.07 – 1.09)	1.07 ¶ (1.05 – 1.08)
	Hypercholesterolemia	1.07 ‡ (1.02 – 1.12)	1.09 ¶ (1.05 – 1.13)	1.09 ¶ (1.06 – 1.13)	1.11 ¶ (1.08 – 1.14)	1.09 ¶ (1.07 – 1.12)
	COPD	0.94 † (0.89 – 0.99)	1.08 ¶ (1.04 – 1.13)	1.08 ¶ (1.03 – 1.12)	1.11 ¶ (1.07 – 1.16)	1.10 ¶ (1.04 – 1.14)
	Diabetes	0.86 ¶ (0.81 – 0.90)	0.97 (0.93 – 1.01)	1.01 (0.96 – 1.05)	1.19 ¶ (1.15 – 1.23)	1.15 ¶ (1.11 – 1.20)
	Depression	0.77 ‡ (0.67 – 0.90)	1.00 (0.90 – 1.11)	1.04 (0.95 – 1.14)	1.08 (0.99 – 1.17)	1.03 (0.94 – 1.13)
Black	Hypertension	1.07 † (1.00 – 1.14)	1.12 ¶ (1.07 – 1.18)	1.11 ¶ (1.07 – 1.16)	1.11 ¶ (1.06 – 1.15)	1.11 ¶ (1.07 – 1.16)
	Hypercholesterolemia	1.39 ‡ (1.12 – 1.73)	1.27 ‡ (1.08 – 1.50)	1.24 ‡ (1.08 – 1.43)	1.22 ‡ (1.08 – 1.38)	1.18 † (1.04 – 1.33)
	COPD	1.04 (0.88 – 1.23)	1.20 ‡ (1.05 – 1.37)	1.27 ¶ (1.12 – 1.45)	1.27 ¶ (1.12 – 1.45)	1.33 ¶ (1.16 – 1.53)
	Diabetes	0.86 † (0.74 – 1.00)	1.01 (0.89 – 1.15)	1.07 (0.94 – 1.21)	1.18 ‡ (1.05 – 1.32)	1.19 ‡ (1.06 – 1.33)
	Depression	0.79 (0.44 – 1.43)	0.90 (0.59 – 1.39)	1.30 (0.89 – 1.89)	1.24 (0.84 – 1.85)	1.04 (0.68 – 1.58)
White	Hypertension	1.02 (1.00 – 1.04)	1.08 ¶ (1.07 – 1.10)	1.07 ¶ (1.06 – 1.09)	1.08 ¶ (1.07 – 1.09)	1.06 ¶ (1.05 – 1.08)
	Hypercholesterolemia	1.06 † (1.01 – 1.11)	1.08 ¶ (1.04 – 1.12)	1.08 ¶ (1.05 – 1.12)	1.10 ¶ (1.07 – 1.13)	1.09 ¶ (1.06 – 1.12)
	COPD	0.93 ‡ (0.88 – 0.98)	1.07 ‡ (1.03 – 1.12)	1.06 ‡ (1.02 – 1.10)	1.10 ¶ (1.06 – 1.15)	1.08 ¶ (1.03 – 1.12)
	Diabetes	0.85 ¶ (0.81 – 0.90)	0.96 (0.92 – 1.01)	1.00 (0.96 – 1.05)	1.19 ¶ (1.15 – 1.24)	1.15 ¶ (1.10 – 1.20)
	Depression	0.77 ‡ (0.66 – 0.90)	1.00 (0.90 – 1.12)	1.03 (0.93 – 1.13)	1.07 (0.98 – 1.17)	1.03 (0.94 – 1.13)

95% confidence intervals are listed in parentheses; Significance denoted as: †: p<0.05; ‡: p<0.01; ¶: p<0.001
COPD: Chronic pulmonary disease
Patients without cancer is the reference group
A patient's age, race, registry site, education, and income are controlled in Poisson regressions

Comorbidity Severity

We compared the unadjusted severity of comorbidities between cancer and individuals without cancer by CCI Index (Table 10). The cancer group tended to be healthier than the non-cancer group before cancer diagnosis (CCI score 0.76 vs. 0.93, p<0.001). However, after survivors were diagnosed with prostate cancer in 2000, the difference

between groups diminished by the first time point (i.e., 12/31/01), and disappeared by the second time point (i.e., 12/31/03). At the last two time points, the CCI scores were significantly higher among cancer group than among non-cancer group. Similar findings were observed in subgroup analysis by race. In black men, the CCI score before cancer was significantly lower among cancer patients as compared with individuals without cancer (1.01 vs. 1.17, $p<0.05$). Although there were no significant differences at the first two time points after diagnosis, black cancer patients had significantly higher CCI scores at the 3rd and 4th time points (2.43 vs. 2.15 on 12/31/05 and 2.73 vs. 2.38 on 12/31/07, respectively). In white men, the CCI scores of cancer patients were significantly lower than of individuals without cancer at the first three time points (0.73 vs. 0.91, $p<0.001$; 1.20 vs. 1.27, $p<0.001$; 1.50 vs. 1.56, $p<0.05$). However, white cancer group had significantly higher CCI scores than white non-cancer group at the last two time points (1.91 vs. 1.80, $p<0.001$; 2.04 vs. 1.98, $p<0.05$). We also used the NCICI to compare racial differences in comorbidity severity for prostate cancer patients. The NCICI scores increased with time in both black and white cancer survivors. However, black patients consistently had significantly higher NCICI scores than white patients at each time point, and the magnitude of difference increased over time.

Table 10. Comparison of comorbidity severity across time

			Time point				
			Pre-diagnosis	Post-diagnosis			
Index	Race	Group	12/31/99	12/31/01	12/31/03	12/31/05	12/31/07
CCI	Both	Cancer	0.76 ¶ (0.73-0.78)	1.24 † (1.21-1.27)	1.54 (1.51-1.58)	1.95 ¶ (1.90-2.00)	2.10 ‡ (2.04-2.15)
		Non-cancer	0.93 (0.92-0.94)	1.29 (1.27-1.30)	1.57 (1.55-1.59)	1.81 (1.79-1.84)	2.00 (1.98-2.03)
	Black	Cancer	1.01 † (0.91-1.11)	1.63 (1.50-1.77)	2.01 (1.85-2.17)	2.43 † (2.24-2.62)	2.73 ‡ (2.51-2.95)
		Non-cancer	1.17 (1.10-1.23)	1.59 (1.51-1.67)	1.84 (1.75-1.93)	2.15 (2.05-2.26)	2.38 (2.25-2.50)
	White	Cancer	0.73 ¶ (0.71-0.76)	1.20 ¶ (1.17-1.23)	1.50 † (1.46-1.54)	1.91 ¶ (1.86-1.96)	2.04 † (1.99-2.10)
		Non-cancer	0.91 (0.90-0.93)	1.27 (1.26-1.29)	1.56 (1.54-1.57)	1.80 (1.78-1.82)	1.98 (1.96-2.01)
NCICI	Black	Cancer	0.43 ¶ (0.39-0.48)	0.69 ¶ (0.63-0.75)	0.84 ¶ (0.77-0.91)	1.01 ¶ (0.92-1.09)	1.12 ¶ (1.02-1.21)
	White	Cancer	0.31 (0.30-0.32)	0.51 (0.49-0.52)	0.63 (0.61-0.65)	0.80 (0.78-0.82)	0.84 (0.81-0.86)

95% Confidence intervals are listed in parentheses; Significance denoted as: †: p<0.05; ‡: p<0.01; ¶: p<0.001
NCICI: National Cancer Institute Combined Index; CCI: Charlson Comorbidity Index
Standard errors are listed in parentheses

The results from the GEE models are listed in Table 11. Variables with positive coefficients are associated with higher comorbidity severity. In general, comorbidity severity increased over time because all four time variables are strong predictors for higher CCI score. In addition, elder age, living in area with lower median household income, and living in area with higher proportion of persons without high school degree are associated with a higher CCI score.

A series of Wald tests was conducted to assess the time effect on difference in CCI score between men with and without cancer and between black and white men (Table 12). At baseline, the CCI score of cancer patients was significantly lower than the score of individuals without cancer (-0.158, $p<0.001$). However, this difference became smaller after 2000 and was no longer statistically significant at the last two time points. In addition, the CCI score was not different between black and white men at baseline (0.042, $p=0.24$), but it increased more among black men over time, signifying an increase in diagnosed comorbidity. Black men had significantly higher CCI score than white men between Time 1 and Time 4.

Another GEE analysis was conducted for prostate cancer survivors only to investigate the factors associated with comorbidity severity as measured by NCICI (Table 11). The significantly positive time indicators suggest that severity of comorbidity increased over time. Elder age was also predictors for higher NCICI score. Higher median household income and receiving XRT were associated with lower NCICI score. The NCICI score was not significantly different between black and white cancer survivors before cancer diagnosis after adjusting for other factors (0.011, $p=0.70$). However, the results from Wald tests indicate that black survivors had significantly higher NCICI scores after cancer diagnosis than white survivors and the magnitude of the difference increased over time (Table 12).

Table 11. Results of generalized estimating equations (GEE) analysis of comorbidity index score

Variables	All subjects	Cancer survivors
Outcome	CCI score	NCICI score
Cancer (non-cancer is the reference)	-0.158 (0.020) ¶	
Black race (white race is the reference)	0.042 (0.036)	0.011 (0.029)
Demographic information		
Age (as of 01/01/00)	0.061 (0.001) ¶	0.027 (0.002) ¶
Median annual household income in $1,000	-0.003 (0.000) ¶	-0.002 (0.000) ¶
Percent persons with a high school diploma	0.005 (0.001) ¶	0.002 (0.001) †
Time point (12/31/99 is the reference)		
Time 1 (12/31/01)	0.434 (0.007) ¶	0.212 (0.006) ¶
Time 2 (12/31/03)	0.805 (0.007) ¶	0.361 (0.007) ¶
Time 3 (12/31/05)	1.148 (0.007) ¶	0.564 (0.007) ¶
Time 4 (12/31/07)	1.444 (0.007) ¶	0.651 (0.007) ¶
Interaction terms		
Black * Case	0.046 (0.064)	
Cancer * Time 1	0.063 (0.015) ¶	
Cancer * Time 2	0.056 (0.016) ¶	
Cancer * Time 3	0.190 (0.017) ¶	
Cancer * Time 4	0.132 (0.017) ¶	
Black * Time 1	0.116 (0.025) ¶	0.064 (0.022) ‡
Black * Time 2	0.164 (0.026) ¶	0.114 (0.023) ¶
Black * Time 3	0.234 (0.027) ¶	0.112 (0.024) ¶
Black * Time 4	0.338 (0.029) ¶	0.186 (0.026) ¶
Marital status (ever married is the reference)		
Never married		-0.000 (0.029)
Unknown		-0.026 (0.023)
Cancer grade (well differentiated is the reference)		
Moderately differentiated		-0.161 (0.032) ¶
Poorly differentiated		-0.166 (0.034) ¶
Undifferentiated		-0.154 (0.116)
Unknown or missing		-0.148 (0.046) ‡
Primary cancer treatment (watchful waiting is the reference)		
Surgery		-0.031 (0.021)
Radiation therapy		-0.046 (0.018) †
Constant	-3.315 (0.112) ¶	-1.328 (0.135) ¶
Number of observations (n)	218,472	38,209

Standard error is listed in parentheses; Significance denoted as: †: p<0.05; ‡: p<0.01; ¶: p<0.001
CCI: Charlson Comorbidity Index; NCICI: National Cancer Institute Combined Index
A survivor's registry site is also controlled in the model (results not shown)

Table 12. Time trend of group difference in comorbidity severity

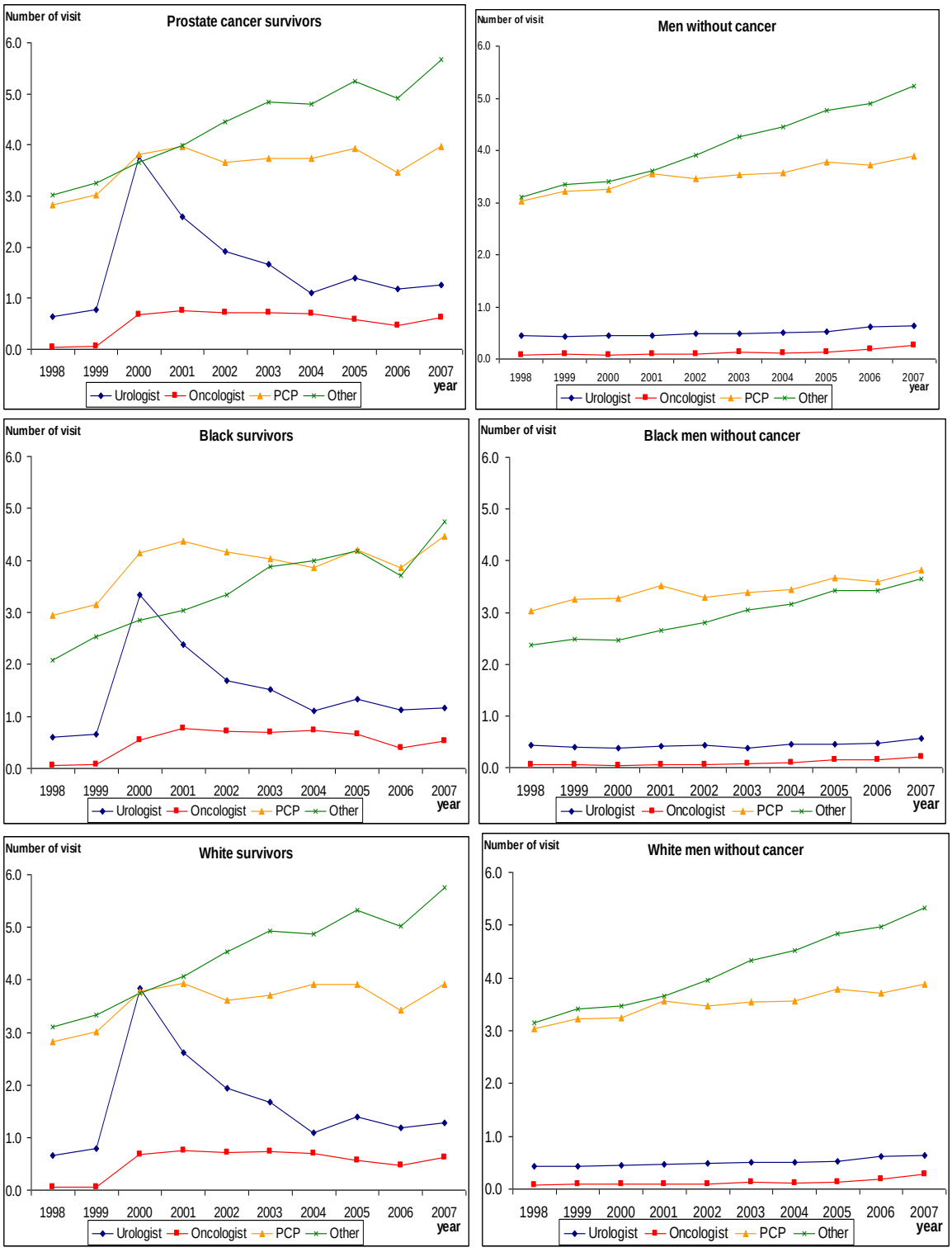
Outcomes	CCI score		NCICI score
Comparison	Cancer survivors vs. individuals without cancer	Black men vs. white men	Black survivors vs. white survivors
Time point			
0 (12/31/99)	-0.158 ¶	0.042	0.011
1 (12/31/01)*	-0.095 ¶	0.158 ¶	0.075 †
2 (12/31/03)*	-0.102 ¶	0.206 ¶	0.125 ¶
3 (12/31/05)*	0.032	0.276 ¶	0.123 ¶
4 (12/31/07)*	-0.026	0.380 ¶	0.197 ¶

*Difference between groups is the sum of baseline difference and time interaction from the corresponding GEE model. Wald test is conducted to evaluate whether there was group difference at each time point.
Significance denoted as: †: p<0.05; ‡: p<0.01; ¶: p<0.001
CCI: Charlson Comorbidity Index; NCICI: National Cancer Institute Combined Index

Physician Visits

Before 2000, the total number of office visits by cancer patients was not different from the number by the individuals without cancer (Figure 5). Cancer patients had significantly more total office visits than individuals without cancer right after cancer diagnosis, but the difference in total office visits diminished in later time periods. Before cancer diagnosis in 2000, cancer survivors had more visits to prostate cancer specialists but fewer visits to PCPs than the individuals without cancer. As we expected, survivors' made more office visits to prostate cancer specialists after cancer diagnosis. However, their visits to PCPs and other specialists also increased after cancer diagnosis. The average number of visit to urologists increased substantially from 0.8 in 1999 to 3.8 in 2000. Although the number of visits to prostate cancer specialists decreased after 2000, survivors still made more visits to their prostate cancer specialists than individuals without cancer. In addition, survivors made more visits to their PCPs after their cancer diagnosis (from 3.0 in 1999 to 3.8 in 2000), especially among black survivors (from 3.2 in 1999 to 4.1 in 2000). Due to the data error in physician claims, the average number of office visit by survivors might be underestimated in 2004.

Figure 5. Number of annual office visits by type of specialty[1]



PCP: primary care physician

[1]Eight weeks after the dissertation was defended on 12/04/2009, the SEER-Medicare Program Reported an error in 2004 physician claims data.http://healthservices.cancer.gov/seermedicare/seermed_2004_data_letter.pdf Therefore, the number of office visit might be underestimated in 2004.

We also examined whether diabetes and hypertension newly diagnosed after cancer were more likely to be identified by prostate cancer specialists, rather than by PCPs. The prevalence rate of diabetes in cancer survivors changes from 15.3% on 12/31/1999 to 20.9% on 12/31/2001. The provider specialty was unknown in 16.1% of the new diabetes cases diagnosed between 2000 and 2001. Approximately 40.6% of the new diabetes cases were diagnosed by PCPs but only 4.4 % of the cases were diagnosed by prostate cancer specialists ($p<0.001$). The rest of the new cases were identified by other specialists (38.8%). Similar findings were observed among new hypertension cases diagnosed between 2000 and 2001. The proportion of cases diagnosed by unknown specialty was 20.0%. The new hypertension cases diagnosed by prostate cancer specialists and PCPs were 3.1% and 47.2%, respectively ($p<0.001$). Other specialists diagnosed 29.7% of the new hypertension.

4.5 Discussion

As survivorship issues continue to grow, identification and treatment of comorbidities becomes increasingly relevant for cancer survivors. The existence of comorbidities may not only influence the choice of cancer treatment, but also may affect the health-related quality of life, morbidity, and mortality of cancer survivors (3-6). Although measurement of comorbidity is commonly included in regression analyses of cancer survivorship studies, it is usually measured cross-sectionally, rather than treated as a time-variant variable.

To our knowledge, the current study is the first one to examine the longitudinal relationship between prostate cancer and diagnosis of other comorbidities. We selected a cohort of prostate cancer cases who were diagnosed in 2000 and examined their claims for up to ten years. We also included a comparison group of Medicare beneficiaries without cancer to eliminate the effect of aging on comorbidity. In our study, we found that more comorbid conditions were identified after cancer diagnosis. The prevalence rates of

comorbidities and overall comorbidity scores of prostate cancer survivors increased at a faster rate after their cancer diagnosis than those observed of individuals without cancer during the same time periods. Although the increases in the prevalence rates of depression, diabetes, and hypertension may be caused by the side effects of hormonal and radiation therapy (22, 23, 59), the same pattern was observed for COPD which has not been found to be associated with cancer treatment. In addition, similar findings were found in the GEE models controlling for cancer treatments. Moreover, we controlled for receiving hormonal therapy as an additional covariate in sensitivity analysis and still found similar results (result not shown). Therefore, it is possible that these changes were associated with more contact with the health care system because cancer survivors visited their health care providers more often after cancer diagnosis. We found that cancer survivors made more office visits not only to their prostate cancer specialists (including urologists) but also to their PCPs after the cancer diagnosis. This phenomenon was especially true among black cancer survivors. In addition, we expected prostate cancer specialists to become the main health care provider for cancer survivors and to supplant some of the responsibilities of care provided by PCP. However, it seems that cancer survivors still received their primary care for other health conditions from PCPs because the majority of newly diagnosed comorbid conditions after cancer were identified by PCPs, not by prostate cancer specialists. Therefore, a diagnosis of prostate cancer may provide a chance for some patients who were not previously engaged in the health care system to have regular contact with their PCPs, which increases the likelihood of finding other health conditions.

In our study, racial differences were observed in comorbidity severity and the differences varied across time. Black cancer survivors consistently had higher NCICI scores than white survivors, meaning that they had a risk to die from causes other than cancer than white cancer survivors. Although black patients generally have more comorbidities than

white patients (32, 91, 92), it is also likely that more underdiagnosed comorbid conditions among black patients were found after the cancer diagnosis. In addition, black cancer patients made more visits to PCPs and other specialists than black individuals without cancer during the same time period. However, the numbers of office visits to PCPs and other specialists were not different between white cancer and white non-cancer groups. Although black patients tend to have more comorbidities than white patients, they tend to use less medical care possibly because of limited access to care and less trust in their physicians. Thus, a diagnosis of prostate cancer may represent a golden opportunity for black men to gain access to care for other comorbidities.

Many other cancer studies controlled comorbidity as a time-invariant variable in their survival analyses (27, 32, 63). Methodologically, this approach may be inappropriate because we found the CCI and NCICI scores increased significantly across time. Future studies may want to control for a time-variant comorbidity score which could better reflect the risk for dying from causes other than cancer. In addition, our study found that black patients had consistently higher comorbidity scores than white patients and the magnitude of difference increased over time. Thus, previous survival analyses controlling for a time-invariant baseline comorbidity index score may under estimate the racial differences in comorbidity. We suggest that future studies to use time-variant comorbidity index scores which may be more appropriate to adjust for racial differences in mortality among prostate cancer survivors.

The main limitations of this study were similar to those observed in observational studies using administrative datasets. The results of this study may not be generalizable to non-SEER regions because Medicare beneficiaries living in the SEER regions are less likely to be white, live in poverties, reside in rural areas, and enroll in managed care plans (70). Medicare beneficiaries who were diagnosed with cancer before age 67 were excluded from

our analyses because we were unable to obtain their claims data before Medicare enrollment. Therefore, the findings from our study may not be generalized to younger prostate cancer survivors. The results from our study may not be generalized to HMO enrollees who were excluded from our analyses because information about their medical care was not available. Since risk factors, treatment options, and survival rates vary by types of cancer, different cancers may have different influence on the rates of and severity associated with various comorbidities. Therefore, the results from our study may not be generalizable to other types of cancer survivors. Due to data limitations, we were unable to observe the diagnosis of comorbidities before a patient enrolled in the Medicare program. Thus, it is likely that our study underestimated the true prevalence of each chronic condition. However, we expected that this problem has a similar influence on both the cancer and non-cancer groups. We did not consider cure function for comorbid conditions when we measured cumulative comorbidity prevalence and severity. This assumption may be more appropriate for some diseases (e.g., COPD and diabetes) than others (e.g. peptic ulcer and hypertension). However, we expected the influence of this assumption to be similar among both cancer and non-cancer groups.

In addition, the CCI and NCICI scores were the aggregated weight of chronic conditions observed in insurance claims. Although the severity of a disease may vary across patients, the severity of patients diagnosed with same type of diseases is weighted in the same way. Without a detailed review of patient medical records, we were unable to differentiate the severity of the disease among individuals. In addition, we measured the comorbidity prevalence and severity among individuals who remained alive at different time points. A “survivor effect” might exist in the time trend of diagnosis. In other words, those who remain alive at a time point may be healthier (i.e., fewer comorbidities) than those who die before that point. Since individuals with localized or regional prostate cancer and the

general non-cancer population have very similar survival rates (9), we expected the survivor effect to be similar between them. In sensitivity analysis, we restricted our samples to those who survive until the end of study (results not shown). The results from this approach did not differ from our primary findings. We selected patients diagnosed with prostate cancer in 2000 because they are the most recent cohort to fulfill our longitudinal study design. In sensitivity analysis (results not shown), we used patients who were diagnosed with prostate cancer in 1997 and applied the same study design. The findings were unchanged.

4.6 Conclusion

The benefit of prostate cancer screening remains controversial because most the prostate cancer patients are diagnosed at early stage (9). Previous studies did not find evidence to support that a reduction in cancer mortality rate from the early diagnosis of prostate cancer (18, 21, 95). In addition, prostate cancer treatments may cause adverse effects, such as incontinence and erectile dysfunction (22, 23). Therefore, some researchers have criticized the overdiagnosis and overtreatment of the low-risk prostate cancer patients (15-17). However, a diagnosis of prostate cancer at early stage may have some unexpected positive effects on other health conditions. Our study found that a diagnosis of prostate cancer may be associated with detection of previously underdiagnosed comorbid conditions. Identifying occult diseases at their early stages may lead to effective intervention and ultimately to better health outcomes. We also found that survivors had more contact with their health care providers after their cancer diagnosis, which might increase their chances of receiving appropriate management for comorbidities. Survivorship programs should incorporate management of comorbidities as one of their focuses for cancer survivors, since comorbidities were diagnosed in this population more commonly.

CHAPTER 5. ASSOCIATION BETWEEN CANCER AND USE OF NECESSARY CARE FOR COMORBID HEALTH CONDITIONS AMONG ELDERLY MEN WITH PROSTATE CANCER IN THE UNITED STATES

5.1 Abstract

Background: Since prostate cancer survivors are more likely to die from non-cancer causes than from their cancer, coexisting comorbidities are important health issues for this population. This study examined whether patients are more likely to receive necessary ambulatory care after their prostate cancer diagnosis.

Methods: Patients diagnosed with localized/regional prostate cancer at age 67-84 in 2000 (n=9,053) were identified from the Surveillance, Epidemiology, and End Results-Medicare Program. A comparison group of Medicare beneficiaries with no history of cancer also were included (n=43,926). Indicators from the refined Access to Care for the Elderly Project were used to examine the use of necessary care for non-cancer comorbidities. The proportion of eligible patients receiving necessary care for each indicator was calculated every two years from 1998 through 2007. Composite scores were calculated for indicators of clinical assessment for chronic conditions, management of chronic conditions, follow-up after hospitalization, preventable adverse outcomes avoided, work-up at initial diagnosis, and overall use of necessary care. A generalized estimating equations (GEE) model was used to assess racial differences in use of necessary care among cancer survivors.

Results: After 2000, the cancer group was more likely to receive more necessary care for their comorbid conditions than the non-cancer group, especially for clinical assessment and management of chronic conditions. Results from the GEE analysis indicate that black survivors tend to use less care than white survivors, but the difference diminished after their cancer diagnosis.

Conclusions: A diagnosis of prostate cancer may represent an opportunity for survivors to improve their use of necessary care for other comorbidities, especially for black survivors. Further studies are necessary to examine whether the improvement is associated with better health outcomes.

Keywords: prostate cancer, comorbidities, use of care, SEER-Medicare,

5.2 Introduction

Prostate cancer is the most often diagnosed cancer among men in the United States. The incidence of prostate cancer has increased dramatically as a result of prostate-specific antigen (PSA) testing, which substantially increased since the mid-1990s (14). However, the use of the PSA screening is controversial and equivocal (15-17). At present, more than 90% of prostate cancer patients are diagnosed with localized or regional stage cancer, which are highly survivable (9). Results from the randomized Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial showed that the mortality rates from prostate cancer did not differ between patients who received annual PSA screening or usual care (18). Previous studies also found potential psychological harms by prostate screening (15, 21) and adverse effects, such as incontinence and erectile dysfunction, caused by cancer treatments (15, 22, 23). Therefore, researchers have questioned whether it is necessary to diagnose and treat

patients with early stage prostate cancer (15-17). For many survivors, prostate cancer and its treatment may constitute only a fraction of medical history. Other comorbid conditions may play a more important role in a survivor's health, longevity, and physical function. However, the quality of care for other comorbid conditions has not been the focus of previous cancer survivorship research.

Although a diagnosis of prostate cancer at early stage may not reduce the risk of cancer mortality, it may have some effects on the management of other comorbid conditions. Cancer diagnosis may represent "a teachable moment" for risk factor reduction because patients tend to be more aware of their other health problems after cancer diagnosis (48-50). To prevent cancer recurrence and to increase the likelihood of survival, cancer survivors often attempt to quit smoking, to eat healthier, and to engage in regular exercise (48-50, 52, 53, 55, 56). These behavioral changes are associated with better health-related outcomes (51, 57, 58). In a previous study, we found that prostate cancer survivors made more visits not only to their oncology specialists but also to their primary care physicians (PCPs) and other specialists after their cancer diagnosis (Chapter 4). This regular contact with the health care system may increase the chance of receiving appropriate medical care. We also found that some chronic conditions that were potentially underdiagnosed prior to the cancer diagnosis were identified after a diagnosis of prostate cancer. Therefore, the cancer diagnosis may provide an opportunity to better control comorbidities.

However, comorbidities may worsen after cancer diagnosis. Long-term and late effects of cancer treatments are commonly observed among cancer survivors. For example, chemotherapy and radiation therapy may have negative effects on erectile function, cardiovascular disease, or mental health (22, 23, 59). In addition, cancer patients may not think that the continued management of other comorbidities is as important after their cancer diagnosis. Survivors may receive less care for comorbidities because their care may consist

primarily of specialty care provided by specialist physicians, with little attention to primary care needs (36). Insufficient primary care may lead to development of other comorbidities or the worsening of existing comorbidities.

Few studies have investigated the use of care for other comorbid conditions among cancer survivors. A previous study found that breast cancer survivors received more preventive care than the non-cancer controls (35), suggesting that breast cancer patients' enhanced participation in the health care system may explain better quality of care. However, different findings were reported in colorectal cancer patients. Despite the higher prevalence of comorbidities, colorectal cancer survivors were more likely to underuse necessary care for their comorbid conditions than non-cancer controls (36). Since risk factors, treatment options, and survival rates vary by types of cancer, the results from these studies may not be generalized to other types of cancer survivors. In addition, both of the studies measured the use of care cross-sectionally by following 5-year cancer survivors for two years. Although the authors examined the use of care among long term survivors, they did not analyze whether the same patterns of care use exist even before the cancer diagnosis. To our knowledge, no published study has examined the use of care for other comorbid conditions longitudinally among prostate cancer patients.

The purpose of this study is to investigate whether diagnosis of prostate cancer creates an opportunity to improve use of necessary care among Medicare beneficiaries. We used the refined Access to Care for the Elderly Project (ACE-PRO) indicators to examine the receipt of care of prostate cancer patient for a maximum of ten years. We first measured the use of care for each indicator in two-year intervals. Indicators with similar nature were grouped together and compared across time. We expected an increase in the proportion of patients receiving necessary care after cancer diagnosis. In addition, we conducted subgroup analyses to examine whether the findings differ by race. Finally, we used

regression analyses to examine whether black survivors used less necessary care for their comorbid conditions after controlling for other confounders.

5.3 Methods

Data Sources

Our data were obtained from the Surveillance, Epidemiology, and End Results registry (SEER)-Medicare Program. The SEER-Medicare data are population-based data that combine SEER cancer registry information with Medicare enrollment and claims files (70, 72). The SEER Program is a national cancer registry which covers more than 25% of the US population. It routinely collects data on patient demographics, tumor site, stage at diagnosis, primary course of treatment and aggregate measures of social economic status (SES) information including regional median household economic and educational status (69, 70). We used the data from the SEER-17 which provides the latest data available for our longitudinal follow-up. The SEER-17 includes cancer registries of the Arizona Native American, Alaska Natives, nine states (California, Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah), and seven regions (Atlanta, Detroit, rural Georgia, Los Angeles, San Francisco, San Jose, and Seattle). Medicare is the primary health insurer for 97% of the US population ages 65 years and older. A beneficiary's disease diagnoses, treatments, and services received are available in the Medicare claims. However, data are not available for health maintenance organization (HMO) enrollees, services not covered by Medicare (i.e., outpatient prescription drugs and long term care), and services provided by Veterans Affairs or Medicaid, or by Medicare supplement programs (i.e., Medigap policies) (70).

Cohort Selection

Patients diagnosed with localized or regional (i.e., Stage I, II, or III) prostate cancer in 2000 were included in this study. Compared with non-cancer population, these cancer patients' five-year relative survival rate is approximately 100% (9). We excluded patients who were diagnosed with distant (i.e., Stage IV) prostate cancer because their five-year relative survival rate is only 32% (9). The claims of each patient were examined for up to ten years, beginning from January 1, 1998 through his death or December 31, 2007. To be eligible for inclusion in the study, patients must have been continuously enrolled in Medicare Part A and Part B and never enrolled in HMO during the study period. To observe the use of necessary care before cancer diagnosis, we included only patients were at age 67 or older as of January 1, 2000, thus allowing for two years of observation prior to diagnosis. Medicare beneficiaries who are eligible for Medicare because of disability or the presence of end-stage renal disease before age 65 were excluded from the analyses as well. Other exclusion criteria included: age 84 and over as of January 1, 2000; prior cancer history; diagnosis with a second cancer within six months; noninvasive tumors (i.e., carcinoma in situ); unstaged prostate cancer; diagnosis at death or via autopsy; or missing; race other than black or white; or missing SES variables.

To control for the effect of aging, we selected a comparison group from the 5-percent random sample of patients without cancer in the SEER-Medicare data. Inclusion criteria for the non-cancer group were: male gender; qualified for Medicare benefit because of age; age between 67 and 84 years as of January 1, 2000; continuously enrolled in Medicare Part A and Part B and never enrolled in the HMO program during the study period; and living in areas covered by the SEER-17 registry. We did not to use matching technique to further narrow down the non-cancer group. Instead, we used all of the non-cancer patients who are qualified for our inclusion/exclusion criteria. Since the non-cancer group, by definition, had never been diagnosed with any cancer in the study timeframe, it would be arbitrary and

potentially biased to assign an index date (i.e., date of cancer diagnosis) to them by matching technique. We used regression analyses to adjust for the influence caused by baseline differences between cancer and non-cancer.

Variable Definitions

A cancer patient's age, race, and date of death are available from both SEER and Medicare data. Demographic information from these two sources is highly consistent (69). Since the demographic data for the comparison group are available only in the Medicare enrollment file, we employed Medicare's Enrollment Database as our primary source to identify age, race, and vital status for both groups. Empirically, data aggregated at the census tract level are more likely to reflect a patient's socioeconomic status (SES) than are zip code level data (69). However, the SES information for the comparison group is available only at the zip code level; hence we controlled for median household income and percentage of residents with less than a high school degree at zip code level from the 2000 Census for both groups in our analyses. We also used the Charlson Comorbidity Index (CCI) to assess the severity of comorbidities at different time points. The CCI is a commonly used measure of comorbidity in epidemiologic and outcomes research (27, 38, 39, 63, 74). A higher comorbidity score represents more severe health problems. For the subgroup analysis for prostate cancer survivors, we used the National Cancer Institute Combined Index (NCICI) to measure comorbidity severity. The NCICI, which adapts the comorbid conditions from the CCI, was developed specifically for the use with SEER-Medicare data by weighing comorbidity differently by cancer site (40). As with the CCI, higher NCICI scores indicate greater comorbidity severity.

We used both SEER indicator and Medicare claims within six months of cancer diagnosis to identify primary cancer treatment. Surgery and radiation therapy (XRT) are consistently reported in SEER and Medicare claims data (>90% agreement) (93, 94).

Surgery was defined as procedures performed with curative intent or in anticipation of a subsequent curative procedure (27). We used: (1) the indicator for whether a cancer-directed surgery was performed; (2) International Classification of Diseases, 9th Revision, (ICD-9) procedure codes 60.5 and 60.6; Current Procedural Terminology (CPT) codes 55810, 55812, 55815, 55840, 55842, 55845, 55866 from Medicare claims; and (3) site-specific surgery codes 30–90 from the SEER data to identify radical prostatectomy and procedures performed on regional lymph nodes. XRT was defined as external beam therapy, brachytherapy, or therapeutic isotope radiation therapy as listed in the SEER data.(63) We used: (1) the indicator for whether a cancer-directed XRT was performed; (2) ICD-9 procedure codes 92.2x, V58.0, V66.1, V67.1, CPT codes 77301, 77400–77499; revenue center codes 0330–0339 from Medicare claims; and (3) site-specific radiation codes 1–5 in the SEER data to identify XRT. Men who receive both surgery and XRT were classified as having surgery because some patients may receive XRT after an incomplete or unsuccessful surgery (27, 63).

The type of care provider was classified based on the specialty information in the Medicare Carrier Claims (36). Oncology specialists were defined as sub-specialists in urology (code 34), hematology oncology (code 83), medical oncology (code 90), surgical oncology (code 91), or radiation oncology (code 92). Primary care physicians were defined as physicians in general practice (code 01), family practice (code 08), internal medicine (code 11), geriatric medicine (code 38), or multi-specialty group practices (code 70).

Quality of Care Measures

We used the refined Access to Care for the Elderly Project (ACE-PRO) indicators from the Medicare Payment Advisory Commission (MedPAC) to assess use of necessary ambulatory care among elderly Medicare beneficiaries (64). The MedPAC, an independent Congressional agency, advises the US Congress on issues affecting the Medicare program.

The ACE-PRO indicators were originally developed for MedPAC by researchers from the RAND Corporation in 2000 (34). MedPAC has used the ACE-PRO indicators to study the access to and quality of care associated with various geographic and socioeconomic factors, and has used the results of these analyses in their reports to Congress (64). The ACE-PRO indicators were updated in 2006 to reflect changes in performance measurement and clinical practice. The refined ACE-PRO indicators have been tested and validated on Medicare claims by MedPAC (64).

The refined ACE-PRO indicators consist of 40 indicators for medical conditions covering anemia, angina, breast cancer, colorectal cancer, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, depression, diabetes, gastrointestinal bleeding, hypertension, and stroke or transient ischemic attack. Six indicators were excluded from our analysis because they were developed specifically either for women or for other cancers. Based on the suggestion of MedPAC, the remaining 34 indicators were categorized into five groups by their type of care (Table 5) (64).

We estimated the use of necessary care in every two-year time period (64). For each indicator, we first used the ICD-9 codes to identify the number of individuals who were qualified for it (i.e., denominator). We then used the CPT codes to identify the number of qualified individuals who met the requirement of the indicator (i.e., numerator). The ratio of numerator to denominator represents the proportion of individuals used the necessary care. For example, we assessed the eye care indicator by calculating the proportion of individuals with a history of diabetes mellitus that had comprehensive eye exam.

$$eye\,care\,indicator_t = \frac{number\,of\ \ diabetic\,patients\,who\,had\,eye\,exam_t}{number\,of\ \ patients\,with\,a\ \ prior\,history\,of\ \ diabetes_t}$$

For each person, we also calculated composite scores for clinical assessment in chronic condition, management of chronic condition, follow-up after hospitalization, possible

adverse outcomes avoided, and work-up at initial diagnosis. Finally, we calculated an overall composite score by dividing the sum of numerators to the sum of qualified denominators to measure the proportion of eligible care that was received by each person during each time period.

$$overall\,use\,of\ necessary\,care_{it} = \frac{\sum_{j=1}^{34} care\,received_{ijt}}{\sum_{j=1}^{34} qualified\,for\,care_{ijt}}$$

The use of necessary care for each indicator was measured during five time periods (Figure 3). Period 0 measured the baseline use of care in 1998 and 1999 (i.e., two years before the index date (i.e., cancer diagnosis or 2000). Period 1 evaluated whether patients receive necessary care for their comorbidities right after cancer diagnosis (i.e., between 2000 and 2001). Periods 2 and 3 focused on the use of care between 2002 and 2003 and between 2004 and 2005, respectively. The last period, Period 4 (between 2006 and 2007), measured the use of care after patients have survived from prostate cancer for more than five years. The result from this period can be directly compared with the findings from previous studies evaluating the use of care in other types of cancer (35, 36).

The ACE-PRO indicators were originally developed for analysis using two years of data (64). Many indicators use the first year of observation to determine individuals who are qualified for denominators and use the second year to identify numerators. In this study, we made some adjustments to the ACE-PRO method for our ten-year study timeframe. For indicators of clinical assessment, management of chronic conditions, and avoidable adverse outcomes, an individual became qualified for denominator after the year when he was first diagnosed with a chronic condition. For example, if a person was diagnosed with diabetes in 1998 and survived through 2007, he was qualified for the denominator of clinical

assessment indicator for diabetic patient in Period 0, Period 1, Period 2, Period 3, and Period 4. This patient would need at least two outpatient visits per year during a time period to meet the requirements of the indicator. For indicators of follow-up after hospitalization, we used the first event in each time period without another event within 4 weeks following the discharge of the previous event. For the indicators of work-up at initial diagnosis, we examined the care at the first diagnosis in the entire time frame, rather than the first diagnosis in each time period. Our ten years of follow-up allows us to identify the initial diagnosis more precisely than the conventional ACE-PRO method using only two years of data.

Statistical Analyses

For each indicator, we first compared the ratios of numerators to denominators between cancer and non-cancer groups at different time periods. Chi-square tests (78) were conducted to examine whether prostate cancer survivors received the same level of care for their comorbid conditions as the comparison group did. For different types of care, we conducted Student's t tests to compare composite scores between cancer and comparison groups in different time periods.

A multivariate generalized estimating equations (GEE) regression model (80, 81) was conducted to analyze the association between prostate cancer diagnosis and overall use of necessary care. Identity link and normal residuals were used in the GEE model. The effects of cancer on use of necessary care during various time periods were of primary interest. The sum of coefficients of cancer indicator and its interaction term with time was tested by Wald test in each time period (80, 81). Other factors, including age, race, registry site, education, income, and comorbidities, which might be associated with use of care and prostate cancer diagnosis, were controlled for in the model. In addition, we conducted a separate GEE analysis for cancer survivors only to examine whether racial differences in

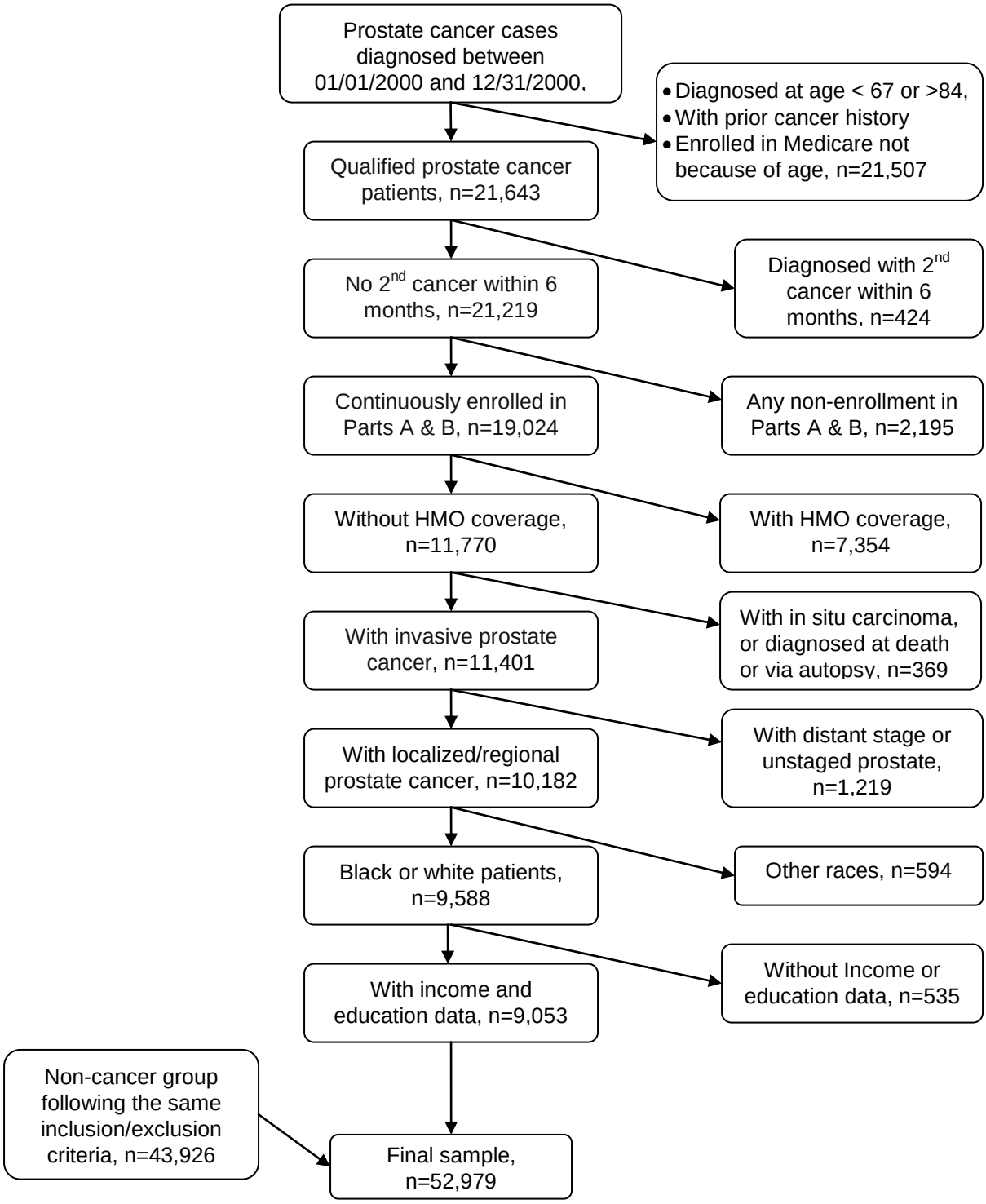
use of care changed after cancer diagnosis. The sum of coefficients of race and interaction terms between race and time was further examined by Wald test (80, 81). In addition to the independent variables in the previous GEE model, we also controlled for marital status, primary cancer treatment, tumor grade, and type of care provider, which were only available for the cancer group.

5.4 Results

Study Sample

Figure 6 presents a flow chart of the sample selection process. A total of 43,150 prostate cancer cases were initially identified in 2000 from the SEER-Medicare data. Employing the inclusion and exclusion criteria described earlier, 9,053 prostate cancer patients and 43,926 Medicare beneficiaries without cancer comprised our study sample.

Figure 6. Procedures to generate the study sample of prostate cancer patients



HMO: health maintenance organization

Table 13. Comparison of baseline characteristics between cancer and non-cancer patients

Sociodemographic Characteristics	Both			Black			White		
	Cancer (n=9,053)	Non-cancer (n=43,926)	p value	Cancer (n=811)	Non-cancer (n=2,466)	p value	Cancer (n=8,242)	Non-cancer (n=41,460)	p value
Age (years) on 01/01/2000, %									
67-69	19.1	19.2	<0.001	22.1	20.4	0.52	18.8	19.1	<0.001
70-74	37.5	33.2		35.9	35.4		37.7	33.1	
75-79	29.6	29.6		27.9	28.1		29.8	29.7	
80-84	13.8	18.0		14.2	16.1		13.8	18.1	
Mean age, year	74.0	74.4	<0.001	73.7	74.1	0.08	74.0	74.5	<0.001
Mean follow-up time, month	105.7	102.8	<0.001	100.6	97.3	<0.01	106.2	103.1	<0.001
Alive as of 12/31/2007, %	65.7	64.1	<0.01	56.0	54.6	0.49	66.6	64.7	<0.001
Registry site, %									
San Francisco	3.0	2.9	<0.001	2.7	3.3	<0.001	3.1	2.9	<0.001
Connecticut	7.6	6.9		3.2	3.6		8.0	7.1	
Detroit	11.7	8.2		33.1	20.4		9.7	7.5	
Hawaii	0.4	0.4		0.1	0.1		0.5	0.5	
Iowa	8.7	8.3		0.9	0.9		9.5	8.7	
New Mexico	2.1	2.6		0.3	0.7		2.3	2.7	
Seattle	5.9	5.3		1.1	1.3		6.4	5.6	
Utah	3.7	3.1		0.4	0.3		4.0	3.2	
Atlanta	3.1	3.1		6.7	7.7		2.7	2.8	
San Jose	1.9	2.1		0.9	0.6		2.0	2.2	
Los Angeles	6.0	6.4		8.0	8.6		5.8	6.3	
Rural Georgia	0.2	0.3		0.5	1.1		0.2	0.2	
California	14.7	17.3		4.1	6.5		15.7	17.9	
Kentucky	5.8	9.0		2.8	5.8		6.1	9.2	
Louisiana	7.0	7.0		17.1	19.6		6.0	6.3	
New Jersey	18.3	17.2		18.3	19.4		18.3	17.1	
Percent persons age 25+ of same race with less than a high school education									
Mean, %	16.2	16.5	0.02	28.2	28.9	0.17	15.0	15.8	<0.001
Annual household income									
Mean, $	51,281	49,140	<0.001	35,544	35,465	0.89	52,829	49,954	<0.001
Charlson Comorbidity Index Score									
12/31/1999	0.76	0.93	<0.001	1.01	1.17	0.02	0.73	0.91	<0.001
12/31/2001	1.24	1.29	0.01	1.63	1.59	0.58	1.20	1.27	<0.001
12/31/2003	1.54	1.57	0.24	2.01	1.84	0.07	1.50	1.56	0.02
12/31/2005	1.95	1.81	<0.001	2.43	2.15	0.01	1.91	1.80	<0.001
12/31/2007	2.10	2.00	<0.01	2.73	2.38	<0.01	2.04	1.98	0.04

Table 13 presents the baseline characteristics of the study sample. Compared with the comparison group, prostate cancer survivors were generally younger and had longer follow-up ($p<0.001$). The proportions of individuals coming from specific registry sites were different between the cancer and comparison groups ($p<0.001$). The cancer group lived in areas with higher median household income and a lower proportion of residents with less than a high school degree. Before 2000, the cancer group had a lower average CCI score than the comparison group did (0.76 vs. 0.93, $p<0.001$). Compared with the non-cancer comparison group, cancer survivors were more likely to be black (9.0% vs. 5.6%, $p<0.001$). Among white men, cancer survivors were more likely to be younger, to have longer follow-up, and to have fewer comorbidities (i.e., a lower CCI score). In addition, white cancer survivors were less likely to live in an area with higher educational attainment ($p<0.001$) and higher median household income ($p<0.001$). Similar findings were observed among black patients. However, except for the length of follow-up ($p<0.01$), registry site ($p<0.001$), and comorbidity score ($p=0.02$), none of the differences in baseline characteristics between the black cancer and comparison groups was statistically significant.

Receipt of Necessary Care

Clinical Assessment of Chronic Conditions

Table 14 shows results of the indicators for clinical assessment and management of chronic conditions. In Period 0, cancer survivors with coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), and congestive heart failure (CHF) were more likely to have regular visits to their physicians than individuals without cancer having the same conditions. No difference was observed between the cancer and comparison groups with respect to diabetes or stroke/transient ischemic attack (TIA). Regardless of comorbid conditions, cancer survivors were more likely to have at least one office visit per year to their physician than were individuals without cancer (84.1% vs. 81.4%, $p<0.001$). For all of the

clinical assessment indicators, cancer patients were more likely to have regular outpatient visits than the non-cancer patients after 2000. Surprisingly, the use of care dropped among cancer group in Period 3, and cancer survivors were less likely to have regular office visits to their physicians than were individuals without cancer. However, the receipt of care as measured by most of the indicators was significantly higher among cancer survivors than among individuals without cancer in the last time period. A similar time trend was observed in subgroup analyses by race. However, the difference in receipt of care between the cancer and non-cancer groups after 2000 was larger among black patients.

Management of Chronic Conditions

Similar findings were observed for the management of chronic condition indicators. After prostate cancer diagnosis, survivors with a history of diabetes were more likely to receive an eye exam but less likely to receive a hemoglobin A1C test. Except for Period 3, cancer survivors with a history of CAD were more likely to receive annual lipid testing than were individuals without cancer. In the period immediately following cancer diagnosis or index date, cancer survivors with CHF were more likely to have had a regular exam for electrolytes and renal function than similar individuals without cancer (81.0% vs. 76.8%, $p<0.001$).

Table 14. Comparison of indicators for clinical assessment and management of chronic conditions [2]

		Sample size (n)		Proportion of patients reaching the goal (%)					
		Both		Both		Black		White	
Indicator	Period (year)	Cancer	Non-Cancer	Cancer	Non-cancer	Cancer	Non-cancer	Cancer	Non-cancer
Clinical assessment in chronic disease									
Two outpatient visits per year in patients with diabetes mellitus	P0 (1998-1999)	855	5,162	96.8	96.0	94.8	92.4	97.2	96.4
	P1 (2000-2001)	1,302	6,511	98.0	92.6 ¶	94.6	89.4 †	98.5	92.9 ¶
	P2 (2002-2003)	1,416	6,940	96.3	91.2 ¶	92.4	87.7	96.9	91.5 ¶
	P3 (2004-2005)	1,924	7,070	85.8	92.0 ¶	80.4	88.1 ‡	86.4	92.3 ¶
	P4 (2006-2007)	1,831	6,977	94.5	92.0 ¶	92.1	86.6	94.7	92.4 ‡
Two outpatient visits per year in patients with coronary artery disease	P0 (1998-1999)	1,507	8,129	97.8	96.4 ‡	94.4	92.4	98.0	96.5 ‡
	P1 (2000-2001)	2,468	11,599	98.3	93.6 ¶	97.7	87.0 ¶	98.3	93.9 ¶
	P2 (2002-2003)	2,783	12,845	97.2	92.4 ¶	95.9	89.3 ‡	97.3	92.5 ¶
	P3 (2004-2005)	3,041	13,127	81.8	92.3 ¶	81.6	89.4 ‡	81.9	92.4 ¶
	P4 (2006-2007)	2,859	12,696	95.1	91.9 ¶	93.0	85.1 ‡	95.3	92.4 ¶
Two outpatient visits per year in patients with stroke / transient ischemic attack	P0 (1998-1999)	333	2,126	95.2	95.2	92.9	92.1	95.4	95.4
	P1 (2000-2001)	730	3,968	98.5	93.2 ¶	95.2	86.2 †	98.8	93.7 ¶
	P2 (2002-2003)	943	5,022	97.5	92.4 ¶	98.5	87.6 ‡	97.4	92.6 ¶
	P3 (2004-2005)	1,224	5,631	85.2	92.3 ¶	86.7	86.2	85.1	92.6 ¶
	P4 (2006-2007)	1,250	5,814	94.6	91.8	94.2	85.7 †	94.6	92.2 ‡
Two outpatient visits per year in patients with COPD / Asthma	P0 (1998-1999)	653	3,693	96.3	94.1 †	95.7	87.5	96.4	94.5
	P1 (2000-2001)	1,261	5,707	97.5	91.3 ¶	95.4	87.5 †	97.8	91.6 ¶
	P2 (2002-2003)	1,486	6,538	96.0	90.5 ¶	93.4	85.5 †	96.3	90.8 ¶
	P3 (2004-2005)	1,782	6,845	82.8	90.4 ¶	77.4	86.3 †	83.3	90.7 ¶
	P4 (2006-2007)	1,676	6,758	94.9	91.1 ¶	94.2	84.8 ‡	94.9	91.4 ¶
Two outpatient visits per year in patients with congestive heart failure	P0 (1998-1999)	364	2,467	98.4	96.2 †	98.1	92.2	98.4	96.5
	P1 (2000-2001)	785	4,126	98.2	94.8 ¶	96.2	86.2 ‡	98.5	95.4 ¶
	P2 (2002-2003)	989	4,904	96.7	94.2 ‡	94.3	88.9	96.9	94.5 ‡
	P3 (2004-2005)	1,325	5,319	86.8	93.5 ¶	83.3	88.3	87.2	93.9 ¶
	P4 (2006-2007)	1,304	5,396	96.0	93.9 ‡	94.7	86.2 †	96.2	94.3 †
One outpatient visits per year in Medicare beneficiaries	P0 (1998-1999)	9,053	43,926	84.1	81.4 ¶	72.4	66.9 ‡	85.2	82.2 ¶
	P1 (2000-2001)	8,599	39,953	96.2	83.4 ¶	90.1	68.8 ¶	96.8	84.3 ¶
	P2 (2002-2003)	7,747	35,981	95.4	85.6 ¶	87.8	72.9 ¶	96.1	86.3 ¶
	P3 (2004-2005)	6,865	32,223	83.8	87.3 ¶	79.2	75.1	84.2	88.0 ¶
	P4 (2006-2007)	5,945	28,176	94.2	88.5 ¶	87.2	75.4 ¶	94.8	89.1 ¶

Table 14. Comparison of indicators for clinical assessment and management of chronic conditions (continued)

Management of Chronic Conditions									
Comprehensive eye exam every 2 years in patients with diabetes	P0 (1998-1999)	855	5,162	64.3	62.2	53.9	56.7	64.9	62.7
	P1 (2000-2001)	1,302	6,511	63.1	63.3	50.3	54.7	64.9	64.0
	P2 (2002-2003)	1,416	6,940	68.6	65.5 †	58.1	56.3	70.1	66.2 ‡
	P3 (2004-2005)	1,924	7,070	74.0	66.6 ¶	69.1	58.2 ‡	74.5	67.2 ¶
	P4 (2006-2007)	1,831	6,977	70.7	67.8 †	60.5	55.4	71.8	68.7 †
Hemoglobin A1C test every year in patients with diabetes	P0 (1998-1999)	855	5,162	72.3	69.8	67.8	57.9	73.0	70.9
	P1 (2000-2001)	1,302	6,511	66.7	66.0	59.9	54.5	67.7	66.9
	P2 (2002-2003)	1,416	6,940	65.0	65.3	54.1	60.7	66.6	65.6
	P3 (2004-2005)	1,924	7,070	45.3	65.8 ¶	51.5	55.1	44.6	66.6 ¶
	P4 (2006-2007)	1,831	6,977	51.3	66.7 ¶	54.8	58.0	51.0	67.3 ¶
Lipid profile every year in patients with diabetes	P0 (1998-1999)	855	5,162	63.3	57.1 ¶	58.3	44.4 ‡	64.1	58.2 ‡
	P1 (2000-2001)	1,302	6,511	57.2	54.7	49.1	38.8 ‡	58.4	56.0
	P2 (2002-2003)	1,416	6,940	63.2	59.7 †	48.8	51.2	65.2	60.4 ‡
	P3 (2004-2005)	1,924	7,070	61.0	63.4	47.9	53.0	62.5	64.2
	P4 (2006-2007)	1,831	6,977	63.3	65.7	54.8	51.1	64.2	66.7
Lipid profile every year in patients with coronary artery disease	P0 (1998-1999)	1,507	8,129	68.5	63.3 ¶	56.7	46.2	69.2	64.0 ¶
	P1 (2000-2001)	2,468	11,599	62.2	58.6 ¶	47.7	39.3	63.3	59.4 ¶
	P2 (2002-2003)	2,783	12,845	63.2	59.8 ¶	52.3	44.5	64.0	60.4 ¶
	P3 (2004-2005)	3,041	13,127	56.9	61.9 ¶	44.7	46.7	57.9	62.6 ¶
	P4 (2006-2007)	2,859	12,696	63.0	62.4	56.7	50.4	63.5	62.8
Measurement of electrolytes and renal function every year in patients with heart failure	P0 (1998-1999)	364	2,467	23.1	25.4	35.8	25.4	20.9	25.4
	P1 (2000-2001)	785	4,126	81.0	76.8 ‡	81.1	68.1 †	81.0	77.4 †
	P2 (2002-2003)	989	4,904	81.0	79.2	82.1	73.6	80.9	79.5
	P3 (2004-2005)	1,325	5,319	78.6	79.9	72.7	74.7	79.3	80.2
	P4 (2006-2007)	1,304	5,396	83.4	81.3	83.2	77.0	83.5	81.6

COPD: chronic obstructive pulmonary disease

Significance denoted as: †: p<0.05; ‡: p<0.01; ¶: p<0.001

Dashed line differentiates pre- and post-cancer era

[2] Eight weeks after the dissertation was defended on 12/04/2009, the SEER-Medicare Program Reported an error in preparing 2004 physician claims data. http://healthservices.cancer.gov/seermedicare/seermed_2004_data_letter.pdf Therefore, the use of necessary care might be underestimated between 2004 and 2005 (i.e. Period 3).

Follow-up after Hospitalization

Indicators of follow-up after diagnosis and having avoidable adverse outcomes are listed in Table 15. In general, the use of necessary care for follow-up after hospitalization was not different between cancer and comparison groups. However, cancer survivors received less care than individuals without cancer in four and two indicators in Period 3 and Period 4, respectively. As compared with blacks without cancer, black cancer survivors were more likely to have a follow-up visit after discharge from the hospital for complications of diabetes in Period 2 (86.2% vs. 72.1%, $p<0.05$). Black cancer survivors also were more likely to have follow-up visit after hospitalization for acute myocardial infarction in Period 1 (88.2% vs. 54.5%, $p<0.05$).

Experiencing Avoidable Adverse Outcomes

Cancer survivors were less likely to have been hospitalized for short-term or long-term complications of diabetes, CHF, and COPD than individuals without cancer in Period 0. Cancer survivors with history of diabetes also were less likely to be hospitalized for their diabetic complications than non-cancer patients in Periods 3 and 4. However, most of the above findings were only observed in white patients. The proportions of patients having avoidable adverse outcomes were not different between black cancer and black non-cancer patients. Since having at least three emergency department visits for CAD and hospitalization for malignant hypertension were rare events, we were unable to detect significant differences between cancer and non-cancer groups for these indicators (results not shown).

Table 15. Comparison of indicators for follow-up after hospitalization and having avoidable outcomes [3]

		Sample size (n)		Proportion of patients reaching the goal (%)					
		Both		Both		Black		White	
Indicator	Period (year)	Cancer	Non-cancer	Cancer	Non-cancer	Cancer	Non-cancer	Cancer	Non-cancer
Follow-up outpatient after hospitalization									
At least one office visit ≤ 4 weeks after discharge of hospitalization for diabetes	P0 (1998-1999)	332	2,558	79.8	76.9	73.1	73.3	81.1	77.3
	P1 (2000-2001)	659	2,522	76.5	79.6	77.4	70.4	76.3	80.4 †
	P2 (2002-2003)	511	2,502	83.0	79.7	86.2	72.1 †	82.5	80.4
	P3 (2004-2005)	519	2,570	71.3	81.1 ¶	70.0	70.5	71.5	82.1 ¶
	P4 (2006-2007)	474	2,482	78.9	79.8	74.1	64.9	79.5	80.9
At least one office visit ≤ 4 weeks after discharge of hospitalization for acute myocardial infarction	P0 (1998-1999)	121	960	85.1	81.5	66.7	64.8	86.1	82.5
	P1 (2000-2001)	164	869	86.0	84.1	88.2	54.5 †	85.7	85.7
	P2 (2002-2003)	166	798	81.9	85.3	83.3	80.0	81.8	85.6
	P3 (2004-2005)	136	718	73.5	85.8 ¶	55.6	77.5	74.8	86.3 ‡
	P4 (2006-2007)	114	650	76.3	86.2 ‡	72.7	74.2	76.7	86.8 ‡
At least one office visit ≤ 4 weeks after discharge of hospitalization for stroke/ transient ischemic attack	P0 (1998-1999)	297	1,999	74.4	72.1	52.2	67.4	76.3	72.5
	P1 (2000-2001)	360	1,915	78.6	74.7	63.6	64.2	80.1	75.5
	P2 (2002-2003)	346	1,779	80.6	76.6	74.3	68.4	81.4	77.2
	P3 (2004-2005)	309	1,573	74.8	78.4	60.0	75.2	76.1	78.6
	P4 (2006-2007)	301	1,512	72.4	78.2 †	67.7	66.3	73.0	79.0 †
At least one office visit ≤ 4 weeks after discharge of hospitalization for congestive heart failure	P0 (1998-1999)	270	2,272	85.6	81.4	79.5	72.2	86.7	82.2
	P1 (2000-2001)	480	2,338	82.3	83.3	78.8	69.7	82.9	84.4
	P2 (2002-2003)	424	2,356	86.8	84.5	80.8	80.6	87.6	84.8
	P3 (2004-2005)	469	2,422	76.3	85.7 ¶	73.3	75.5	76.8	86.4 ¶
	P4 (2006-2007)	454	2,300	84.4	85.6	79.5	76.2	84.9	86.1
At least one office visit ≤ 4 weeks after discharge of hospitalization for gastrointestinal bleeding	P0 (1998-1999)	109	698	84.4	81.4	64.3	72.7	87.4	82.3
	P1 (2000-2001)	175	672	84.6	82.0	81.5	75.0	85.1	82.6
	P2 (2002-2003)	192	695	82.3	81.0	75.0	64.2	83.5	82.4
	P3 (2004-2005)	161	624	78.3	84.0	90.0	68.4	76.6	85.0 †
	P4 (2006-2007)	146	630	82.9	83.5	61.5	79.0	85.0	83.8
At least one office visit ≤ 2 weeks after discharge of hospitalization for depression	P0 (1998-1999)	71	566	50.7	60.4	62.5	53.8	49.2	60.7
	P1 (2000-2001)	144	642	55.6	60.7	27.3	48.8	57.9	61.6
	P2 (2002-2003)	135	650	60.7	63.8	58.3	43.5	61.0	64.6
	P3 (2004-2005)	125	647	45.6	64.5 ¶	50.0	46.2	45.4	64.8 ¶
	P4 (2006-2007)	130	612	63.1	64.7	33.3	51.6	64.5	65.4

Table 15. Comparison of indicators for follow-up after hospitalization and having avoidable outcomes (continued)

		Sample size (n)		Proportion of patients reaching the goal (%)					
		Both		Both		Black		White	
Indicator	Period (year)	Cancer	Non-cancer	Cancer	Non-cancer	Cancer	Non-cancer	Cancer	Non-cancer
At least one hemoglobin or hematocrit test ≤ 4 weeks after discharge of hospitalization for gastrointestinal bleeding	P0 (1998-1999)	109	698	43.1	37.4	21.4	30.3	46.3	38.1
	P1 (2000-2001)	175	672	38.3	37.8	37.0	25.0	38.5	39.0
	P2 (2002-2003)	192	695	49.5	47.2	25.0	41.5	53.7	47.7
	P3 (2004-2005)	161	624	50.3	56.6	50.0	36.8	50.4	57.8
	P4 (2006-2007)	146	630	56.2	52.9	38.5	32.6	57.9	54.3
Having Avoidable Adverse Outcomes									
Hospitalization for serious short term complications of diabetes in patient with diabetic history	P0 (1998-1999)	855	5,162	3.6	6.2 ‡	5.2	12.0	3.3	5.7 ‡
	P1 (2000-2001)	1,302	6,511	3.3	3.6	6.6	4.9	2.8	3.5
	P2 (2002-2003)	1,416	6,940	3.1	3.0	4.0	5.6	3.0	2.8
	P3 (2004-2005)	1,924	7,070	1.7	3.0 ‡	3.1	6.0	1.6	2.8 ‡
	P4 (2006-2007)	1,831	6,977	2.0	3.1 ‡	2.8	4.9	1.9	3.0 †
Hospitalization for serious long term complications of diabetes in patient with diabetic history	P0 (1998-1999)	855	5,162	7.6	11.5 ¶	18.8	14.7	5.9	11.2 ¶
	P1 (2000-2001)	1,302	6,511	8.9	9.3	13.0	13.7	8.3	9.0
	P2 (2002-2003)	1,416	6,940	7.3	8.7	12.1	12.0	6.6	8.4 †
	P3 (2004-2005)	1,924	7,070	6.4	7.8 †	9.7	12.2	6.1	7.5 †
	P4 (2006-2007)	1,831	6,977	4.7	7.7 ¶	7.3	9.8	4.5	7.6 ¶
Hospitalization for heart failure in patients with a history of heart failure	P0 (1998-1999)	364	2,467	13.5	23.0 ¶	17.0	28.5	12.9	22.6 ¶
	P1 (2000-2001)	785	4,126	14.5	15.7	23.6	16.7	13.1	15.6
	P2 (2002-2003)	989	4,904	10.3	11.9	11.3	15.0	10.2	11.7
	P3 (2004-2005)	1,325	5,319	9.3	10.8	12.9	13.9	8.9	10.6
	P4 (2006-2007)	1,304	5,396	8.0	10.2 †	12.2	13.8	7.5	10.1 ‡
Hospitalization for COPD in patients with a history of COPD	P0 (1998-1999)	653	3,693	16.8	25.3 ¶	14.5	30.7 ‡	17.1	24.9 ¶
	P1 (2000-2001)	1,261	5,707	12.4	13.3	13.7	19.3	12.2	13.0
	P2 (2002-2003)	1,486	6,538	9.0	9.5	8.6	11.9	9.1	9.4
	P3 (2004-2005)	1,782	6,845	7.8	8.9	10.7	13.7	7.5	8.6
	P4 (2006-2007)	1,676	6,758	7.4	8.0	12.8	10.1	6.8	7.9

COPD: chronic obstructive pulmonary disease

Significance denoted as: †: p<0.05; ‡: p<0.01; ¶: p<0.001 ; Dashed line differentiates pre- and post-cancer diagnosis era

Since the proportion of patients with “hospitalization for malignant hypertension” or “emergency room visit for coronary artery disease” are very rare. The results of these two indicators are not shown.

[3] Eight weeks after the dissertation was defended on 12/04/2009, the SEER-Medicare Program Reported an error in preparing 2004 physician claims data. http://healthservices.cancer.gov/seermedicare/seermed_2004_data_letter.pdf Therefore, the use of necessary care might be underestimated between 2004 and 2005 (i.e., period 3).

Work-up at Initial Diagnosis

Mixed findings were observed in the use of care for work-up at initial diagnosis (Table 16). Cancer survivors were more likely to receive colonoscopy or barium enema after their initial diagnosis of iron deficiency anemia. A potential explanation is that cancer survivors were more aware of their health condition, which may be associated with the second cancer. However, prostate cancer patients generally received less care than individuals without cancer for other indicators, especially in Period 3.

Use of Care by Composite

Comparison of a composite score for indicators with similar nature is presented in Table 16. In period 0, cancer survivors were more likely to have regular office visits to physician, to have better management of their chronic conditions, and not to have avoidable adverse outcomes than individuals without cancer. After Period 0, cancer survivors had significantly higher composite scores for clinical assessment, management of chronic condition, not having avoidable adverse outcomes, and work-up at initial diagnosis of comorbidities, except for in Period 3. However, cancer survivors had lower composite scores than men without cancers for follow-up after hospitalization in Periods 1 and 3.

Table 16. Comparison of indicators for work-up at initial diagnosis [4]

Indicator	Period (year)	Sample size		Proportion of patients reaching the goal (%)					
		Both		Both		Black		White	
		Cancer	Non-cancer	Cancer	Non-cancer	Cancer	Non-cancer	Cancer	Non-cancer
Work-up at Initial Diagnosis									
Electrocardiography or Holter Monitor within 2 days of initial diagnosis of TIA	P0 (1998-1999)	359	1,899	44.3	45.6	60.6	47.6	42.6	45.5
	P1 (2000-2001)	425	2,002	32.5	37.9 †	31.6	41.7	32.6	37.7
	P2 (2002-2003)	349	1,746	35.2	37.3	33.3	44.7	35.4	36.8
	P3 (2004-2005)	407	1,413	31.7	37.6 †	29.4	34.9	31.9	37.7 †
	P4 (2006-2007)	231	1,210	39.8	37.3	60.0	36.8	37.9	37.3
Carotid angiogram or non-invasive carotid imaging within 2 weeks of initial hospitalization for carotid artery stroke	P0 (1998-1999)	65	451	63.1	74.5	75.0	86.4	62.3	73.9
	P1 (2000-2001)	108	555	50.0	53.5	50.0	36.4	50.0	53.9
	P2 (2002-2003)	85	456	48.2	46.9	100.0	50.0	47.0	46.9
	P3 (2004-2005)	71	389	49.3	51.9	50.0	62.5	49.3	51.7
	P4 (2006-2007)	86	371	50.0	57.1	87.5	63.6	46.2	56.9
Carotid imaging within two months prior to carotid endarterectomy in patients hospitalized for stroke / TIA	P0 (1998-1999)	69	375	97.1	95.5	100.0	100.0	97.0	95.4
	P1 (2000-2001)	90	371	91.1	89.2	100.0	100.0	90.9	89.1
	P2 (2002-2003)	61	315	86.9	92.7	100.0	100.0	86.7	92.6
	P3 (2004-2005)	41	229	92.7	87.3	100.0	100.0	92.1	87.2
	P4 (2006-2007)	40	159	82.5	86.2	100.0	50.0	82.1	86.6
Diagnostic ultrasound, radionuclide ventriculography, or left ventriculogram within 3 months, before or after, initial diagnosis of heart failure	P0 (1998-1999)	943	5,924	58.7	56.0	58.3	51.6	58.8	56.3
	P1 (2000-2001)	929	3,729	57.6	60.0	65.6	56.9	56.7	60.2
	P2 (2002-2003)	646	2,978	59.1	64.0 ‡	56.9	59.9	59.4	64.2 †
	P3 (2004-2005)	1,194	2,582	46.6	62.7 ¶	52.4	62.0	46.1	62.7 ¶
	P4 (2006-2007)	371	2,176	61.2	64.2	56.5	66.7	61.5	64.1
Diagnostic ultrasound, radionuclide ventriculography, or left ventriculogram within 3 months, before or after, hospitalization for heart failure	P0 (1998-1999)	240	1,994	83.3	83.2	88.1	84.5	82.3	83.1
	P1 (2000-2001)	397	1,775	75.8	76.1	75.6	71.4	75.9	76.4
	P2 (2002-2003)	278	1,586	78.1	78.5	80.0	75.9	77.8	78.7
	P3 (2004-2005)	290	1,530	69.0	78.4 ¶	69.7	81.7	68.9	78.2 ‡
	P4 (2006-2007)	263	1,314	77.9	79.3	66.7	85.2	78.8	79.0

Electrocardiography within one month before or three months after initial diagnosis of heart failure	P0 (1998-1999)	966	6,177	68.5	68.1	65.5	67.3	69.1	68.1
	P1 (2000-2001)	929	3,729	68.5	67.0	75.6	67.2	67.7	67.0
	P2 (2002-2003)	646	2,978	73.2	68.6 †	67.7	62.3	73.8	68.9 †
	P3 (2004-2005)	1,194	2,582	59.4	70.3 ¶	60.0	63.6	59.4	70.6 ¶
	P4 (2006-2007)	371	2,176	67.7	68.0	87.0	65.6 †	66.4	68.1
Chest X-Ray within one month before or three months after initial diagnosis of heart failure	P0 (1998-1999)	937	6,092	64.5	64.5	64.3	64.7	64.5	64.5
	P1 (2000-2001)	929	3,729	67.7	65.4	73.3	65.9	67.1	65.4
	P2 (2002-2003)	646	2,978	60.7	66.2 ‡	56.9	64.7	61.1	66.3 †
	P3 (2004-2005)	1194	2,582	56.8	64.9 ¶	64.6	62.8	56.2	65.0 ¶
	P4 (2006-2007)	371	2,176	64.7	64.5	60.9	63.4	64.9	64.5
At least one inpatient or outpatient visit, within four weeks following initial diagnosis of gastrointestinal bleeding	P0 (1998-1999)	569	2,806	77.7	80.0	80.0	80.5	77.4	79.9
	P1 (2000-2001)	821	2,518	71.6	68.7	73.8	73.9	71.4	68.3
	P2 (2002-2003)	771	2,101	70.8	71.5	66.7	74.8	71.2	71.3
	P3 (2004-2005)	590	1,567	71.5	75.7 †	67.4	66.3	71.8	76.2 †
	P4 (2006-2007)	280	1,391	72.5	76.3	72.0	78.2	72.5	76.2
Colonoscopy or barium enema within one month before or three months after initial diagnosis of iron deficiency anemia	P0 (1998-1999)	1,450	7,203	47.0	49.5	53.1	49.4	45.9	49.5 †
	P1 (2000-2001)	1,803	5,188	46.3	36.8 ¶	43.9	35.1	46.5	36.9 ¶
	P2 (2002-2003)	1,020	4,047	51.3	45.4 ¶	55.8	39.9 †	50.9	45.7 ‡
	P3 (2004-2005)	1,146	3,098	57.4	53.0 ‡	52.1	42.9	57.8	53.6 †
	P4 (2006-2007)	379	2,674	49.3	50.5	58.6	45.3	48.6	50.7
Hemoglobin or hematocrit test within one to six months after initial diagnosis of anemia	P0 (1998-1999)	339	1,999	33.3	29.2	28.3	26.3	34.1	29.5
	P1 (2000-2001)	713	2,070	25.9	22.9	27.7	28.1	25.7	22.5
	P2 (2002-2003)	580	1,989	32.6	24.1 ¶	32.8	26.1	32.6	24.0 ¶
	P3 (2004-2005)	686	1,655	21.1	25.9 †	16.7	30.8	21.5	25.5 †
	P4 (2006-2007)	322	1,660	27.6	24.9	34.5	24.7	27.0	24.9

TIA: transient ischemic attack
Significance denoted as: †: p<0.05; ‡: p<0.01; ¶: p<0.001
Dashed line differentiates pre- and post-cancer diagnosis era

[4] Eight weeks after the dissertation was defended on 12/04/2009, the SEER-Medicare Program Reported an error in preparing 2004 physician claims data. http://healthservices.cancer.gov/seermedicare/seermed_2004_data_letter.pdf Therefore, the use of necessary care might be underestimated between 2004 and 2005 (i.e. Period 3).

Table 17. Comparison of composite scores between cancer and non-cancer groups [5]

		Sample size		Proportion of eligible care was received (%)					
		Both		Both		Black		White	
Indicator	Period (year	Cancer	Non-cancer	Cancer	Non-cancer	Cancer	Non-cancer	Cancer	Non-cancer
Clinical assessment in chronic conditions	P0 (1998-1999)	9,053	43,926	83.8	81.0 ¶	71.7	66.3 ‡	85.0	81.8 ¶
	P1 (2000-2001)	8,599	39,953	96.0	82.5 ¶	89.8	67.8 ¶	96.6	83.3 ¶
	P2 (2002-2003)	7,747	35,981	94.9	84.2 ¶	87.0	70.6 ¶	95.6	84.9 ¶
	P3 (2004-2005)	6,865	32,223	80.3	85.8 ¶	75.6	73.3	80.7	86.4 ¶
	P4 (2006-2007)	5,945	28,176	92.9	86.9 ¶	86.2	73.4 ¶	93.5	87.5 ¶
Management of chronic condition	P0 (1998-1999)	2,223	12,245	63.1	59.2 ¶	55.0	47.5 †	64.0	59.9 ¶
	P1 (2000-2001)	3,398	16,051	64.2	61.7 ‡	53.1	48.6	65.3	62.5 ¶
	P2 (2002-2003)	3,685	17,098	66.2	63.2 ¶	55.7	53.2	67.1	63.7 ¶
	P3 (2004-2005)	4,009	17,060	59.4	65.0 ¶	52.2	53.6	60.1	65.6 ¶
	P4 (2006-2007)	3,722	16,255	64.8	65.8	59.6	56.4	65.2	66.3
Follow-up after hospitalization	P0 (1998-1999)	885	6,161	76.4	74.3	68.4	68.3	77.4	74.8
	P1 (2000-2001)	1,441	6,016	74.4	76.8 †	70.4	68.0	74.8	77.5 †
	P2 (2002-2003)	1,236	5,879	79.4	78.1	78.9	70.9	79.4	78.6
	P3 (2004-2005)	1,189	5,732	70.8	79.9 ¶	69.4	72.3	70.9	80.4 ¶
	P4 (2006-2007)	1,117	5,471	77.1	79.2	70.3	67.4	77.7	79.8
Avoidable adverse outcomes	P0 (1998-1999)	3,950	19,975	96.9	94.7 ¶	95.2	91.8 ‡	97.0	94.9 ¶
	P1 (2000-2001)	5,815	25,204	97.4	97.0 †	95.8	95.3	97.5	97.5 †
	P2 (2002-2003)	5,913	25,911	98.1	97.7 †	97.3	96.4	98.1	97.8 †
	P3 (2004-2005)	5,760	25,190	98.1	97.8 †	97.3	96.4	98.2	97.9
	P4 (2006-2007)	5,195	23,337	98.3	97.9 ‡	96.6	96.9	98.5	98.0 ¶
Work-up at initial diagnosis	P0 (1998-1999)	2,640	13,821	55.4	57.0	58.9	55.3	54.9	57.2 †
	P1 (2000-2001)	3,277	11,597	49.8	47.7 †	50.0	47.2	49.8	47.7 †
	P2 (2002-2003)	2,465	9,910	53.0	50.5 †	53.3	48.3	53.0	50.6 †
	P3 (2004-2005)	2,801	8,331	48.9	53.8 ¶	50.3	47.5	48.8	54.1 ¶
	P4 (2006-2007)	1,394	7,276	52.6	52.9	61.8	50.9 †	51.9	53.0
Overall use of care	P0 (1998-1999)	9,053	43,926	77.4	73.8 ¶	64.2	58.4 ¶	78.4	74.5 ¶
	P1 (2000-2001)	8,599	39,953	85.7	75.6 ¶	78.5	62.0 ¶	86.4	76.4 ¶
	P2 (2002-2003)	7,747	35,981	86.8	78.6 ¶	79.1	66.0 ¶	87.5	79.3 ¶
	P3 (2004-2005)	6,865	32,223	76.0	80.9 ¶	72.6	69.5	76.3	81.5 ¶
	P4 (2006-2007)	5,945	28,176	86.4	82.1 ¶	80.7	71.6 ¶	86.9	82.6 ¶

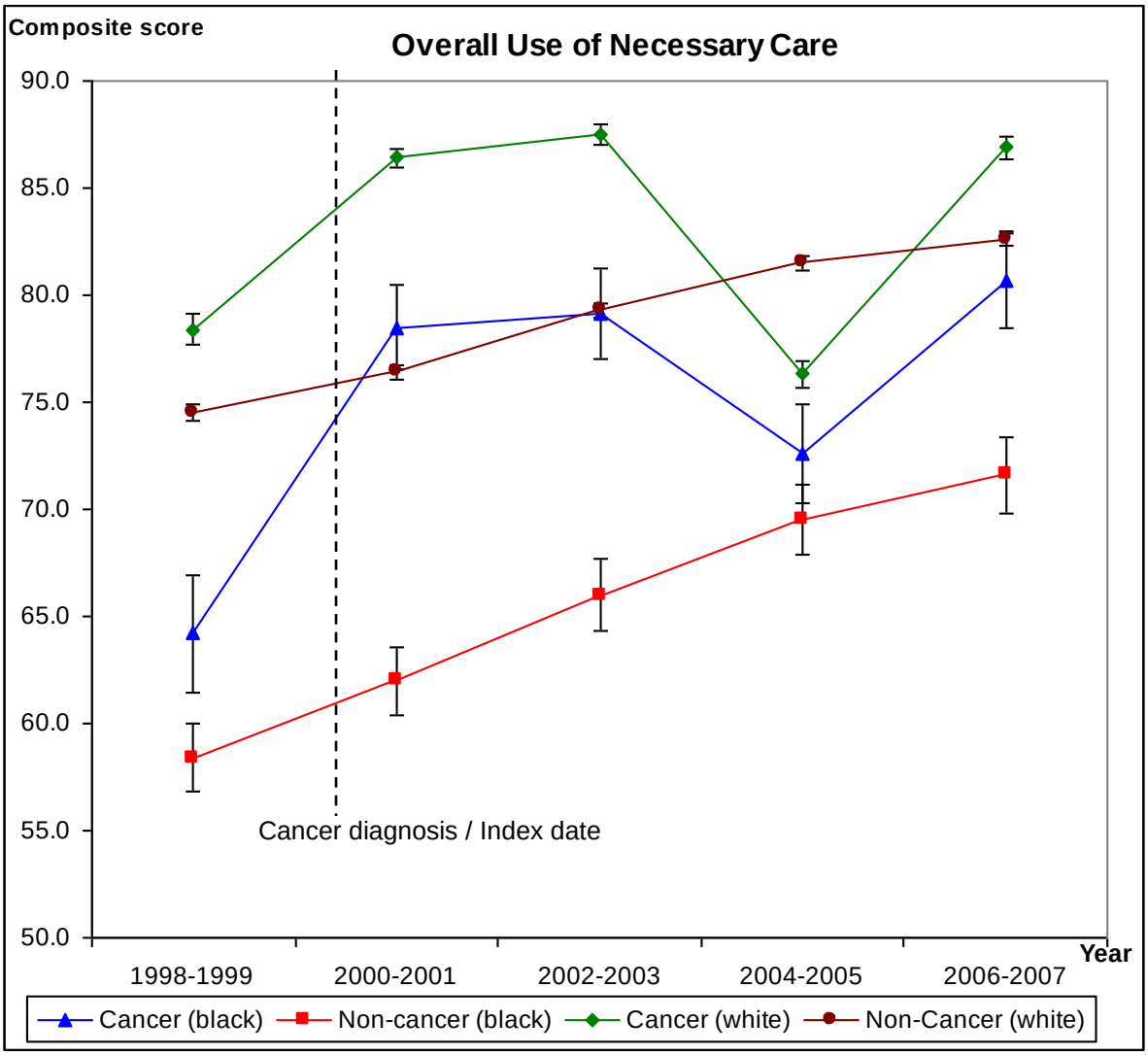
Significance denoted as: †: p<0.05; ‡: p<0.01; ¶: p<0.001 ; Dashed line differentiates pre- and post-cancer diagnosis era

[5] Eight weeks after the dissertation was defended on 12/04/2009, the SEER-Medicare Program Reported an error in preparing 2004 physician claims data. http://healthservices.cancer.gov/seermedicare/seermed_2004_data_letter.pdf Therefore, the use of necessary care might be underestimated between 2004 and 2005 (i.e. Period 3).

Overall Use of Care

Figure 7 shows the time trend for the composite score of overall use of necessary care by race. In white men, the composite score of the comparison group improved steadily over time. Before 2000, the white cancer survivors received a higher proportion of necessary care than the white men who never had cancer. The difference in composite score between cancer survivors and individuals without cancer became larger in Period 1 and diminished across time. However, the composite score of cancer survivors became significantly lower than the comparison group's score in Period 3. Similar time trend was observed among black men. Black cancer survivors received higher proportion of necessary care than black men without cancer in Period 0. The difference became larger in Period 1 and diminished over time. However, the composite score of black cancer survivors dropped in Period 3 and was not significantly different from the score of black men without cancer.

Figure 7. Time trend of overall use of necessary care



The vertical bars represent a 95% confidence interval for each composite score.
Note: the drop in use of care might be caused by data error in 2004 physician claims.
http://healthservices.cancer.gov/seermedicare/seermed_2004_data_letter.pdf

We used a GEE model to examine whether cancer survivors had a higher composite score for overall use of necessary care compared to men without cancer after 2000 controlling for other factors (Table 18). In the GEE model, variables with positive coefficients are associated with more use of necessary care. The result indicates that the use of necessary care increased over time because the time indicators were all significantly positive as compared with baseline. Elder age, higher income, and higher comorbidity index scores were associated with higher use of necessary care. Living in an area with higher proportion of persons without high school degree was associated with less use of necessary care.

Wald tests were conducted to further examine the difference between men with and without cancer and between black and white men during various time periods (Table 19). In general, cancer survivors received more necessary care than men without cancer did. At baseline (i.e., Period 0), cancer survivors received significantly more necessary care than men without cancer did (3.81, $p<0.001$). The difference in use of necessary care became larger after 2000, and the largest difference was observed in Period 1 (10.08, $p<0.001$). However, cancer survivors used significantly less necessary care than men without cancer did in Period 3 (-5.39, $p<0.001$). In addition, racial disparity in use of necessary care was consistently observed among elderly men. Although the racial difference diminished over time, black men still received significantly less care than white men did.

Another GEE analysis was conducted for prostate cancer survivors only to identify the factors associated with use of necessary care (Table 18). We found elder age, and higher comorbidity index score were associated with less use of necessary care. Higher household income, ever having married, and ever receiving surgery or XRT were associated with more use of necessary care. We also examined the relationship between type of care provider and use of necessary care. Survivors who visited both PCPs and prostate cancer

specialists received significantly much more care than those who visited neither of them ($p<0.001$). However, survivors who visited only PCPs or only specialists received comparable amount of care than those who visited both types of provider.

Wald tests were conducted to examine the racial difference in use of necessary care across time. In Period 0, black survivors received significantly less care than white survivors did (-5.75, $p<0.001$), but the difference diminished after cancer diagnosis (Table 19). Black survivors still received less care in Period 1 (-2.95, $p<0.001$) and Period 2 (-2.20, $p<0.01$). However, no such significant difference was observed in Period 3 (1.07, $p=0.23$) and Period 4 (-0.63, $p=0.51$).

Table 18. Results of generalized estimating equations (GEE) analyses of use of necessary care

Variables	All patients	Cancer group only
Cancer (non-cancer is the reference)	3.81 (0.36) ¶	
Black race (white race is the reference)	-13.77 (0.62) ¶	-5.75 (0.75) ¶
Age (as of 01/01/00)	0.11 (0.02) ¶	-0.06 (0.03) †
Median annual household income in $1,000	0.03 (0.01) ¶	0.01 (0.01)
Percent persons with less than a high school diploma	-0.27 (0.01) ¶	-0.02 (0.01)
Comorbidity Index score	1.64 (0.05) ¶	-1.40 (0.15) ¶
Time indicators (1998 – 1999 is the reference)		
Period 1 (2000 - 2001)	1.07 (0.17) ¶	-0.81 (0.32) †
Period 2 (2002 - 2003)	3.24 (0.17) ¶	1.16 (0.32) ¶
Period 3 (2004 - 2005)	4.71 (0.18) ¶	-1.86 (0.33) ¶
Period 4 (2006 - 2007)	5.22 (0.20) ¶	2.27 (0.35) ¶
Interaction terms		
Black * cancer	4.29 (1.00) ¶	
Cancer * Period 1	6.27 (0.39) ¶	
Cancer * Period 2	4.20 (0.40) ¶	
Cancer * Period 3	-9.22 (0.42) ¶	
Cancer * Period 4	0.02 (0.44)	
Black * Period 1	2.93 (0.62) ¶	2.80 (0.99) ‡
Black * Period 2	3.83 (0.65) ¶	3.55 (1.03) ‡
Black * Period 3	5.90 (0.68) ¶	6.82 (1.08) ¶
Black * Period 4	6.13 (0.73) ¶	5.12 (1.15) ¶
Marital status (ever married is the reference)		
Never married		-0.85 (0.51)
Unknown		1.28 (0.41) ‡
Cancer grade (well differentiated is the reference)		
Moderately differentiated		-0.64 (0.55)
Poorly differentiated		-1.09 (0.59)
Undifferentiated		-1.06 (2.15)
Unknown or missing		-1.02 (0.80)
Cancer-related treatment (watchful waiting is the reference)		
Surgery (no surgery is the reference)		1.41 (0.37) ¶
Radiation therapy (no radiation therapy is the reference)		2.57 (0.32) ¶
Type of care provider (visit both PCP or specialist is the reference)		
Visit PCP only		-0.84 (0.31) ‡
Visit specialist only		-0.09 (0.39)
Visit neither PCP nor specialist		-53.95 (0.35) ¶
Constant	68.52 (1.77) ¶	93.81 (2.38) ¶
Number of observations (n)	218,472	38,209

Standard error is listed in parentheses; Significance denoted as: †: p<0.05; ‡: p<0.01; ¶: p<0.001

Note: A survivor's registry site is also controlled in the model (results not shown)

Note: comorbidity index score and type of care provider are time-variant variables. Charlson Comorbidity Index was used for the GEE model using the entire sample. National Cancer Institute Combined Index was used for the subgroup analysis using prostate cancer survivors only.

Note: the drop in use of care might be caused by data error in 2004 physician claims. http://healthservices.cancer.gov/seermedicare/seermed_2004_data_letter.pdf

Table 19. Time trend of group difference in overall use of necessary care

	All subjects		Cancer group only
	Cancer survivors vs. individuals without cancer	Black men vs. white men	Black survivors vs. white survivors
Time period			
0 (1998 - 1999)	3.81 ¶	-13.77 ¶	-5.75 ¶
1 (2000 - 2001)*	10.08 ¶	-10.84 ¶	-2.95 ¶
2 (2002 - 2003)*	8.01 ¶	-9.94 ¶	-2.20 ‡
3 (2004 - 2005)*	-5.39 ¶	-7.87 ¶	1.07
4 (2006 - 2007)*	3.83 ¶	-7.64 ¶	-0.63

*Difference between groups is the sum of baseline difference and time interaction from the corresponding GEE model. Wald test is conducted to evaluate whether there was group difference at each time point.
Significance denoted as: †: p<0.05; ‡: p<0.01; ¶: p<0.001

5.5 Discussion

Previous studies have criticized the overdiagnosis and overtreatment of low-risk prostate cancer patients (15-17). Since prostate cancer is a latent disease, approximately 23% to 42% of screen-detected cases would not have been diagnosed before death in the absence of PSA screening (15, 96). Although it is unclear whether cancer treatment can improve survival among patients with localized or regional prostate cancer, previous studies found that cancer treatments often cause adverse effects, such as incontinence and erectile dysfunction (15, 22, 23). However, prostate cancer and its treatment may constitute only a fraction of medical history for many survivors. Other comorbid conditions may play a more important role for a survivor's health, longevity, and physical function. However, the diagnosis and management of other comorbid conditions have not been the focuses of previous cancer survivorship research.

In this study, we found that prostate cancer survivors consistently used more necessary care than individuals without cancer did. Although the difference in use of necessary care existed even before cancer diagnosis, the magnitude of difference became larger after diagnosis. It is possible that prostate cancer was diagnosed because cancer survivors already had more contact with their health care providers before their cancer diagnosis than individuals without cancer had. After cancer diagnosis, more survivors started to make regular visits to their care providers and received better care from them. Therefore, a diagnosis of prostate cancer may represent “a wake-up call” for elderly men to be engaged in the health care system.

Black patients are traditionally a vulnerable population experiencing poor quality of care (34-36). As we expected, black patients consistently received less necessary care for their comorbid conditions, regardless of whether they were cancer survivors or not. Interestingly, we found that a cancer diagnosis created an opportunity to reduce this racial disparity. After their cancer diagnosis, black prostate cancer survivors increased their overall use of necessary care. This main reason for this finding was because more black patients began to have regular office visits to their physicians after cancer diagnosis. Therefore, a prostate cancer diagnosis may create an opportunity for this population to be more aware of their health and to further improve their quality of care.

Among cancer survivors, the use of necessary care surprisingly dropped between 2004 and 2005 but increased back between 2006 and 2007. Although this finding might be partly explained by the data error in 2004 physician claims, another potential explanation is the enactment of Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA). The MMA reduced the reimbursements for Medicare Part B chemotherapy drugs from 95% of average wholesale prices in 2003 to 80-85% in 2004 (97). In 2005, the reimbursements were further reduced to 106% of average selling prices which tend to be

substantially lower than the average wholesale prices (97). To compensate the potential loss, the MMA also increased the reimbursements for administration services of chemotherapy provided by oncologists substantially (97, 98). However, the increases in reimbursements for corresponding services provided by urologists were much smaller (97, 98). Therefore, it is possible that some urologists may limit the number of Medicare patients they see and send their patients to hospital. Since some patients may feel inconvenient to receive their care from hospital, their adherence to therapy could decrease (98). Therefore, the implementation of MMA may limit a survivor's access to urologists, who tend to provide a large proportion of health care for prostate cancer survivors (Chapter 4). In 2006, urologists were allowed to obtain chemotherapy drugs for their patients from a third party contractor through a process called competitive acquisition (97, 98). This policy change may explain the improvement in use of necessary care from 2004-2005 to 2006-2007. Further studies are necessary to examine the impact of MMA on quality of care and health outcomes on prostate cancer survivors.

This study, which is the first to examine a wide range of quality of care indictors for non-cancer conditions among prostate cancer survivors, has several strengths. Although the ACE-PRO indicators have been used to study the access to and quality of care associated with various geographic and socioeconomic factors, they have never been used to assess the care among prostate cancer survivors. Our longitudinal study design allows us to measure the use of necessary care pre- and post-cancer diagnosis, instead of measuring it cross-sectionally. Therefore, we are able to examine the time trend of care and the potential effect of cancer diagnosis. In this study, we included all of the 5-percent Medicare qualified patients in our non-cancer group and did not to use a matched control group. Results from our non-cancer group allow us to have a clear picture about the use of necessary care in the general population without cancer.

The main design issues of this observational study results from the limitations of administrative datasets. The overall population covered by SEER is comparable to the general US population with regard to measures of poverty and education (68). However, the results of this study may not be generalizable to non-SEER regions because Medicare beneficiaries living in SEER regions are less likely to be white, reside in rural areas, and enroll in managed care plans (70). Medicare beneficiaries who were diagnosed with cancer before age 67 were excluded from our analyses because we were unable to obtain their claims data before Medicare enrollment. Therefore, the findings from our study may not be generalized to younger prostate cancer survivors. In addition, the results from our study may not be generalized to HMO enrollees because information about their use of care was not available. Since risk factors, treatment options, and survival rates vary by types of cancer, different cancers may have different influence on comorbidities. Therefore, the results from our study may not be generalized to other types of cancer survivors. The time of a disease's first diagnosis is critical for many of the refined ACE-PRO indicators, especially for initial work-up indicators. Due to data limitations, we were unable to observe the diagnosis of comorbid condition before age of 65. The first diagnosis of a comorbid condition that we observed in the Medicare claims may not be the true initial diagnosis. However, we expected that this type 1 error has a similar effect on the cancer and non-cancer groups. When we calculated composite scores to evaluate the use of care, the indicators of necessary care were not weighted. However, some indicators may play more important roles for a patient's health than others.

For each ACE-PRO indicator, only patients who remained alive during the entire two-year time frame were included. Therefore, we were unable to fully examine the use of care for those who died during a time period. Since we only included survivors in our analyses, we might observe a "survivor effect" in the time trends of use of care. That is, those

individuals who remained alive at a time point may be healthier than those individuals who died before that time. We assumed that cancer and non-cancer patients who died during the study periods were un-informatively censored (i.e., death during follow up is independent with use of care). The issues of uninformative censoring assumption should be minor because the five-year relative survival rate of localized or regional prostate cancer patients is approximately 100% as compared with the non-cancer population (9). Therefore, we expected the survivor effect to be similar between cancer and non-cancer groups. In sensitivity analysis, we restricted our samples to those individuals who survived during the entire study time frame and obtained similar results as the findings our primary analyses (results not shown).

The ACE-PRO indicators were originally developed to measure underuse of necessary care. Fulfilling the requirement of an indicator does not guarantee optimal use of care. Further studies are necessary to develop measurements for detecting overuse or misuse of necessary care. In addition, the majority of the ACE-PRO quality of care indicators measure whether a patient visited his care providers when necessary. Other indicators measure whether a patient received necessary examinations or treatment for his comorbid conditions. However, none of them measures the quality of care by evaluating a patient's health outcomes. Since results from laboratory report are generally unavailable in claims data, further studies are necessary to assess a survivor's quality of care using his medical record.

5.6 Conclusion

In our previous study, we found that black cancer patients consistently had higher comorbidity index scores than white cancer patients did (Chapter 4). We also found that the racial difference in comorbidity became larger after cancer diagnosis. One explanation is

that more previously underdiagnosed comorbid conditions were detected after cancer diagnosis among black survivors than among white survivors. In this study, we found that cancer patients increased their use of necessary care after cancer diagnosis. The magnitude of improvement was more substantial among black patients than among white patients. Therefore, a diagnosis of prostate cancer may represent an opportunity to eliminate racial disparity in quality of care. In the next chapter, we examine whether racial disparity in mortality of prostate cancer survivors remains after we control for time-variant comorbidity index scores (i.e., severity) and use of care for comorbid conditions.

CHAPTER 6. RACIAL DISPARITY IN SURVIVAL AMONG ELDERLY MEN DIAGNOSED WITH PROSTATE CANCER IN THE UNITED STATES

6.1 Abstract

Background: Racial disparity in survival is consistently observed among prostate cancer survivors. This study compared various methods to examine racial disparity and other risk factors for overall, cancer, and non-cancer mortality.

Methods: The sample consisted of 882 black and 6,613 white patients diagnosed with stage 1-4 prostate cancer between the ages of 67-84 in 2000 from the Surveillance, Epidemiology, and End Results-Medicare Program. The claims of each patient were examined from the cancer diagnosis until his death or December, 2007. Proportional hazards (PH) models were conducted to examine racial disparity in overall mortality controlling for time-varying comorbidity and use of necessary care, neither of which have been controlled for in previous studies. PH and competing-risk models were conducted subsequently to identify risk factors for cancer and non-cancer mortality.

Results: After controlling for age, registry site, marital status, and socioeconomic status, black survivors had a significant higher risk for overall mortality than white survivors (hazard ratio [HR]=1.24; 95% confidence interval [CI]: 1.10-1.41). The HR decreased after additional adjustment for cancer stage, grade, and treatment (HR=1.15, 95%CI: 1.01-1.30). The racial difference was not significant after further adjustment for time-varying comorbidity and use

of care (HR=1.07, 95%CI: 0.95-1.22). Although PH and competing-risk models yielded similar results for cancer-specific mortality, their findings were somewhat different for non-cancer mortality. Use of care, a potentially modifiable factor, was consistently associated with lower risks of mortality.

Conclusion: Racial disparities in prostate cancer survival are due to differences in SES, stage, grade, primary treatment, comorbidities, and use of care. Efforts to increase early diagnosis, appropriate treatment, and post-diagnosis use of care among black survivors may be necessary to improve their survival and further eliminate racial disparities in prostate cancer survival.

Keywords: prostate cancer, survival, racial disparity, risk factor, comorbidities, use of care, competing-risk model

6.2 Introduction

Racial disparity in health outcomes of prostate cancer survivors has been observed in many previous studies (8, 24-27). Prostate cancer incidence and mortality rates for black men are approximately twice the rates for white men (9). Black survivors are more likely to be diagnosed with advanced prostate cancer (31) and also have a lower survival rate than white survivors (26, 27, 29-31). Various studies have tried to identify the factors that may explain the racial differences in overall and cancer mortality rates. A study using California cancer registry data found that racial disparities in survival were completely explained by treatment option, stage, grade, year of diagnosis, and socioeconomic status (SES) (30). However, other studies using data from national registries found that even after controlling for SES, treatment options and pre-existing comorbidities, black survivors diagnosed with

localized prostate cancer still had worse overall and prostate cancer survival rates than those observed in white men (27, 29). A meta-analysis found that black survivors had higher rate of cancer recurrence, prostate cancer mortality, and overall mortality than white survivors (33). After controlling for comorbidity, type of prostate cancer screening, or access to health care, racial differences diminished for overall mortality but still existed for cancer recurrence and prostate cancer mortality.

Comorbidity is an important predictor for mortality rates among cancer survivors (27, 29, 33, 40). However, previous cancer studies usually controlled only for the pre-existing comorbidity before the cancer diagnosis in their survival analyses (27, 29, 33). In a previous study, we found that comorbidity index score (i.e., comorbidities) increased after prostate cancer diagnosis, especially among black survivors (Chapter 4). Not only did the black prostate cancer survivors continuously have a higher average comorbidity score than white survivors, the magnitude of difference increased after cancer diagnosis. Therefore, allowing comorbidities to vary over time (i.e., with a time-varying comorbidity index score) may better reflect the longitudinal racial difference in risks of dying from causes other than cancer. In another study, we found that black prostate cancer survivors consistently underutilized necessary care for their comorbidities than the white survivors (Chapter 5), but the difference diminished after cancer diagnosis. Therefore, a diagnosis of prostate cancer may create an opportunity not only to identify previously underdiagnosed comorbidities among black patients but also to improve their quality of care. Effective control of comorbidity in black cancer patients may help improve life expectancy and lead to a reduction in survival disparities (37). However, the use of necessary care for comorbidities has never been controlled for in previous cancer survival analyses.

Although the majority of prostate cancer survivors die from causes other than cancer (9), most of previous cancer survivorship studies focused on overall or cancer-specific

mortality (26, 27, 29-31, 33), rather than non-cancer mortality. Since prostate cancer is highly survivable, it also is very important to identify the risk factors for non-cancer mortality with appropriate methodology. Typically, cancer survivorship studies used proportional hazard (PH) model (75) to identify risk factors for cancer-specific mortality (26, 27, 29-31). Patients who died from causes other than cancer were treated as censored cases, which implicitly assumed the risks of dying from cancer and other causes are independent.

The purpose of this study is to adopt various methods to assess racial disparity and other risk factors for mortality among prostate cancer survivors. We used the data from the Surveillance, Epidemiology, and End Results registry (SEER)-Medicare Program to identify the prostate cancer patients who were diagnosed in 2000. Each patient's claims were examined from diagnosis until death or December 31st, 2007, whichever came first. We first examined whether a racial disparity in survival remained after controlling for time-varying comorbidity and use of necessary care, neither of which have been controlled for in previous studies. We then investigated the effect of controlling for static or time-varying comorbidity on overall mortality. Finally, we compared the findings from PH and competing-risk models examining risk factors for cancer and non-cancer mortality.

6.3 Methods

Data Sources

The SEER-Medicare data are population-based data that combine SEER cancer registry information with Medicare enrollment and claims files (70, 72). We used the latest data from the SEER-17 cancer registries, including Arizona Native Americans, Alaska Natives, nine states (California, Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah), and seven regions (Atlanta, Detroit, rural Georgia, Los Angeles, San Francisco, San Jose, and Seattle). The SEER Program routinely collects data on

patient demographics, marital status, primary tumor site, stage at diagnosis, primary course of treatment, and cause of death. It also collects SES information measured from the US Census Bureau that reflect the characteristics of a census tract in which a patient resided (69). The aggregated SES variables include median household income, percentage of residents living under poverty level, and educational status at census tract level (69, 70). SEER registry data are linked with Medicare claims and include a beneficiary's disease diagnoses, treatments, and services received. However, these health care data are unavailable for health maintenance organization (HMO) enrollees, services not covered by Medicare (e.g., long term care), services provided by Veterans Affairs or Medicaid, or by Medicare supplement programs (i.e., Medigap policy) (70).

Cohort Selection

Men diagnosed with localized, regional, and distant prostate cancer in 2000 were included in this study. The data of each survivor were examined for up to eight years, beginning from the month of cancer diagnosis through his death or December, 2007, whichever came first. To be eligible for inclusion in the study, survivors must have been continuously enrolled in Medicare Part A and Part B during the entire study period. To observe baseline comorbidity severity and use of necessary care, we included only patients who were diagnosed with prostate cancer at age 67 or older as of January 1, 2000, thus allowing for two years of observation prior to diagnosis. Medicare beneficiaries who were eligible for Medicare because of disability or the presence of end-stage renal disease before age 65 were excluded from the analyses. HMO enrollees also were excluded, as services provided by HMOs are not included in the SEER–Medicare data. Other exclusion criteria included: prior cancer history, diagnosis with a second cancer within six months of diagnosis, noninvasive tumors (i.e., carcinoma in situ), unstaged prostate cancer, diagnosis after age 84, diagnosis at death or via autopsy, and missing income and education information.

Survivors of other races were excluded from the analyses because we focused on the racial difference between black and white survivors, who have the largest survival disparity. Finally, we excluded registries with fewer or equal than 10 black prostate cancer cases in 2000 because black race only consists of a very small proportion of their populations.

Variable Definitions

Demographic variables are available from both SEER and Medicare data, and the information found in the two sources is highly consistent (69). Since a patient's comorbidity and use of care are measured from the Medicare data, we employed Medicare Enrollment Database as our primary source to identify age, race, and vital status when observing inconsistencies between these two data sources. Empirically, data aggregated at the census tract level are more likely to reflect a patient's SES than are zip code level data (69). Therefore, we included median household income, percentage of residents living below poverty level, percentage of residents with less than a high school degree at census tract level from the 2000 Census in our analyses. We identified cancer stage, tumor grade, and marital status from the SEER data.

The date of death is available in both Medicare and SEER data, but is derived from different sources and covers different time periods. The Medicare death date was obtained from Medicare Enrollment Database, which is updated nightly by the Social Security Administration; and includes death data through December, 2007. The SEER death date is primarily obtained from state death certificates, but it is sometimes acquired from the Medicare Enrollment Database when state data are unavailable, whereas SEER Program has this information only until December, 2005. We used Medicare as the primary source to identify time of death for overall mortality because it allows us to have a longer observation timeframe (i.e., up to eight years). However, since the cause of death is only available from

the SEER Program, a patient's data was examined only until December, 2005, when we disaggregated mortality by cause.

The type of primary treatment for prostate cancer was identified from the SEER data and Medicare claims within six months of cancer diagnosis. Surgery is defined as procedures performed with curative intent or in anticipation of a subsequent curative procedure (27). To identify radical prostatectomy and procedures performed on regional lymph nodes, we used: (1) the SEER indicator for whether a cancer-directed surgery was performed; (2) procedure codes from Medicare claims (International Classification of Diseases, 9th Revision, [ICD-9] 60.5 and 60.6; Current Procedural Terminology [CPT] codes 55810, 55812, 55815, 55840, 55842, 55845, 55866); and (3) site-specific surgery codes 30–90 from the SEER data. Radiation therapy (XRT) is defined as external beam therapy, brachytherapy, or therapeutic isotope radiation therapy as listed in the SEER data (63). Specifically, we used: (1) the SEER indicator for whether cancer-directed radiotherapy was performed; (2) ICD-9 procedure codes 92.2x, V58.0, V66.1, V67.1, CPT codes 77301, 77400–77499; revenue center codes 0330–0339 from Medicare claims; and (3) site-specific radiation codes 1–5 from the SEER data to identify XRT. Men who receive both surgery and XRT will be classified as having surgery because some patients may receive XRT after an incomplete or unsuccessful surgery (27, 63).

We measured comorbidity severity using the National Cancer Institute Combined Index (NCICI), which was developed specifically for the use with SEER-Medicare data to adjust for the risk of dying from causes other than cancer (40). We applied the weighting scheme for prostate cancer and accumulated the weighted comorbidities to establish a single index. A higher NCICI score represents more severe health problems. A patient's NCICI score was measured as of December 31st in each of 1999, 2001, 2003, and 2005. The procedures used to calculate NCICI score are described in Chapter 3.

The use of necessary care for non-cancer comorbidities was measured by the refined Access to Care for the Elderly Project (ACE-PRO) indicators from the Medicare Payment Advisory Commission (MedPAC) (64). The refined ACE-PRO indicators evaluate the use of care for clinical assessment and management of chronic condition, follow-up after hospitalization, avoidable adverse outcomes, and work-up at initial diagnosis. We used 34 indicators to examine the use of ambulatory care for medical conditions including anemia, angina, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, depression, diabetes mellitus, gastrointestinal bleeding, hypertension, and stroke or transient ischemic attack. A composite score for overall use of care was calculated for the proportion of qualified necessary care that was received in each two-year period (64). The sum of the number of indicators for necessary care received and possible adverse outcomes avoided was divided by the total number of eligible indicators during each time period. Additional details are provided in Chapter 5.

Statistical Analyses

Kaplan-Meier survival curves (82) were used to compare the unadjusted survival (measured in months) by race and cancer stage. Log-rank tests were conducted to evaluate whether black patients have different survival rates as compared with white patients. We then assessed adjusted racial disparity in overall mortality using Cox proportional hazards (PH) models (75). We compared the hazard ratio (HR) of black race after controlling for factors which have been shown to be potentially responsible for racial disparity, such as a patient's age, registry site, marital status, SES, cancer disease information (i.e., stage, grade, and treatment). Finally, we evaluated the effect of additional adjustment for time-varying NCICI score and use of care on racial disparity in overall survival.

Since prostate cancer is highly survivable, the majority of prostate cancer survivors die from causes other than cancer (9). Prostate cancer and other causes are competing

risks for cancer patients' mortality because a patient who dies from one of these causes can never die from the other. At present, there is no valid mathematic method to examine whether the competing risks are independent (76). However, these risks are very likely dependent because the presence of prostate cancer (i.e., the risk of dying from cancer) may change the risk of dying from other comorbidities. For example, prostate cancer treatments may have negative effects on survivors' cardiovascular disease and mental health (22, 23, 59). In addition, the presence of comorbidities also may complicate treatment management and further affect the risk of dying from cancer. If the competing-risk relationship just described differs by race, the hazard ratio of race directly obtained from a PH model would be biased. To account for the competing risks in our survival analysis, we use the Cumulative Incidence Curve method developed by Fine and Gray (77). Their competing-risk model allows the dependence of competing risks in the PH model and estimates hazard ratios of independent variables for competing risks (i.e., cancer and non-cancer deaths) separately.

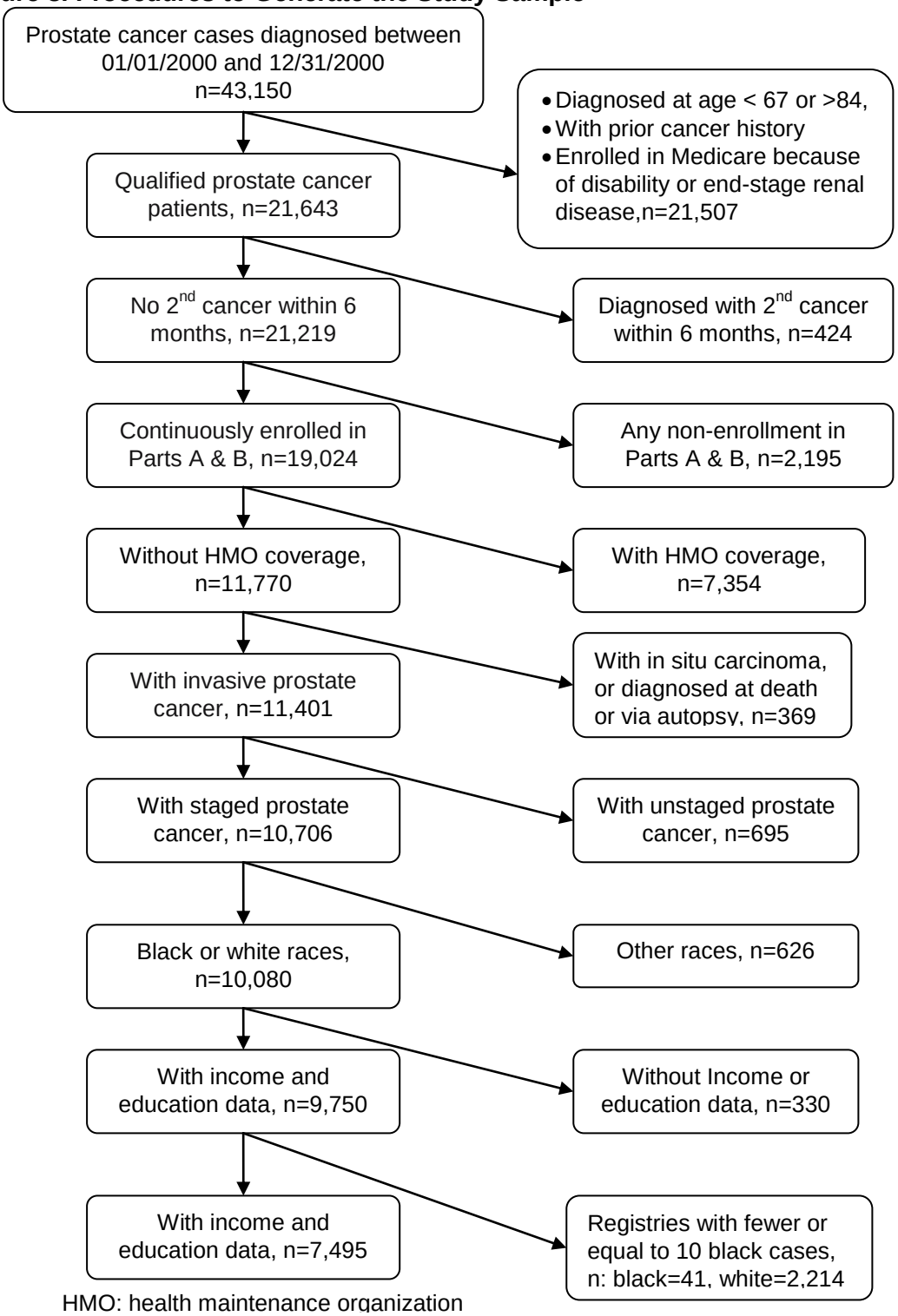
In addition, we identified the risk factors for overall, cancer, and non-cancer mortality among men with prostate cancer. A patient's demographic information, cancer disease information, SES, comorbidity, and use of care were examined in the regression models. We first compared the results of PH models controlling for static or time-varying comorbidity scores. The PH assumption was assessed using both graphical and goodness-of-fit approaches for each variable (83). Finally, we compared the models using PH (i.e., the approach commonly used in the current literature) or competing-risk regression analyses to identify risk factors for dying from cancer or other causes. STATA ® 11.0 (The StataCorp, College Station, TX) was employed to estimate all models, including competing-risk models.

6.4 Results

Study sample

A flow chart of the selection process of study sample is presented in Figure 8. A cohort of 43,150 prostate cancer patients was initially identified in 2000 from the SEER-Medicare data. Employing the inclusion and exclusion criteria described earlier, a total of 7,495 prostate cancer patients comprise our study sample.

Figure 8. Procedures to Generate the Study Sample



HMO: health maintenance organization

Table 20 describes the characteristics of black and white prostate cancer patients. At diagnosis (based on age as of 1/1/2007), both black and white prostate cancer patients were approximately 74 years old. Black cancer patients were more likely to have distant prostate cancer ($p<0.001$), grade 3 and 4 tumors (i.e., more serious, $p<0.01$), and to have died by the end of the observation period ($p<0.001$) than white cancer survivors. White cancer patients were more likely to have received radiation therapy or surgery ($p<0.001$) than black patients. In terms of comorbidities, black cancer patients had more comorbidities prior to cancer diagnosis and continued to have more post-diagnosis comorbidities than white cancer patients ($p<0.001$). Despite a greater burden of comorbidity, black patients were less likely to receive necessary care than white patients at any point in time ($p<0.001$). Demographically black and white cancer patients differed. Compared to white cancer patients, black cancer patients were less likely to have been married, live in areas with lower socioeconomic status, as measured by income and educational attainment in census tract of residence; two-thirds of black cancer patients were obtained from three registries (i.e., Detroit, Louisiana, and New Jersey).

Table 20. Comparison of baseline characteristics between black and white patients

	Black (n=882)	White (n=6,613)	p-value
Mean Age as of 01/01/2000	73.8 (0.15)	74.1 (0.05)	0.10
Mean follow-up time (month)	67.1 (1.01)	74.7 (0.32)	<0.001
Alive as of 12/31/2007 (%)	51.4	62.9	<0.001
Prostate cancer stage (%)			
Localized or regional	90.8	95.7	<0.001
Advanced	9.2	4.3	
Prostate cancer grade (%)			
1 (well differentiated)	3.0	4.7	<0.01
2 (Moderately differentiated)	64.6	67.6	
3 (Poorly differentiated)	24.6	22.2	
4 (Undifferentiated)	0.8	0.3	
Unknown or missing	7.0	5.2	
Primary cancer treatment			
Watchful waiting (%)	35.6	22.4	<0.001
Surgery (%)	24.0	25.2	
Radiation therapy (%)	40.4	52.4	
National Cancer Institute Combined Index			
01/01/2000 (baseline)	0.42 (0.02)	0.32 (0.01)	<0.001
01/01/2002	0.69 (0.03)	0.53 (0.01)	<0.001
01/01/2004	0.86 (0.04)	0.66 (0.01)	<0.001
01/01/2006	1.04 (0.04)	0.84 (0.01)	<0.001
Composite score for use of necessary care			
1998-1999 (baseline)	62.2 (1.38)	78.3 (0.32)	<0.001
2000-2001	77.8 (1.02)	86.4 (0.26)	<0.001
2002-2003	78.7 (1.08)	87.7 (0.26)	<0.001
2004-2005*	72.7 (1.18)	78.3 (0.35)	<0.01
Socioeconomic status			
Median household income ($)	31,205 (577)	58,790 (347)	<0.001
% of persons living below poverty level	20.9 (0.68)	7.0 (0.10)	<0.001
% of persons without a high school education	29.5 (0.48)	15.5 (0.15)	<0.001
Marital status at cancer diagnosis (%)			
Ever married	73.0	80.9	<0.001
Never married	14.7	5.9	
Unknown or missing	12.2	13.2	
Registry site, %			
San Francisco	2.8	4.1	<0.001
Connecticut	3.1	10.0	
Detroit	32.5	12.8	
Atlanta	6.9	3.6	
Los Angeles	8.3	7.9	
Greater California	5.1	21.6	
Kentucky	3.2	8.2	
Louisiana	19.2	8.2	
New Jersey	18.9	23.5	

Standard errors are listed in parentheses

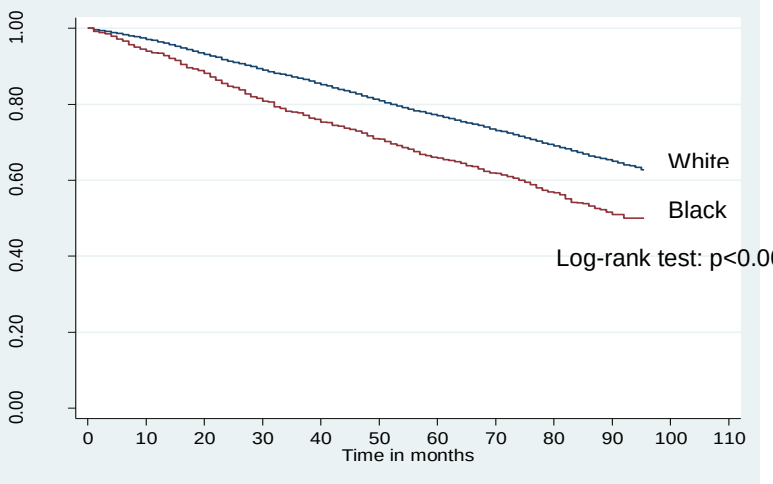
*Note that the decrease in use of care might be caused the data error in 2004 physician claims.

Unadjusted Comparison of Survival by Race

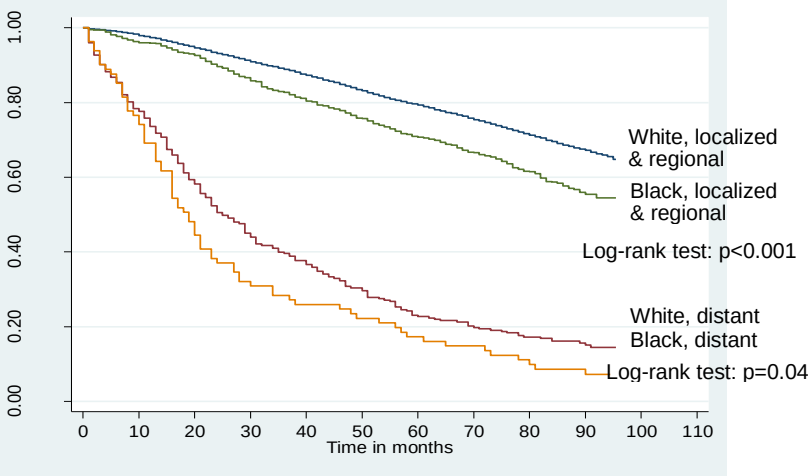
Figure 9 presents a series of comparisons of Kaplan-Meier survival curves by race. Black patients consistently had a lower probability of overall survival as compared with white patients (log-rank test $p< 0.001$) (Figure 9a). Among those with localized or regional prostate cancer, black patients had a significantly lower overall survival rate than white patients ($p<0.001$) (Figure 9b). This racial difference was still statistically significant among those with distant prostate cancer ($p=0.04$). The black cancer patients had significantly higher risks for death from both cancer and non-cancer causes than white patients (log-rank tests, $p<0.001$) (Figures 9c and 9d). At the end of observation period (12/31/2005), black patients were more likely to die both from cancer (15.6% vs. 10.9%, $p<0.001$) and from other causes (21.3% vs. 14.9%, $p<0.001$) than white patients.

Figure 9. Comparison of Kaplan-Meier survival curves by race

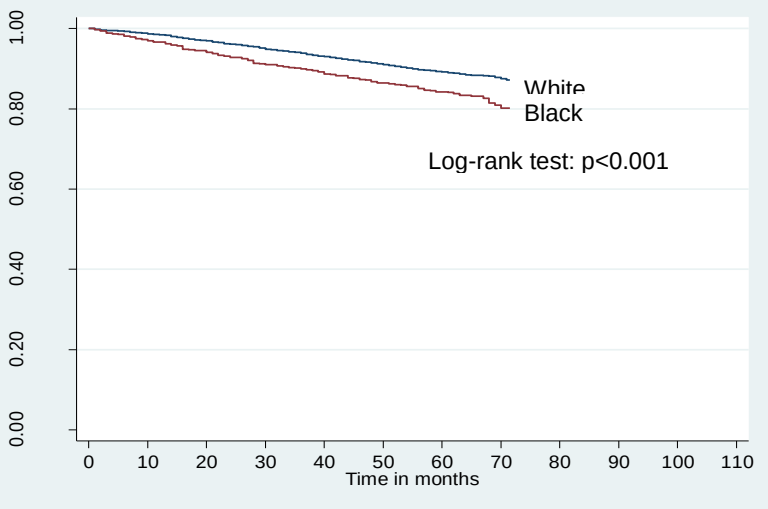
9a. Survival curves for overall mortality by race



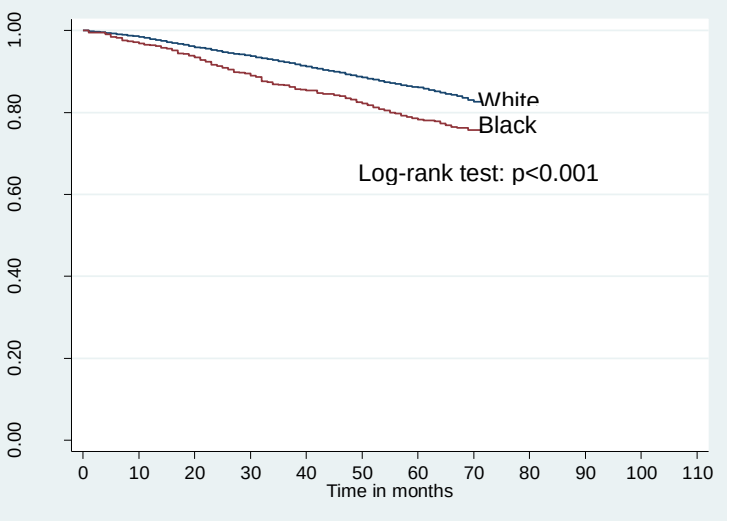
9b. Survival curves for overall mortality by race and cancer stage



9c. Survival curves for cancer mortality by race



9d. Survival curves for non-cancer mortality by race



Note that a patient's data were examined for up to 72 months in figures 9c and 9d due to data limitation.

Effect of Adjustment for Confounders on Racial Disparity

A series of time-to-event regression analyses were conducted with the goal of identification of the factors that potentially explain the racial disparity (Table 21). After adjustment for age only, black survivors had a higher risk for overall mortality than white survivors. Although the HR associated with black race was substantially decreased, it was still statistically significant after adding a patient's registry site, marital status, SES, disease stage, grade, and treatment to the regression model. However, the racial difference in overall mortality was no longer statistically significant after controlling for a time-varying NCICI score and use of necessary care, neither of which have been used in previous studies. Thus, although cancer stage, grade, treatment, and SES were the primary factors responsible for the racial difference in risk of overall mortality, comorbidity and use of necessary care can also explain part of this racial disparity. We used similar procedures to assess racial disparity in cancer and non-cancer mortality using competing-risk models and observed very similar results.

Table 21. Effect of confounder adjustment on racial difference in overall mortality

	Cause of death					
Controlled confounders	All	P value	Cancer	P value	Non-cancer	p value
Age	1.63 (1.47 – 1.81)	<0.001	1.54 (1.28 – 1.85)	<0.001	1.58 (1.35 – 1.85)	<0.001
Age, registry, marital status, SES	1.24 (1.10 – 1.41)	<0.01	1.32 (1.05 – 1.66)	0.02	1.14 (0.93 – 1.39)	0.20
Age, registry, marital status, SES, treatment, stage, grade	1.15 (1.01 – 1.30)	0.03	1.12 (0.89 – 1.42)	0.34	1.11 (0.90 – 1.35)	0.32
Age, registry, marital status, SES, treatment, stage, grade, comorbidity	1.12 (0.99 – 1.27)	0.08	1.13 (0.89 – 1.42)	0.32	1.06 (0.87 – 1.29)	0.57
Age, registry, marital status, SES, treatment, stage, grade, comorbidity, use of necessary care	1.07 (0.95 – 1.22)	0.27	1.09 (0.86 – 1.37)	0.49	1.02 (0.83 – 1.24)	0.87

95% confidence intervals are listed in parentheses.
SES: socioeconomic status
Comorbidity (time-varying) is measured by National Cancer Institute Combined Index (40).
Use of care is measured by indicators from the refined Access to Care for the Elderly Project (64).

Risk Factors for Overall Mortality

We used several PH models to identify the risk factors for overall mortality (Table 22) Race, age, marital status, SES, stage, grade, treatment, comorbidity, and use of care were examined in two PH models. Model 1 adjusted for comorbidity severity at diagnosis, which was the common approach in previous cancer survival analyses. Model 2 controlled for a time-varying comorbidity score. The HRs of distant stage and moderate differentiated cancer grade were not constant over time in Model 2. Thus, the baseline hazard was stratified by these two binary variables in Model 2 to fulfill the PH model assumption.

Table 22. Different Cox PHs models examining risk factors for overall mortality

Variable	Model 1		Model 2	
	HR	p value	HR	p value
Demographic information				
Black race (white race is the reference)	1.08 (0.95 – 1.23)	0.22	1.07 (0.95 – 1.22)	0.28
Age as of 01/01/2000	1.09 (1.08 – 1.10)	<0.001	1.08 (1.07 – 1.09)	<0.001
Socioeconomic status				
Median annual household income in $1,000	1.00 (1.00 – 1.00)	0.02	1.00 (1.00 – 1.00)	0.05
% living below poverty level	1.00 (1.00 – 1.00)	0.81	1.00 (1.00 – 1.00)	0.88
% without a high school education	1.00 (1.00 – 1.01)	0.06	1.00 (1.00 – 1.01)	0.09
Marital status (ever married is the reference)				
Never married	1.08 (0.94 – 1.25)	0.27	1.09 (0.95 – 1.25)	0.23
Unknown or missing	1.00 (0.88 – 1.13)	0.99	1.03 (0.91 – 1.18)	0.60
Cancer grade (well differentiated is the reference)				
Poorly differentiated	2.03 (1.63 – 2.52)	<0.001	2.14 (1.72 – 2.66)	<0.001
Undifferentiated	3.81 (2.34 – 6.21)	<0.001	3.88 (2.38 – 6.32)	<0.001
Unknown or missing	2.16 (1.69 – 2.77)	<0.001	2.21 (1.72 – 2.83)	<0.001
Cancer treatment (watchful waiting is the				
Surgery	0.80 (0.72 – 0.90)	<0.001	0.77 (0.69 – 0.86)	<0.001
Radiation	0.65 (0.59 – 0.72)	<0.001	0.66 (0.60 – 0.72)	<0.001
Comorbidity index score				
Static NCICI at baseline	1.81 (1.71 – 1.92)	<0.001		
Time-varying NCICI			1.77 (1.70 – 1.85)	<0.001
Proportion of necessary care received	0.57 (0.49 – 0.66)	<0.001	0.53 (0.46 – 0.61)	<0.001

95% confidence intervals are in parenthesis.

HR: hazard ratio; NCICI: National Cancer Institute Combined Index

A survivor's registry site is also controlled in the model (results not shown).

Distant stage and moderately differentiated cancer grade are stratified to fulfill the PH assumptions

The results from both models indicate that racial disparity in overall mortality was completely explained by other covariates (Model 2 in Table 22 is the final model shown in Table 21). Elder age and lower family income were predictors for higher mortality rates. In Model 1, the mortality risk of patients with distant prostate cancer was approximately four times of the risk of patients with localized or regional cancer. In addition, higher cancer grade was associated with higher risk of mortality. Patients receiving XRT were more likely to survive than those who did not have XRT. The use of necessary care, which has not been controlled for in previous cancer survival analysis, was a strong predictor for lower mortality rate. An increase in the proportion of necessary care received from 0% to 100% was associated with a reduction in overall mortality rate by half.

Risk Factors for Cancer and Non-cancer Mortality

We also identified the risk factors for cancer (Table 23) and non-cancer (Table 24) mortality using both Cox PH and competing-risk models. We used a PH model and treated survivors who died from other causes as censored cases (i.e., the approach currently used in the literature). Since distant stage cancer violated the PH assumption, it was treated as stratification variables in Model 3 to fulfill the model assumption. We compared these results to a competing-risk model that incorporates the dependence between the risks of cancer and non-cancer mortality. Both models indicated that elder age, distant cancer stage, higher tumor grade, and higher comorbidity score were associated with higher cancer mortality rates. Patients using more necessary care were less likely to die from their prostate cancer.

Table 23. Comparison of results from proportional hazards and competing-risk regression models examining cancer mortality

Variable	Model 3		Model 4	
	Proportional hazards		**Competing-risks**	
	HR	p value	HR	p value
Demographic information				
Black race (white race is the reference)	1.10 (0.88 – 1.38)	0.38	1.09 (0.86 – 1.37)	0.49
Age as of 01/01/2000	1.05 (1.04 – 1.07)	<0.001	1.04 (1.03 – 1.06)	<0.001
Socioeconomic status				
Median annual household income in $1,000	1.00 (0.99 – 1.00)	0.17	1.00 (0.99 – 1.00)	0.16
% living below poverty level	1.00 (0.99 – 1.01)	0.83	1.00 (0.99 – 1.01)	0.98
% without a high school education	1.00 (0.99 – 1.01)	0.92	1.00 (0.99 – 1.01)	0.69
Marital status (ever married is the reference)				
Never married	0.92 (0.71 – 1.19)	0.52	0.88 (0.66 – 1.17)	0.37
Unknown or missing	1.04 (0.82 – 1.32)	0.73	1.02 (0.80 – 1.30)	0.89
Distant stage (local/regional stage is the reference)			7.48 (6.17 – 9.08)	<0.001
Cancer grade (well differentiated is the reference)				
Moderately differentiated	1.86 (1.09 – 3.17)	0.02	1.86 (1.08 – 3.21)	0.03
Poorly differentiated	4.60 (2.23 – 6.76)	<0.001	4.41 (2.55 – 7.63)	<0.001
Undifferentiated	9.84 (4.42 – 21.89)	<0.001	11.12 (5.19 – 23.83)	<0.001
Unknown or missing	4.52 (2.57 – 7.96)	<0.001	4.28 (2.41 – 7.61)	<0.001
Cancer treatment (watchful waiting is the reference)				
Surgery	0.93 (0.77 – 1.14)	0.49	0.96 (0.78 – 1.19)	0.73
Radiation	0.83 (0.70 – 0.99)	0.04	0.92 (0.76 – 1.11)	0.38
Time-varying comorbidity measured by NCICI	1.24 (1.13 – 1.35)	<0.001	1.14 (1.03 – 1.25)	0.008
Proportion of necessary care received	0.56 (0.44 – 0.71)	<0.001	0.63 (0.49 – 0.80)	<0.001

95% confidence intervals are in parenthesis.
HR: hazard ratio; NCICI: National Cancer Institute Combined Index
A survivor's registry site is also controlled in the model (results not shown).
Distant stage is stratified in Model 3 to fulfill the PH assumptions

We also compared PH and competing-risk models for non-cancer mortality. In these models, elder age and higher comorbidity were associated with higher risks for non-cancer mortality, whereas receiving surgery and more necessary care are related to lower risks. PH and competing-risk models yielded different results for prostate cancer stage. Although stage was a predictor for dying from causes other than cancer in the PH model, it was associated with lower risk for non-cancer mortality in the competing risk model.

Table 24. Comparison of results from proportional hazards and competing-risk regression models examining non-cancer mortality

Variable	Model 5		Model 6	
	Proportional hazards		**Competing-risks**	
	HR	p value	HR	p value
Demographic information				
Black race (white race is the reference)	1.02 (0.84 – 1.23)	0.85	1.02 (0.83 – 1.24)	0.87
Age as of 01/01/2000	1.09 (1.08 – 1.11)	<0.001	1.09 (1.07 – 1.10)	<0.001
Socioeconomic status				
Median annual household income in $1,000	1.00 (0.99 – 1.00)	0.05	1.00 (0.99 – 1.00)	0.08
% living below poverty level	1.00 (0.99 – 1.01)	0.88	1.00 (0.99 – 1.00)	0.78
% without a high school education	1.00 (1.00 – 1.01)	0.26	1.00 (1.00 – 1.01)	0.27
Marital status (ever married is the reference)				
Never married			1.14 (0.91 – 1.44)	0.25
Unknown or missing	1.16 (0.96 – 1.40)	0.13	1.15 (0.96 – 1.38)	0.14
Distant stage (local/regional is the reference)	1.31 (1.00 – 1.71)	0.05	0.72 (0.54 – 0.98)	0.04
Cancer grade (well differentiated is the reference)				
Moderately differentiated	1.13 (0.85 – 1.49)	0.41	1.09 (0.82 – 1.44)	0.56
Poorly differentiated	1.36 (1.02 – 1.83)	0.04	1.23 (0.91 – 1.66)	0.18
Undifferentiated	1.70 (0.68 – 4.27)	0.26	1.26 (0.49 – 3.22)	0.63
Unknown or missing	1.44 (1.02 – 2.04)	0.04	1.28 (0.89 – 1.83)	0.18
Cancer treatment (watchful waiting is the reference)				
Surgery	0.73 (0.62 – 0.86)	<0.001	0.71 (0.60 – 0.83)	<0.001
Radiation			0.58 (0.50 – 0.67)	<0.001
Time-varying comorbidity measured by NCICI	2.14 (2.01 – 2.27)	<0.001	2.17 (2.04 – 2.30)	<0.001
Proportion of necessary care received	0.44 (0.35 – 0.55)	<0.001	0.50 (0.40 – 0.62)	<0.001

95% confidence intervals are in parenthesis.
HR: hazard ratio; NCICI: National Cancer Institute Combined Index
A survivor's registry site is also controlled in the model (results not shown).
Never married and radiation therapy are stratified in Mode 5 to fulfill the PH assumptions

6.5 Discussion

Summary of the findings

Racial disparity in survival among prostate cancer patients has been previously reported in multiple studies (26, 27, 29, 30). Although time-varying comorbidities and use of necessary care for non-cancer conditions are potential confounders for racial disparity in survivor, neither of them have been controlled in previous cancer survival analyses. In our

study, we found that these two variables may explain part of racial disparity in mortality, especially in non-cancer mortality. Although the racial disparity in overall mortality was largely explained by racial differences in cancer disease stage, grade, treatment and SES at diagnosis, this racial disparity disappeared after further adjustment for a survivor's time-varying comorbidity score and use of necessary care. We suggest future cancer studies measure these two variables and control them in their survival analyses examining racial disparity in survival.

In our main analysis, a time-varying NCICI score was used to control for comorbidity, but the results from models using a static NCICI at baseline yielded similar results. However, since a time-varying comorbidity score may better reflect the racial difference in risk of non-cancer death than a static score (Chapter 4), future cancer survivorship studies should still consider controlling for dynamic comorbidity in their analytic models. In addition, we measured a patient's comorbidity using the Charlson Comorbidity Index (CCI), which was commonly used in cancer survivorship studies (38). However, measuring comorbidity scores by either CCI or NCICI did not change the findings from our regression models.

Although the majority of prostate cancer survivors die from causes other than cancer (9), non-cancer mortality has not been the focus of current cancer survivorship studies. In our study, we identified the risk factors for dying from cancer or other causes. Since the risks of cancer and non-cancer mortality are likely dependent, a competing-risk model may be more appropriate than a PH model. In fact, the results were very similar from PH and competing-risk models. The only important difference was that distant prostate cancer stage was a risk factor for non-cancer mortality in the PH model but a protective factor in the competing-risk model. Future cancer survivorship studies should adopt competing-risk model, especially when risks of dying from cancer and non-cancer mortality are likely dependent.

MedPAC has used the ACE-PRO indicators to study the access to and quality of care among Medicare beneficiaries (64). However, MedPAC has never investigated whether more use of necessary care in the ACE-PRO indicators is associated better health outcomes. To our knowledge, this study is the first one to control for a patient's use of necessary care in cancer survival analyses. Across different models, we found that more use of care is consistently associated with longer survival. Although this variable is intended to measure the use of necessary care for non-cancer comorbidities, it may be a good proxy for a patient's quality of cancer care. Therefore, more use of necessary care was associated with not only a lower cancer mortality rate but also a lower non-cancer mortality rate. Since use of necessary care is a potentially modifiable factor, policy makers and health care providers should encourage cancer patients to receive more necessary care for their non-cancer comorbidities to improve survival.

Limitations

The main design issues of this study are related to the limitations of administrative datasets. The results of this study may not be generalizable to non-SEER regions because Medicare beneficiaries living in the SEER regions are less likely to be white, live in poverties, reside in rural areas, and enroll in managed care plans (70). Since we only included prostate cancer survivors who were diagnosed in 2000, the results may not be generalized to survivors diagnosed in a different year. In addition, Medicare beneficiaries who were diagnosed with cancer before age 67 were excluded from our analyses because we are unable to obtain their claims data before Medicare enrollment. Thus, the findings from our study may not be generalized to younger prostate cancer patients. The results from our study may not be generalized to HMO enrollees who are excluded from our analyses because information about their medical care is not available. Since risk factors, treatment options, and survival rates vary by types of cancer, different cancers may have different

influence on comorbidities. Therefore, the results from our study of prostate cancer may not be generalized to other types of cancer patients.

Similar with our previous two studies (i.e., Chapters 4 and 5), we used a fixed time frame to measure NCIC score for every patient. For a survival analysis, this approach was not as precise as measuring the comorbidities by using individual patient's cancer diagnosis date. For example, the NCICI score on December 31st, 1999 may not fully capture the baseline comorbidities of a patient who was diagnosed with prostate cancer on July, 1st, 2000. In addition, the composite score for use of necessary care was also measured by a fixed time frame (i.e., every two calendar years). Therefore, the composite score may not truly reflect how care was received right before a patient's death. Measuring the use of necessary care in every two-year interval prior to a patient's death might be a better predictor for mortality than our current approach. Despite the potential limitation related to using a fixed time frame for every patient, we believe that the influence of this measurement issue should not differ by race. Thus, our findings of racial difference in mortality are still robust.

Due to data limitations, there was potential for omitted variable bias in our analysis (99). Health status, a variable that is associated with health care utilization and mortality, is not collected in the SEER-Medicare data. A patient with poor health status may be too sick to receive necessary ambulatory care and have a high likelihood of dying. Since we were not able to control for health status in our analytic model, the observed HR for use of necessary care may be inconsistent. However, since race is exogenous and the relationship between health status and mortality should not differ by race, we believe that the HR of race is still valid. In the future, prospective studies collecting health status information are necessary to further investigate the relationship between use of care and survival.

6.6 Conclusion

Racial disparity in survival is also observed among survivors with other survivable cancers (e.g., breast or colorectal cancer (8, 9)). Future studies are necessary to examine whether the racial disparity remains after additional adjustment for time-varying comorbidities and use of necessary care. We also suggest future studies to adopt competing-risk models, rather than PH models, to identify risk factors for dying from either cancer or non-cancer causes.

CHAPTER 7. STUDY LIMITATIONS AND FUTURE RESEARCH AGENDA

7.1 Summary of Findings

This dissertation examined the dynamics of diagnosis and use of necessary care for comorbidities in Medicare beneficiaries with prostate cancer, the most prevalent cancer among elderly men in the United States. Previous cancer survivorship studies of prostate cancer measure comorbidity cross-sectionally, either at the index date or at a certain time point after cancer diagnosis. In addition, although the majority of prostate cancer survivors die from causes other than cancer, little is known about the use of necessary care for non-cancer comorbid conditions among this population. This dissertation sought to examine whether survivors are more likely to be diagnosed with comorbidities after their prostate cancer diagnosis. In addition, to our knowledge, this study is the first one to examine a wide range of quality of care indictors for non-cancer conditions among prostate cancer survivors. We further examined whether use of necessary care, a potential modifiable factor, is associated with mortality rates and whether it changes the relationship between racial and survival among prostate cancer survivors.

In Chapter 4, we found that more comorbid conditions were identified after cancer diagnosis. The prevalence rates of comorbidities and overall comorbidity scores of prostate cancer survivors increased at a faster rate after their cancer diagnosis than those rates observed among individuals without cancer during the same time periods. In addition, we also observed that cancer survivors had more contact with the health care system after

cancer diagnosis. Survivors made more office visits not only to their prostate cancer specialists (including urologists) but also to their primary care physicians after the cancer diagnosis. Although we hypothesized that cancer specialists, by virtue of their increased contact with survivors, might provide primary care for other health conditions, the majority of newly diagnosed comorbidities after cancer were identified by PCPs, rather than by prostate cancer specialists. Therefore, a diagnosis of prostate cancer may provide a chance for some patients who were not previously engaged in the health care system to have regular contact with their PCPs, which increases the likelihood of finding other health conditions.

In Chapter 5, we found that prostate cancer survivors consistently used more necessary care than individuals without cancer did. Although the difference in use of necessary care existed even before cancer diagnosis, the magnitude of difference became larger after cancer diagnosis. It is possible that prostate cancer was diagnosed because cancer survivors already had more contact with their health care providers before their cancer diagnosis than individuals without cancer had. After cancer diagnosis, more survivors started to make regular visits to their care providers and received more care from them. Therefore, a diagnosis of prostate cancer may represent “a wake-up call” for elderly men to be engaged in the health care system.

Although the use of necessary care among survivors substantially improved after cancer diagnosis in 2000, it surprisingly dropped between 2004 and 2005 but increased back between 2006 and 2007. Although this finding might be partly explained by the data error in 2004 physician claims, a potential explanation is the enactment of Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA). The MMA reduced the reimbursements for Medicare Part B chemotherapy drugs from 95% of average wholesale prices in 2003 to 80-85% in 2004 (97). In 2005, the reimbursements were further reduced to 106% of average selling prices which tend to be substantially lower than the

average wholesale prices (97). To compensate the potential loss, the MMA also increased the reimbursements for administration services of chemotherapy provided by oncologists substantially (97, 98). However, the increases in reimbursements for corresponding services provided by urologists were much smaller (97, 98). Therefore, it is possible that some urologists may limit the number of Medicare patients they see and send their patients to hospital. Since some patients may feel inconvenient to receive their care from hospital, their adherence to therapy could decrease (98). Therefore, the implementation of MMA may limit a survivor's access to urologists, who tend to provide a large proportion of health care for prostate cancer survivors (Chapter 4). In 2006, urologists were allowed to obtain chemotherapy drugs for their patients from a third party contractor through a process called competitive acquisition (97, 98). This policy change may explain the improvement in use of necessary care from 2004-2005 to 2006-2007.

In Chapters 4 and 5, we found that a diagnosis of prostate cancer may have positive effect on both detection and management of non-cancer comorbidities. These findings are especially true for black cancer survivors. Black cancer survivors consistently had higher prevalence rates of comorbidities and NCICI scores than white survivors, meaning that they had a higher risk of dying from causes other than cancer than white cancer survivors. However, the racial differences became larger after prostate cancer diagnosis. Although black men generally have more comorbidities than white men (32, 91, 92), it is also possible that more previously underdiagnosed comorbidities were detected after cancer diagnosis among black survivors than among white survivors. However, black patients consistently received less necessary care for their comorbid conditions, regardless of whether they were cancer survivors or not. Interestingly, we found that this racial disparity decreased after cancer diagnosis because black prostate cancer survivors improved their overall use of necessary care. The main reason for this finding is likely that more black survivors began to

have more regular office visits to their physicians after cancer diagnosis. Therefore, a prostate cancer diagnosis may create an important opportunity for black men to be more aware of their health and to obtain necessary care for comorbid conditions.

In Chapter 6, we found that racial differences in comorbidities and use of necessary care may explain some of racial disparity observed in mortality, especially in non-cancer mortality. Although the disparity in overall mortality was largely explained by racial differences in cancer disease information (i.e., stage, grade, and treatment) and SES, racial disparity disappeared after further adjustment for comorbidities and use of necessary care. In addition, we found that more use of care consistently was associated with longer survival. Although this measure of care is intended to evaluate the use of necessary care for non-cancer comorbidities, it may be a good proxy for a patient's quality of cancer care. Therefore, more use of necessary care was associated with not only a lower cancer mortality rate but also a lower non-cancer mortality rate. Further prospective studies are necessary to further investigate whether there is causal relationship between use of necessary care and mortality among cancer survivors.

Although the benefit of diagnosing localized or regional prostate cancer at an early stage remains controversial, diagnosis of prostate cancer at an early stage may have some unexpected positive effects on non-cancer comorbidities. In this study, a diagnosis of prostate cancer was associated with not only more detection of comorbidities but also more use of necessary care for these conditions. These above findings were especially true among black survivors. Therefore, researchers should not only examine the cancer-related health outcomes but also consider the relationship between prostate cancer and detection and management of comorbidities when they evaluate the overall benefit of prostate cancer screening.

7.2 Study Limitations

7.2.1 Data Issues

The main limitations of this study were similar to those observed in observational studies using administrative datasets. The results of this study may not be generalizable to non-SEER regions because Medicare beneficiaries living in the SEER regions are less likely to be white, live in poverty, reside in rural areas, and enroll in managed care plans (70). Medicare beneficiaries who were diagnosed with cancer before age 67 were excluded from our analyses because we were unable to obtain their claims data before Medicare enrollment. Therefore, the findings from our study may not be generalized to younger prostate cancer survivors. The results from our study also may not be generalized to HMO enrollees who were excluded from our analyses because information about their medical care was not available. Since risk factors, treatment options, and survival rates vary by types of cancer, different cancers may have different influence on the rates of and severity associated with various comorbidities. Therefore, the results from our study may not be generalizable to survivors of other types of cancer.

In this study, we selected patients diagnosed with prostate cancer in 2000 because they are the most recent cohort for which we had sufficient data. In sensitivity analysis, we used patients who were diagnosed with prostate cancer in 1997 and applied the same study design. The main findings of this dissertation were unchanged, except for the use of necessary care between 2004 and 2005. The use of care among the 1997 cancer cohort did not drop substantially in Period 3 as what we observed among the 2000 cancer cohort. Therefore, this finding supports our explanation that the change in use of care between 2004 and 2005 might be associated with the data error in 2004 physician claims or the implement of MMA.

Due to data limitations, we were unable to observe the diagnosis of comorbidities before a patient enrolled in the Medicare program at age of 65. In Aim 1, it is likely that our

study underestimated the true prevalence of each chronic condition. However, we expect that this problem has a similar influence on both the cancer and non-cancer groups. In Aim 2, the time of a disease's first diagnosis is critical for many of the refined ACE-PRO indicators, especially for initial work-up indicators. Since we were unable to observe the diagnosis of comorbid condition before age of 65, the first diagnosis of a comorbid condition that we observed in the Medicare claims may not be the true initial diagnosis. Our findings may be biased if patients receive more/less care for their true initial diagnosis before 65 than for their first diagnosis after 65. However, we expected that this type 1 error has a similar effect on the cancer and non-cancer groups.

7.2.2 Design Issues

The CCI and NCICI scores represent an aggregated weight of chronic conditions observed in insurance claims. Specifically, although the severity of a disease may vary across patients, the severity of patients diagnosed with same type of diseases is weighted in the same way. Without a detailed review of patient medical records, we were unable to differentiate the severity of the disease among individuals. In addition, we assumed that comorbid conditions were incurable when we measured cumulative comorbidity prevalence and severity. This assumption may be more appropriate for some diseases (e.g., COPD and diabetes) than others (e.g. peptic ulcer and hypertension). For example, some patients with a history of hypertension may have normal blood pressure through diet control or regular exercise. Therefore, we might overestimate the comorbidity prevalence and severity. However, we expected the influence of this assumption to be similar among both cancer and non-cancer groups.

The ACE-PRO indicators were originally developed to measure underuse of necessary care. Fulfilling the requirement of an indicator does not guarantee optimal use of care, however. For example, some patients who overused necessary care may still be

classified as using appropriate care by the ACE-PRO indicators. Further studies are necessary to develop measures for detecting overuse or misuse of necessary care. In addition, the majority of the refined ACE-PRO indicators measure quality of care by examining whether a patient visited to his care providers when necessary. However, the indicators do not evaluate whether this patient received necessary examine or treatment during his visit. In addition, none of the refined ACE-PRO indicators measures the quality of care by evaluating a patient's health outcomes. Since results from laboratory tests are generally unavailable in claims data, it is not possible to link the results from ACE-PRO measure to intermediate health outcomes. Therefore, further studies are necessary to assess a survivor's quality of care using his medical record. Finally, when we calculated composite scores to evaluate the use of care, the indicators of necessary care were not weighted. However, some indicators may play more important roles for a patient's health than others, and therefore were not reflected in the ACE-PRO composite.

When we calculated comorbidity prevalence and severity in Aim 1, we only included individuals who remained alive at a specific time point. In Aim 2, individuals who died during a time period were excluded because the ACE-PRO indicators were developed to measure the use of care for those who remained alive during the entire two-year time frame. Therefore, we may observe a "survivor effect" in Aims 1 and 2. In other words, those who are alive at a time point may be healthier (i.e., fewer comorbidities) than those who die before that point. We assumed that cancer and non-cancer patients who died during the study periods were un-informatively censored (i.e., death during follow up is independent with use of care). The effect of uninformative censoring assumption should be minor because the five-year relative survival rate of localized or regional prostate cancer patients is approximately 100% as compared with the non-cancer population (9). Therefore, we expected the survivor effect to be similar between cancer and non-cancer groups. In

sensitivity analyses, we restricted our samples to those who survived during the entire study time frame and obtained similar results as the findings from our primary analyses.

In Aim 3, there was potential for omitted variable bias due to data limitations (99). Health status, a variable that is associated with health care utilization and mortality, is not collected in the SEER-Medicare data. Patients with poor health status may be too sick to receive necessary ambulatory care and be more likely to die than those with good health status. Since we were not able to control for health status in our analytic model, the use of necessary care may have endogeniety issue (99). Therefore, extra caution is necessary when interpreting the observed HR of use of necessary care. However, since our key independent variable, race, is exogenous and the relationship between health status and mortality should not differ by race, we believe that the potential for omitted variable bias does not affect the HR of race.

7.3 Future Research Agenda

The findings and the limitations of this dissertation suggest some potential directions for future research. Specific directions for future studies are listed in Table 25.

Table 25. Directions for future research

Other cancers	■ Examine detection of comorbidities longitudinally ■ Examine use of care for comorbidities longitudinally ■ Survival analysis ♦ Control for use of care ♦ Report proportional hazards assumptions ♦ Control for time-varying comorbidities ♦ Adopt competing-risk model, if appropriate, when examining cancer or non-cancer mortality
Use medical records	■ Include younger survivors ■ Identity comorbidities diagnosed prior to 65 ■ Differentiate severity among patients with the same disease ■ Identify overuse or misuse of types of care ■ Measure quality of care for other types of care ♦ Procedure (e.g., prescription drug) ♦ Outcomes (e.g., lab data)
Use of care	■ Use the refined ACE-PRO indicators ♦ Develop a shorter version ♦ Evaluate the use of care among patients with a certain disease ♦ Examine the influence on other health outcomes ♦ Examine the influence on medical expenditures
MMA	■ Examine the influence MMA on: ♦ Services provided by urologist (e.g., workload) ♦ Prostate cancer patients' other treatments (e.g., incontinence) ♦ Other patients treated by urologists (e.g., bladder cancer patients)

ACE-PRO: Access to Care for the Elderly Project
MMA: Medicare Prescription Drug, Improvement, and Modernization Act of 2003

One of the most important future directions is to conduct similar studies among survivors diagnosed with other highly survivable cancers. For example, patients diagnosed with localized breast or colorectal cancer have very high 5-year relative survival rates (>90%)

(9). Although co-existing comorbidities also play an important role for these survivors' health, the longitudinal relationships between these cancers and the detection and management of non-cancer health conditions have not been fully investigated. Applying the study design of this dissertation to other cancer survivors allows us to determine whether the potential positive effect of cancer diagnosis on non-cancer comorbidities is unique to prostate cancer survivors. Similarly, racial disparity in survival is also observed among survivors with breast or colorectal cancer (9).

We have some methodological suggestions for future studies examining racial disparity in survival among cancer survivors. First, researchers should always test proportional hazard (PH) model assumptions and report their solutions for the violated assumptions. In addition, instead of a fixed comorbidity score at cancer diagnosis, future studies should control for a time-varying comorbidity score which may better reflect the dynamic nature of the risk of dying from causes other than cancer. In addition, future studies should control for use of necessary care which is a strong predictor for longer survival in our study. Finally, we suggest future studies to adopt competing-risk models, rather than PH models, when the outcome of interest is either cancer or non-cancer mortality, since the risks of dying from cancer or other causes are likely dependent.

We also recommend future studies to use medical records to investigate comorbidities among cancer survivors. Although studies using medical records generally have lower external validity than studies using nationwide claims data, medical records have several advantages over Medicare claims. First, researchers will be able to include younger survivors and identify comorbidities which were diagnosed before age of 65. Second, medical records may provide enough information to differentiate the severity of the same disease among individuals. Third, a survivor's overall quality of care may be examined comprehensively through medical records. Researchers may identify not only underuse but

also overuse and misuse of necessary care. Fourth, researchers will be able to measure whether a patient receives necessary physical exam or treatment (e.g., prescription drug) for his comorbidities. Finally, future studies may assess a patient's health outcomes by reviewing his laboratory report in medical record.

The Medicare Payment Advisory Commission (MedPAC) uses the refined ACE-PRO indicators to study the access and the quality of care among Medicare beneficiaries, and uses the results of these analyses in their reports to Congress (64). However, no previous published studies have used these indicators to examine use of care. Although the ACE-PRO (40 items) covers broad ranges of disease group and type of care, evaluating each indicator and calculating an overall composite score for use of care require a lot of time and computing codes, which are not available directly from MedPAC. To promote the use of ACE-PRO for future research, efforts are necessary to shorten the measurement without hurting its internal validity. In addition, the ACE-PRO is primarily used to examine the geographic and socioeconomic variations in use of care (64). Future studies are necessary to investigate whether patients with a certain disease (e.g., Alzheimer's disease) tend to use less necessary care than the general Medicare beneficiaries, and to further evaluate whether use of care is associated with survival. Finally, we suggest future studies to examine the longitudinal relationship between use of necessary care and medical expenditures and other health outcomes.

Future studies are needed to examine the impact of MMA on the services provided by urologists who tend to be affected by the new policy the most. It is important to examine not only whether urologists saw fewer prostate cancer survivors between 2004 and 2005 but also whether prostate cancer survivors received less care for their non-cancer conditions (e.g., incontinence) from urologists after MMA. Finally, we suggest future studies to

investigate the potential influence of MMA on the quality of care and health outcomes in other cancer (e.g., bladder) survivors treated by urologists.

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