The Effects of Comorbid Asthma and Long-term Use of Corticosteroids on Clinical Outcomes of Prostate Cancer Patients

by

Nan Huo

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Approved by

Jingjing Qian, Chair, Associate Professor of Health Outcomes Research and Policy
C. Edward Chou, Associate Professor of Health Outcomes Research and Policy
Kimberly Garza, Associate Professor of Health Outcomes Research and Policy
Zeng Peng, Associate Professor of Mathematics and Statistics

Abstract

Objectives: This study 1) examined burden of asthma among prostate cancer patients, asthma and prostate cancer treatment patterns, and factors associated with concurrent asthma, 2) assessed the associations between comorbid asthma and clinical outcomes among patients with prostate cancer, and 3) assessed the associations between long-term use of inhaled corticosteroids and clinical outcomes for patients with prostate cancer and comorbid asthma.

Methods: Three retrospectives, population-based cohort analyses used the 2007-2014 Surveillance, Epidemiology, and End Results (SEER)-Medicare-linked database to identify newly diagnosed patients with prostate cancer. Comorbid asthma was identified in a 12-month baseline period prior to the prostate cancer diagnosis. Types of asthma and prostate cancer treatments were identified in 12 months after prostate cancer diagnosis. The exposure to corticosteroids use was identified in an up to 18 months observation period before and after prostate cancer diagnosis and further classified as different levels based on exposure periods (long vs. short) and dosages (high vs. low/intermediate). Two simple linear regression models were applied to test the trends in the annual prevalence of comorbid asthma among prostate cancer patients and the non-cancer comparison group. Cumulative rates of clinical outcomes (i.e., all-cause, prostate cancer related, and cardiovascular-related hospitalizations and emergency department (ED) visits) were estimated, and Cox proportional hazards models were used to identify the association between asthma and corticosteroids use with clinical outcomes.

Results: The trend in the prevalence of comorbid asthma (15.71% in 2014) was stable in prostate cancer patients in 2007-2014 (P=0.35). Compared with prostate cancer patients without asthma, risks of all-cause and prostate cancer related hospitalizations, ED visits, and mortality (all-cause only) were higher in patients with asthma. Exposing to long-term (≥6 months) and/or high dosage (≥7.5 mg/day) of corticosteroids put patients with higher risks of all-cause hospitalizations, ED visits, and mortality compared to those without corticosteroids use.

Conclusions: The existence of comorbid asthma and long-term and/or high dosage of exposure to corticosteroids put prostate cancer patients at higher risks in hospitalization, ED visits, and mortality. It is important for healthcare providers to screen and understand the burden and needs of managing comorbidities such as asthma among patients with prostate cancer.

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ADT	Androgen Deprivation Therapy
AR	Androgen Receptor
BRCA	Prostate Cancer Susceptibility Gene
CAB	Combined androgen Blockade
CRPC	Castrate Resistant Prostate Cancer
CDC	Centers for Disease Control
CMS	Centers for Medicare and Medicaid Services
DHT	Dihydrotestosterone
ED	Emergency Department
GINA	Global Initiative for Asthma
HER2/neu	Human Epidermal Growth Factor Type 2 Receptor
HPA	Hypothalamic–pituitary–adrenal
HPC1	Hereditary prostate cancer gene 1
ICS	Inhaled Corticosteroids
LHRH	Luteinizing Hormone-releasing Hormone
LABA	Long-acting Beta-adrenoceptor Agonists
mCRPC	metastatic Castration-Resistant Prostate Cancer
NHIS	National Health Interview Survey
NCI	National Cancer Institute
PSA	Prostate-specific Antigen
SABA	Short-acting Beta2-adrenoceptor Agonists
SEER	Surveillance, Epidemiology, and End Results

Chapter 1 Introduction

1.1 Overview

Prostate cancer is the second most common cancer in males.[1-4] In 2017, about 220,000 men were diagnosed with prostate cancer and led to nearly 27,000 deaths.[2,5] It has been projected that the total expenditures for prostate cancer care will reach approximately $16.34 billion in 2020.[6,7] Some risk factors associated with prostate cancer include androgen,[8] diets,[9] environmental factors such as Agent Orange, obesity, and chronic prostate inflammation.[10] Evidence also indicates that systemic inflammatory response, not only prostate inflammation, contributes to prostate cancer etiology.[11] Therefore, inflammation has been considered an important pathway to cause prostate cancer, and it is possible that males with a long-term inflammatory response are at increased risk of prostate cancer.[12-18]

Asthma is one of the most common allergic diseases in the United States (U.S.).[19,20] It is a complex and chronic inflammatory disorder that is associated with airway hyper-responsiveness and tissue remodeling of the airway structure.[21] According to the Centers for Disease Control and Prevention (CDC), 1 in 13 Americans have asthma.[19,20] In 2016 about 26.5 million Americans, including 20.3 million adults and 6.1 million children, had been diagnosed with asthma.[19] Due to the high prevalence of asthma and associated high healthcare utilization, there is an immense economic burden for both patients and the healthcare system.[22-24] For example, during 2008-2013, asthma related direct medical cost was $50.3 billion, and the indirect cost was $32 billion (missed workdays was responsible for $3 billion and asthma-related mortality for $29 billion).[24]

A Canadian study indicated a high proportion of asthma among prostate cancer patients, which found that 12% of prostate cancer patients had asthma.[15] It is important for healthcare providers to screen and understand the burden and needs of managing comorbidities such as asthma among patients with prostate cancer. However, there is lacking evidence in the burden of asthma among prostate cancer patients in the U.S. Moreover, some evidence has shown that asthma treatments may have potential harm to patients with prostate cancer, which might affect long-term clinical outcomes and eventually patient survival.[15] For example, corticosteroid agents, the preferred treatment for maintenance control of persistent asthma that is also widely used in the treatment for all types of prostate cancer, may promote prostate tumor progression when long-term used.[14] However, the relationships between comorbid asthma and its long-term treatment and clinical outcomes among patients with prostate cancer remain unclear. Knowledge gaps exist in the burden of comorbid asthma, how comorbid asthma affects prostate cancer outcomes, and the associations between long-term corticosteroid agents (inhaled and oral) use and clinical outcomes among patients with prostate cancer and comorbid asthma.

1.2 Overall Objective

The overall objective of this study was to assess the associations between comorbid asthma and long-term use of corticosteroid agents (inhaled and oral) and clinical outcomes among patients with prostate cancer. We used the 2007-2014 Surveillance, Epidemiology and End Results (SEER) Medicare data, the linked data files between the SEER program of cancer registries that collect clinical, demographic and cause of death information for persons with cancer and the Medicare administrative claims for covered health care services from the time of a person's Medicare eligibility until death. The outcomes of this study were to examine the impact of comorbid asthma and its treatment patterns among patients with prostate cancer, as well as to inform the safety and effectiveness of long-term use of corticosteroids agents among patients with prostate cancer and comorbid asthma. Findings of this study will help practitioners optimize medication treatment strategies for patients with comorbid asthma and prostate cancer. The three specific aims are described in the next session.

1.3 Specific Aims

1.3.1 Specific Aim 1: To examine the proportion of comorbid asthma among prostate cancer patients and treatment patterns among patients with concurrent asthma and prostate cancer.

In this descriptive aim, annual proportions of comorbid asthma were examined among and compared between newly diagnosed prostate cancer patients and patients without cancer ("non-cancer" control group). The factors that associate with asthma among prostate cancer patients were also identified. In addition, the first 12 months of prostate cancer treatment patterns (i.e., type, frequency) among newly diagnosed prostate cancer patients with and without comorbid asthma were assessed. Asthma treatment patterns among prostate cancer patients and non-cancer patients also were assessed. Prostate cancer treatments (including surgery, radiation, chemotherapy, and others) and asthma pharmacological treatments, including quick-relief medications, inhaled corticosteroids, oral corticosteroids, long-acting beta-agonists, and other maintenance treatment such as anticholinergics, cromolyn, theophylline, phosphodiesterase inhibitors, leukotriene modifiers, and immunomodulators were identified in the SEER-Medicare medical and pharmacy claims data files.

1.3.2 Specific Aim 2: To assess the associations between comorbid asthma and clinical outcomes for patients with prostate cancer.

We conducted a retrospective, new user cohort analysis and examined the overall incidence of clinical outcomes in 24 months of follow up among newly diagnosed prostate cancer patients with comorbid asthma and those without asthma. Then we identified factors associated with clinical outcomes. Factors assessed included patient's age, race/ethnicity, socioeconomic status, presence of comorbidity, cancer stage and tumor characteristics, and prostate cancer treatments.

Hypothesis: Prostate cancer patients with comorbid asthma have worse clinical outcomes compared to those without comorbid asthma.

Clinical outcomes included all-cause mortality, all-cause emergency department (ED) visits and hospitalizations, and prostate cancer related ED visits and hospitalizations within 24 months after the initial prostate cancer diagnosis.

1.3.3 Specific Aim 3: To assess the associations between long-term use of corticosteroids and clinical outcomes for patients with prostate cancer and comorbid asthma.

Among newly diagnosed prostate cancer patients with comorbid asthma, we conducted a retrospective, new user cohort analysis and compared the incidence of all-cause, prostate related, and cardiovascular related ER visit, hospitalization, as well as all-cause mortality between long-term corticosteroids (both inhaled and oral) users (define as patients who were prescribed inhaled or oral corticosteroid medications pre-post prostate cancer diagnosis for at least 6 months) and short-term users (defines as patients who were prescribed inhaled or oral corticosteroid medications pre-post prostate cancer diagnosis less than 6 months) or nonusers (define as patients who were never prescribed inhaled or oral corticosteroid medications in the study periods). In addition, among corticosteroids users, the average daily dosage of corticosteroids treatment was also measured and categorized as low or intermediate (<7.5mg/day) and high (≥ 7.5mg/day). The mutually exclusive groups (including non-users, short-term and low/intermediate dosage, short-term and high dosage, long-term and low/intermediate dosage, and long-term and high dosage) categorized based on duration and dosage of corticosteroids treatment were independent variable assessed for this aim.

Hypothesis: Patients with long-term use of corticosteroids have worse clinical outcomes compared to those without long-term use of corticosteroids.

1.4 Significance

The overall purpose of this study was to fill the knowledge gaps in the burden of comorbid asthma, the associations between comorbid asthma and long-term use of corticosteroids with prostate cancer and its clinical outcomes. Specifically, this study evaluated 1) what's the proportion of comorbid asthma among patients with prostate cancer and how they are treated; 2) whether prostate cancer patients with comorbid asthma are associated with worse clinical outcomes such as mortality and hospitalization; and 3) whether long-term use of corticosteroids among patients with prostate cancer and comorbid asthma impacted patient's clinical outcomes. Increased understanding of the burden and clinical outcomes of comorbid asthma among patients with prostate cancer will shed light on the importance of asthma screening for prostate cancer patients and on disease management strategies for patients with both conditions. Furthermore, for patients with prostate cancer and comorbid asthma, if long-term use of corticosteroids is associated with worse clinical outcomes, physicians might consider adjusting treatment strategies for optimizing patient outcomes among this vulnerable population. In addition, the safety of long-term use of corticosteroids among patients with prostate cancer and comorbid asthma was evaluated and findings will help health providers optimize medication treatment strategies for patients with prostate cancer and comorbid asthma.

This study was the first to investigate the associations between comorbid asthma and long-term use of corticosteroids with prostate cancer and clinical outcomes using the population-based dataset in the U.S. Previous studies investigating the association between asthma and prostate cancer only used local, hospital-based electronic medical records or standardized conditions data. We performed analyses of population-based data that reflect the large, real-world data. This study used the SEER-Medicare data, including national cancer registries linked with Medicare administrative claims data, to further investigate the associations between comorbid asthma and long-term use of corticosteroids with prostate cancer and clinical outcomes. The information gained from this real-world investigation may provide a more reliable estimate of the treatment pattern of prostate cancer patients with comorbid asthma in the U.S. The findings obtained through this study may make a valuable contribution to clinical practice, public health, and care of cancer patients. **Additionally, findings from this study provide the opportunity to investigate the safety and effectiveness of treatment strategies for patients with multiple chronic conditions such as asthma and prostate cancer.** It helps researchers and clinical practitioners better understand some of the potential safety issues that may influence prostate cancer treatment. As a result, oncologists may have sufficient evidence about appropriate disease management in order to maximize the benefit of corticosteroids with the duration that can be safely administered in prostate cancer patients with comorbid asthma.

Chapter 2 Literature Review

2.1 Burden of Prostate Cancer in the United States

Based on the report of the American Cancer Society, prostate cancer is the most common non-skin cancer among males in the United States.[1-4] According to the data from Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics, there will be 11 percent of men born today will be diagnosed with prostate cancer during their lifetime.[1-4] In 2010-2014, the most frequently diagnosed with prostate cancer age is 65-74. The median age at diagnosis and at death for prostate cancer was 66 and 80 years of age, respectively. In 2015, prostate cancer was diagnosed in about 220,000 men and caused nearly 27,000 deaths. The incidence rates of prostate cancer have been decreased by 5.8% each year over the last ten years, and motility rates have been decreased by 3.4% each year. Based on the data from SEER, the incidence of prostate cancer was 119.8 per 100,000 men per year, and there were an estimated 3,085,209 men with prostate cancers in 2014. In 2017, an estimate of 161,369 men is expected to have new diagnoses, accounting for 9.6% of all new cancer cases among men. Due to the effective screening test (e.g. Prostate-specific antigen, PSA) application for prostate cancer in the recent ten years, most of the prostate cancer is localized or regional.[25-27] Effective screening and timely intervention are the important reasons why prostate cancer patients have much improved survival rates.[25-28]

Although prostate cancer has an excellent survival rate over the last 20 years, it remains the second leading cause of cancer death among men (after lung cancer) regardless of races and ethnicities.[2,29,30] Due to the earlier detection and treatment, the mortality rate of men with prostate cancer is lower than other types of cancer. [2,29,30] Based on the 2010-2014 cases and death, the age-adjusted mortality rate of men with prostate cancer was 20.1 deaths per 100,000 persons. [2,29,30] However, African-American men had the highest mortality rate (40.2 death per 100,000) compared to other racial groups. [2,29,30]

Generally, the 5-year relative survival rate of men with prostate cancer has improved over time, from 66.0 % in 1975 to 99.3 % in 2017.[4] Recent statistics from the 18 SEER graphic areas have reported that the overall 5-year relative survival for 2003-2017 was 89.2%, with 90.4% in Caucasian American men and 78.7% in African American men.[4] Survival rates also vary among stages.[4] For instance, the 5-year relative survival for prostate cancer patients diagnosed with the localized stage (i.e., confined to the primary site) is 98.6%, compared with only a 24.3% 5-year relative survival for those diagnosed with the distant stage (i.e., metastasis).[4]

Improvements in prostate cancer survival have also come with substantial costs. In fact, national cancer care expenditures have been constantly increasing in the US.[31] In 2014, national direct expenditures of all cancer sites were $136.47 billion. The top five types of cancer with the highest direct costs were breast cancer, colorectal cancer, lung cancer, lymphoma cancer, and prostate cancer, accounting for 14.14 billion, 12.12 billion, 12.14 billion, and 11.85 billion respectively.[31] Further, in 2020 total expenditures of care for all cancer sites are projected to reach approximately $157.77 billion for all cancer sites and $16.34 billion for prostate cancer, assuming a 2% annual increase in medical costs in the initial (i.e., the period after diagnosis) and final phases (i.e., the last year of life) of care.[6,7,31] The largest proportions of increase in healthcare expenditures are expected for prostate cancer and prostate cancer in the continuing phase (i.e., the period between the initial phase and last year of life phase), accounting for 27% and 38% respectively.[6,7,31] Cost for prostate cancer care is also substantial for individual patients.[6,7,31] The estimates of lifetime direct medical costs per prostate cancer patient range from

$25,000 to $100,000.[6,7,31] Indirect costs such as losses in time and productivity associated with cancer care are also other components of the economic burden for prostate cancer patients.[6,7,31] In 2014, indirect costs of prostate cancer ranked among the top three most expensive cancer types and were estimated at $10.9 billion, accounting for approximately 9% of the total present value of lifetime earning lost.[6,7,31]

2.2 Risk Factors of Prostate Cancer

Prostate cancer risk factors include older age, family history of prostate cancer at young age, smoking,[32] high-dose radiation, prolonged hormone replacement therapy, elevated blood levels of testosterone, high level plasma phospholipid fatty acids.[33] Modifiable risk factors include being overweight or obese,[34] physical inactivities, [35] alcohol consumption,[36] vasectomies,[37] prostatitides,[38] sexually transmitted infections,[39] and sexual behaviors such as having many lifetime sexual partners or starting sexual activity early in life.[40] In addition to family history, inherited genetic mutations are responsible for approximately 5-10% and 4-40% of all prostate cancer.[41-43] These include mutations mostly in prostate cancer susceptibility gene (BRCA), BRCA2 genes, Hereditary prostate cancer gene 1 (HPC1). [41-43]

Comorbidities are coexisting non-cancer medical conditions that are distinct from the principal cancer diagnosis. Evidence indicated that among prostate cancer patients, relatively low frequencies of comorbidities were congenital anomalies, brain and other neurological disorders, and other anemias, and the highest frequencies were found for cardiovascular diseases, genitourinary system disease, endocrine, nutritional/metabolic and immunity disorders, respire system diseases, and digestive system disease.[44] Prior studies have demonstrated that the number and severity of comorbidities at the time of cancer diagnosis strongly influence mortality from non-cancer causes and may also influence cancer-specific survival.[45-47] Studies have shown that prostate cancer patients with high comorbidity and short life expectancy are less likely to receive aggressive therapy. [45-47] These patients are also more likely to participate in active surveillance initiatives.

2.3 Overview of Prostate Cancer Treatment Strategies

Like other types of cancers, treatment strategies for prostate cancer usually are based on disease progression. The first decision to be made in managing prostate cancer is whether treatment is needed based on the estimation of life expectancy and risk stratification.[48-51] Estimation of life expectancy is one of the key determinants of primary treatment.[25,51-54] The evaluation of the risk stratification is based on cancer's stage, grade, and patients' PSA level. [25,51-54] Combining with the evaluation results of the risk stratification, physicians can determine the treatment strategies for patients with prostate cancer. If a patient's estimated life expectancy is less or equal five years, and in low risk stratification, treatment is not usually required. [25,51-54] For these patients, active surveillance or observation are common management strategies.[51] Active surveillance includes observation and regular monitoring without invasive treatment. In the context of the prostate disease, this disease management strategy usually comprises regular PSA blood tests and prostate biopsies.[25,51-54] Active surveillance is often used when an early stage, slow-growing prostate cancer is suspected. However, watchful waiting may also be suggested when the risks of surgery, radiation therapy, or hormonal therapy outweigh the possible benefits.[48,55-57]

Typically, for those patients who need to be treated, prostate cancer management can be divided into 1) local (i.e., surgery, radiation therapy, or both) and/or 2) systemic (i.e., chemotherapy, hormone therapy, biologic therapy, targeted therapy, or combination of these). Treatment selection and prognosis are also evaluated by certain predictive factors, including the following: clinical and histopathological features of the primary tumor, stage of disease, PSA level and Gleason grade, progesterone receptor status, presence of human epidermal growth factor type 2 receptor (HER2/neu) overexpression, and patient characteristics (i.e., comorbidity, age).[25,45,48,51,55-58] In general, prostate cancer can be classified into 1) non-invasive (stage 0) and 2) invasive prostate cancers. Invasive prostate cancer can also be further categorized into an early stage of cancer that has not spread to the skin, chest wall, or distant organ (stages I and II) and later stage or advanced stage (stages III and IV). Anticancer pharmacological treatments can target either non-invasive or invasive prostate cancer. [25,45,48,55-58]

2.3.1 Surgical removal of the prostate, or prostatectomy, is a common treatment either for early stage prostate cancer or for cancer that has failed to respond to radiation therapy. The most common type is radical prostatectomy.[48,51,52,54,56] Radical prostatectomy is effective for tumors that have not spread beyond the prostate. [48,51,52,54,56] The cure rates depend on the PSA level and Gleason grade. [48,52,54,56] However, it may cause nerve damage that may significantly alter the quality of life of the prostate cancer survivor.[51,59-61] Radical prostatectomy has traditionally been used alone when the cancer is localized to the prostate.[51,56] In the event of positive margins or locally advanced disease found on pathology, adjuvant radiation therapy may offer improved survival. Surgery may also be offered when cancer is not responding to radiation therapy. [51,56] However, because radiation therapy causes tissue changes, prostatectomy after radiation has higher risks of complications. Another type is radical perineal prostatectomy when the surgeon removes the prostate through an incision in the perineum, the skin between the scrotum and anus. Radical prostatectomy can also be performed laparoscopically, through a series of small incisions in the abdomen, with or without the assistance of a surgical robot. [51,56]

2.3.2 Radiation therapy, also known as radiotherapy, is often used to treat all stages of prostate cancer.[51,56] It is also often used after surgery if the surgery was not successful at curing cancer.[51,56] Radiotherapy uses ionizing radiation to kill prostate cancer cells. When absorbed in tissue, ionizing radiation such as gamma and x-rays damage the DNA in cancer cells, which increases the probability of apoptosis (cell death).[51,56] Normal cells can repair radiation damage, while cancer cells are not. Radiation therapy exploits this fact to treat cancer. Two different kinds of radiation therapy are used in prostate cancer treatment: external beam radiation therapy and brachytherapy (specifically prostate brachytherapy). The side effects of radiation therapy might occur after a few weeks into treatment, such as diarrhea and mild rectal bleeding due to radiation proctitis, as well as potential urinary incontinence and impotence. [51,56] Symptoms tend to improve over time except for erections that typically worsen as time progresses.

2.3.3 Androgen Deprivation Therapy (ADT) is frequently used for patients with clinically localized prostate cancer, biochemical failure without metastases or for metastatic castration naïve prostate cancer, Salvage therapy fails, patients who were diagnosed with advanced prostate cancer with a PSA above 10.[51,56] ADT is a systemic treatment strategy that affects the entire body, not just the localized area of the prostate gland. ADT is effective because prostate cancer cells develop and grow in the presence of testosterone, the male androgen produced mostly by the testes. Limiting the production of testosterone and dihydrotestosterone (DHT) that is a hormone produced in the prostate and required for the growth and spread of most prostate cancer cells are two targets for ADT.[51,56] There are two main goals for ADT, one is to lower androgen levels, and another one is to stop androgens from working. Orchiectomy (surgical castration) is the only opinion for non-medication treatment to reduce androgen level in ADT.[51,56] Even though this is a type of surgery, its main effect is as a form of hormone therapy.[51,56] In this operation, the surgeon removes the testicles, where most of the androgens (testosterone and DHT) are made. This causes most prostate cancers to stop growing or shrink for a time. For medication use to reduce androgens level, the most common mode of ADT is the use of Luteinizing hormone-releasing hormone (LHRH) agonists, also called LHRH analogs or GnRH agonists. These drugs can lower the amount of testosterone made by the testicles.[51,56] Treatment with these drugs is sometimes called chemical castration or medical castration because they lower androgen levels just as well as orchiectomy. LHRH agonists are injected or placed as small implants under the skin. Depending on the drug used, they are given anywhere from once a month up to once a year. The LHRH agonists available in the United States include Leuprolide (Lupron, Eligard), Goserelin (Zoladex), Triptorelin (Trelstar), and Histrelin (Vantas). Beside LHRH agonists use, LHRH antagonist, such as Degarelix (Firmagon) can be used for ADT. It works like the LHRH agonists, but it lowers testosterone levels more quickly and doesn't cause tumor flare like the LHRH agonists do. Although LHRH agonists and antagonists can stop the testicles from making androgens, other cells in the body, including prostate cancer cells themselves, can still make small amounts of androgens, which can help cancer growth. Abiraterone (Zytiga) that blocks an enzyme called CYP17 can stop these cells from making androgens in ADT.[51,56]

Besides lowering androgens level directly, drugs that stop androgens from working is another common treatment strategy in ADT. Because androgens must bind to a protein in the prostate cell called an androgen receptor to work, anti-androgens are drugs that bind to these receptors to stop androgens' working. The drugs of this type treatment include Flutamide

(Eulexin), Bicalutamide (Casodex), and Nilutamide (Nilandron). Anti-androgens are not often used by themselves in the US. An anti-androgen may be added to treatment if orchiectomy or an LHRH agonist or antagonist is no longer working by itself. An anti-androgen is also sometimes given for a few weeks when an LHRH agonist is first started to prevent a tumor flare. An anti-androgen can also be combined with orchiectomy or an LHRH agonist as first-line **hormone therapy**. This is called combined androgen blockade (CAB). There is still some debate as to whether CAB is more effective in this setting than using orchiectomy or an LHRH agonist alone. Enzalutamide (Xtandi) and Apalutamide (Erleada) are newer types of anti-androgens. Normally when androgens bind to their receptor, the receptor sends a signal to the cell's control center, telling it to grow and divide. These drugs block this signal. These drugs can often be helpful in men whose cancer is no longer responding to other forms of hormone therapy (known as castrate-resistant prostate cancer). Enzalutamide is typically used for metastatic cancer (cancer that has spread to other parts of the body), while Apalutamide is typically used for non-metastatic cancer.

However, hormonal therapy rarely cures prostate cancer because cancers that initially respond to hormonal therapy typically become resistant after one to two years. Therefore, in most cases, the cancer cells can grow without requiring testosterone and make the ADT ineffective. At this point, the cancer is called "castrate resistant prostate cancer" (CRPC). Many studies in the literature have suggested that ADT will only work for a short period of time, probably not much longer than 18 to 24 months, before the cancer becomes castrate resistant.[56,62,63]

Although there is no doubt that ADT is efficacious in delaying disease progression and alleviating symptoms from metastatic disease, ADT is associated with multiple and significant side effects.[51,64-68] The common side effects include hot flashes, impaired sexual function, loss of desire for sex, diarrhea, nausea, itching, and weakened bones because when ADT medications are first given, testosterone levels go up briefly before falling to very low levels.[51,64-67] This effect is called flare and results from the complex way in which these drugs work. Men whose cancer has spread to the bones may have bone pain. If cancer has spread to the spine, even a short-term increase in tumor growth because of the flare could press on the spinal cord and cause pain or paralysis. Flare can be avoided by giving drugs called anti-androgens for a few weeks when starting treatment with ADT, especially LHRH agonists. Besides these common side effects, hormonal therapy, especially LHRH agonists using, may increase the risk of diabetes and cardiovascular disease.[66,68,69] Because of hormone therapy can weaken bones and lead to bone pain, pain medicine and corticosteroids are usually used for bone pain management. However, evidence indicated that ADT also had been associated with increased risk of sudden cardiac death in men with coronary artery disease, especially combining with corticosteroid medications.[66,69] Other ADT drugs such as Enzalutamide and Apalutamide, can cause some nervous system side effects, including dizziness and, rarely, seizures. Men taking one of these drugs are more likely to fall, which may lead to injuries. Abiraterone can cause joint or muscle pain, high blood pressure, fluid buildup in the body, hot flashes, upset stomach, and diarrhea.[70]

2.3.4 Chemotherapy is an optional treatment for prostate cancer patients if prostate cancer has spread outside the prostate gland, and hormone therapy does not work. Recent research has also shown that chemotherapy might be helpful if given along with hormone therapy.[48,51] To treat prostate cancer, chemotherapy regimens are typically used one at a time. These chemotherapy drugs include Docetaxel (Taxotere), Cabazitaxel (Jevtana), Mitoxantrone (Novantrone), and Estramustine (Emcyt).[51] In most cases, the first chemotherapy drug to use is docetaxel, combined with the corticosteroids.[71] Corticosteroids are commonly used in the treatment of cancer because of their anti-inflammatory activities.[72] Corticosteroids can mimic endogenous cortisol or mineralocorticoids and thus activate the glucocorticoid receptor to up-regulate the expression of anti-inflammatory proteins and down-regulate expression of proinflammatory proteins. In prostate cancer, corticosteroids also may have a direct effect on tumor-induced pain. Thus, in the treatment of prostate cancer, corticosteroids are used both to counteract toxic effects associated with specific cancer therapeutics and to manage tumor-related symptoms.[51,72]

Although corticosteroids are used in prostate cancer to help manage treatment-related toxic effects and disease-related morbidities, corticosteroids still have their own side-effects of long-term use. The common side effects of long-term corticosteroids use include edema, hypertension, weight gain, hyperglycemia/steroid-induced diabetes, and glaucoma.[73] Mover, for those men with prostate cancer who have completed multiple years of androgen deprivation therapy (ADT) should be considered with caution if corticosteroid medications need to be used, because these patients may be at an elevated risk of cardiovascular and metabolic disease. In addition, osteoporosis that caused by long-term corticosteroid medications is a majority side-effect of corticosteroids treatment. For example, evidence indicated that low doses of prednisone (6 mg/day) for only 6 months may increase the rate of osteoporotic fractures within 1 year. Corticosteroids also can affect T-cells as well, and lead to reduce function of the immune system.[73] Owing to the immunosuppressive effects of corticosteroids, patients may be at increased risk for infection.[74]

2.4 Burden of Asthma and Allergies and the Potential Impact on Cancer

Asthma is a chronic inflammatory disease of the lungs, causing increased airways reactivity to various stimuli. Allergy and asthma are indicators of altered immune system dynamics and an excessive inflammatory response. Asthma is one of the most common allergic diseases in the world.[19,20] It is a chronic lung disease with characteristics that are variable and recurrent and include reversible airflow obstruction and bronchospasm. Asthma can cause recurring periods of coughing, wheezing, tachypnea, dyspnea, hypoxemia, and mucus plugging. During the years 2001-2010, an estimated 25.7 million Americans, including 18.7 million adults and 7.0 million children, had been diagnosed with asthma, estimated from the National Health Interview Survey (NHIS) data.[75] Asthma not only affects the function of the body but also reduces the patient's quality of life.

Because asthma is a chronic disease, treatment typically involves symptom management and control by using a variety of medications such as beta-agonists, leukotriene modifiers, corticosteroids, etc.[76] Inhaled corticosteroids (ICS) are the first-line asthma management medication.[77] Evidence has indicated that ICS can significantly reduce airway hyper-responsiveness, effectively prevent acute asthma attacks, improve lung function, decrease asthma severity, and reduce mortality.[78,79] However, current allopathic asthma medications, especially high doses or long-term corticosteroid medication use, may cause many side effects. For example, long-term use of inhaled corticosteroid medications carries a risk for posterior sub-capsular cataracts.[72,80] Other systemic side effects include osteoporosis, growth retardation, glaucoma, and even hypothalamic–pituitary–adrenal (HPA) suppression.[80-83]

Many studies have investigated asthma and allergies, including hay fever, eczema, and allergies to medications, as risk factors for cancer, often as part of comprehensive investigations on other risk factors. Generally, allergies seem to be associated with a decreased risk of pancreatic cancer and non-Hodgkin lymphoma, whereas the observed association between a history of asthma and an increased risk of lung cancer might be due to confounding by smoking.[84] Inflammation is considered an essential pathway for prostate carcinogenesis, and it is possible that men with a hyperactive immune system that produces excessive inflammatory responses are at increased risk of prostate cancer.[15] A recent meta-analysis of the few studies that have investigated the association between atopy and prostate cancer risk (assessed by allergen-specific IgE or skin prick testing) reported evidence of a modest association.[85]

2.5 Overview of Asthma Treatment Strategies

Although there is no cure for asthma, symptoms can be improved by using qualified management strategies. The most effective management for asthma is identifying triggers, such as cigarette smoke, pets, or aspirin, and eliminating exposure to them. If trigger avoidance is insufficient, the use of medication treatment is recommended. Medications are selected based on the severity of illness and the frequency of symptoms. The medication treatment for asthma can be broadly classified into long-term asthma control medications and quick-relief medications. Preventive, long-term control medications reduce the inflammation in patients' airways that leads to symptoms. Quick-relief inhalers (bronchodilators) quickly open swollen airways that are limiting breathing. In some cases, allergy medications are necessary.

Bronchodilators are recommended for short-term relief of symptoms. In those with occasional attacks, no other medication is needed. If the mild persistent disease is present (more than two attacks a week), low-dose inhaled corticosteroids or leukotriene antagonist or a mast cell stabilizer by mouth is recommended. For those who have daily attacks, a higher dose of inhaled corticosteroids is used. In a moderate or severe exacerbation, corticosteroids by mouth are added to these treatments.

Among quick-relief medications for asthma treatment, short-acting beta2-adrenoceptor agonists (SABA), such as salbutamol (albuterol USAN), are the first-line treatment. Usually, these medications are recommended before exercise in those with exercise induced symptoms. Other quick-relief medications include anticholinergic agents, such as ipratropium bromide, provide additional benefit when used in combination with SABA in those with moderate or severe symptoms, and anticholinergic bronchodilators, which can be used if a person cannot tolerate a SABA.

Among long-acting medications, corticosteroids are generally considered the most effective treatment available for long-term control of asthma. Therefore, corticosteroids are generally accepted as the first-line choice of anti-inflammatory therapy for the treatment of asthma. The delivery of topically active corticosteroids directly to the airways by inhalation has revolutionized the anti-inflammatory treatment of asthma. Present asthma management guidelines emphasize the importance of early intervention with inhaled corticosteroids as first-line anti-inflammatory therapy.[86,87] There has been a trend toward the use of higher doses, which seems contrary to most of the available evidence of the dose-response relationships for the efficacy of inhaled corticosteroids in asthma. However, there has been increasing evidence indicated that inhaled corticosteroids are associated with dose-related systemic adverse effects.[80,81,83,88-90] At the same time, there has been increasing awareness that adding long-acting $\beta 2$-agonists, theophyllines, or antileukotrienes may be an option for increase the dose of inhaled corticosteroid, to achieve optimal long-term control. These corticosteroid drugs include fluticasone (Flonase, Flovent HFA), budesonide (Pulmicort Flexhaler, Rhinocort), flunisolide

(Aerospan HFA), ciclesonide (Alvesco, Omnaris, Zetonna), beclomethasone (Qnasl, Qvar), mometasone (Asmanex) and fluticasone furoate (Arnuity Ellipta).

Besides corticosteroid medications, long-acting beta-adrenoceptor agonists (LABA) such as salmeterol and formoterol can improve asthma control when given in combination with inhaled corticosteroids. Evidence suggests that for children who have persistent asthma, a treatment regime that includes LABA added to inhaled corticosteroids may improve lung function.[88,91,92] However, children who require LABA as part of their asthma treatment may need to go to check their lung function more frequently.

Leukotriene receptor antagonists also can be used in addition to inhaled corticosteroids for long-term management among asthma patients. These oral medications, including montelukast (Singulair), zafirlukast (Accolate) and zileuton (Zyflo), help relieve asthma symptoms for up to 24 hours. However, evidence showed that they appear to add limited benefits when added to inhaled steroids.[93] Therefore, these medications are not recommended for asthma management among children.

Because most frequently used medications for long-term asthma control are corticosteroids, they induce the common side effects. The local side effects of inhaled corticosteroid medications include oral candidiasis or thrush, dysphonia, reflex cough, and bronchospasm. Additionally, all inhaled corticosteroids can exhibit dose-related systemic adverse effects. These systemic side effects include, but not only limited to, poor growth, decreased bone density, disseminated varicella infection, easy bruising, cataracts and glaucoma, adrenal gland suppression, or exogenous adrenal insufficiency. Because of long-term maintenance therapy with oral corticosteroids is known to suppress growth in children, current guidelines for the treatment of childhood asthma now suggest the use of early intervention with inhaled corticosteroids to prevent disease progression. Moreover, the administration of exogenous inhaled corticosteroids results in a negative feedback effect on glucocorticoid receptors in the anterior pituitary gland and hypothalamus, which in turn suppresses levels of corticotropin-releasing hormone and corticotropin, respectively, and a consequent reduction in cortisol secretion from the adrenal cortex. Prolonged suppression of corticotropin levels eventually results in atrophy of the adrenal cortex. Third, one of the most significant concerns of long-term corticosteroid therapy for asthma is its potential for adverse effects on bone turnover, resulting in an increased risk for osteoporosis and fracture. Fourth, a severe side effect of long-term use of corticosteroid medications in asthma management that needs to be concerned is immunosuppressive. Therefore, corticosteroid medications are not only anti-inflammatory but also immunosuppressive agents. They are widely used to treat patients with autoimmune diseases or to protect from the rejection of transplanted organs. The effects of corticosteroid medications on cells are mediated through the binding of steroid molecules to specific receptor proteins located in the cytoplasm of target cells. However, the use of immunosuppressive agents may lead to downregulation of the immune system. This may be followed by a higher incidence of respiratory infections. Although the immunosuppressive effects of chronic low dose corticosteroids have not been studied systematically in patients with malignancies, evidence indicated that patients with bronchial asthma exposed to chronic daily corticosteroids experience a blunting of both humoral and cellular immune responses. Finally, evidence indicated that mutations in the androgen receptor (AR) might alter its ligand binding specificity, which may expand agonistic activity to other steroids beyond androgens (e.g., progesterone and estrogens). More recently, prednisolone plasma levels in patients with CRPC receiving corticosteroids were discovered to be sufficient to activate mutant AR. Finally, long-term corticosteroids may engender steroid dependency due to the disruption of the hypothalamic–pituitary–adrenal axis and their abrupt withdrawal may cause steroid withdrawal symptoms (fatigue, gastrointestinal symptoms, weight loss, postural hypotension, tachycardia).

2.6 Burden of Asthma and Asthma Treatment on Prostate Cancer Patients

Even though the systematic review and meta-analysis by Zhu et al. showed that there were no statistically significant associations between allergic conditions and risk of prostate cancer,[85] the burden of comorbid asthma among patients with prostate cancer and how comorbid asthma impacts prostate cancer outcomes still need to be evaluated. While the existing studies found that the proportion (i.e., 14.7% found in Kantor et al. and 14% in El-Zein et al.) of asthma in patients with prostate cancer is higher than the general population,[16,94] these studies did not include real-world, nationally representative U.S. patients with prostate cancer.

In addition, evidence has indicated that due to potential underdiagnosed and undertreatment of asthma in older adults, risks in hospitalizations and ED visits are higher than younger individuals.[95-98] Due to the high proportion of asthma among prostate cancer patients, the burden of extra health service utilization such as hospitalization and ED visits associated with comorbid asthma in addition to what prostate cancer patients already carry can be essential. However, there is limited evidence of how comorbid asthma may impact clinical outcomes for prostate cancer patients.

Finally, evidence has shown that asthma treatments, especially corticosteroid medications use, might have potential harm to patients with prostate cancer, which might affect long-term outcomes and, eventually, patient survival.[15] For example, Severi et al. found that patients who received systemic glucocorticoids showed a strong association with the risk of prostate cancer.

Corticosteroids are commonly used in the treatment of both asthma and prostate cancer. Based on the Global Initiative for Asthma (GINA) guideline of asthma, patients with persistent asthma need to regularly use inhaled corticosteroids, even oral systemic corticosteroids, for at least 3 months for each rotation.[87] However, even GINA guideline suggests asthma patients prefer to receive inhaled corticosteroids after Step 2 treatment (Step 1 treatment: as-needed short-acting β2-agonist (SABA) alone), evidence showed there is an expansion of the indication for ICS in asthma patients who received Step 1 treatment. Although the prevalence of systemic side effects of ICS is lower in comparison with systemic corticosteroids, a high dose of long-term ICS use has the potential to cause systemic side effects. On the other hand, although corticosteroids are used in prostate cancer to help manage treatment-related toxic effects and disease-related morbidities, corticosteroids have their side effects. Therefore, prostate cancer patients with asthma may receive a higher amount of corticosteroids from both prostate cancer and asthma treatments. However, to our knowledge, no published study has investigated the impact of the exposure of corticosteroid on patient's clinical outcomes among prostate cancer patients with asthma.

2.7 Knowledge Gaps and Importance of the Study

Therefore, a thorough understanding of the occurrence of comorbid asthma in prostate cancer patients in a real-world setting has important implications for drug development, clinical practice, and patient management. At the same time, due to the increasing complexity of therapeutic options for managing patients with both conditions has yielded many questions, especially regarding the impact of using corticosteroids for increasingly long periods and how corticosteroids affect the sequencing of the new treatment regimens and outcomes. In order to fill these important knowledge gaps, this study examined the proportion of comorbid asthma among prostate cancer patients and treatment patterns among patients with concurrent asthma and prostate cancer (Aim 1). In addition, this study estimated the incidence of and identified factors associated with clinical outcomes in prostate cancer patients with and without comorbid asthma (Aim 2) and assessed the effects of long-term use of corticosteroid medications on clinical outcomes in prostate cancer patients with comorbid asthma (Aim 3).

Chapter 3 Methods

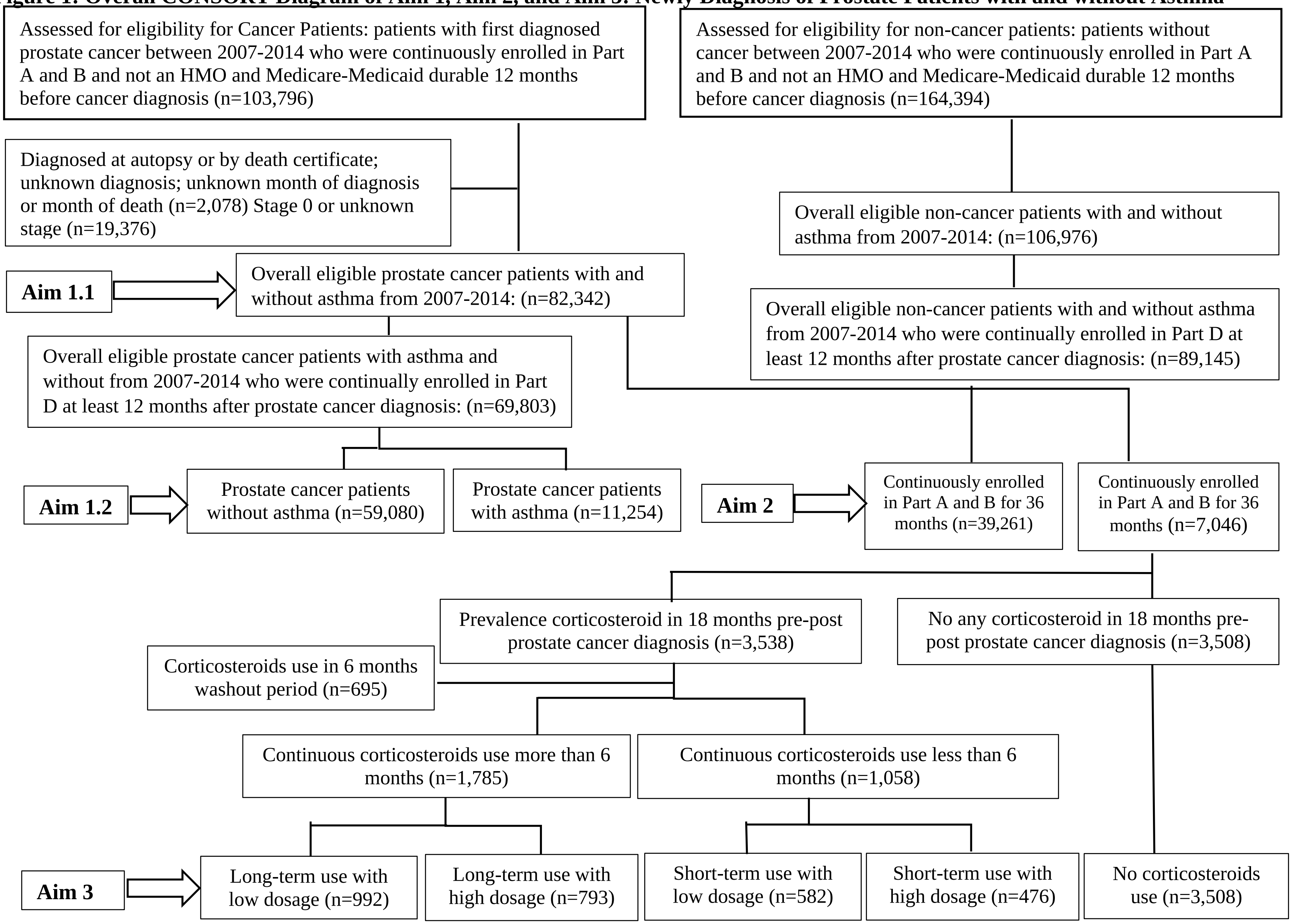
3.1 Approach

3.1.1 Overview of approach:

This retrospective, new-user cohort study 1) examined proportion of comorbid asthma among prostate cancer patients and treatment patterns among patients with concurrent asthma and prostate cancer (Aim 1); 2) estimated the incidence of and identified factors associated with clinical outcomes in newly diagnosed prostate cancer patients with and without comorbid asthma (Aim 2); and 3) examined the effects of corticosteroid medications on clinical outcomes and safety in newly diagnosed prostate cancer patients with comorbid asthma (Aim 3). Specifically, treatment patterns for both prostate cancer and asthma were examined among prostate cancer patients with comorbid asthma in Aim 1. Clinical outcomes assessed in Aims 2 and 3 included all-cause mortality, all-cause ED visits and hospitalizations, and prostate cancer related and cardiovascular related ED visits and hospitalization. In Aim 3, the long-term use of corticosteroid medications after prostate cancer diagnosis was defined as the continued use of corticosteroid medications for at least six months.

Males who were continuously enrolled in the Medicare fee-for-service Part A or Part B during 12 months before the diagnosis of prostate cancer (i.e., the index date) at first diagnosis from 2007 to 2013 were included to ensure an adequate period of Medicare claims for defining comorbidities. Patients were excluded if: 1) they were not continuously enrolled in the SEER-Medicare data 12 months after the index date; 2) they were dual-eligible for Medicare and Medicaid, or were enrolled in Medicare Advantage; 3) prostate cancer was diagnosed at autopsy or not the initial primary tumor diagnosis; or 4) they had missing or unknown cancer stage (Please refer to Figure 1, The overall CONSORT Diagram of Aim 1, Aim 2, and Aim 3).

Figure 1: Overall CONSORT Diagram of Aim 1, Aim 2, and Aim 3: Newly Diagnosis of Prostate Patients with and without Asthma



3.2 Approach by the aim

3.2.1 Aim 1: To examine the proportion of comorbid asthma among prostate cancer patients and treatment patterns among patients with concurrent asthma and prostate cancer.

The SubAim 1.1 estimated the proportion of comorbid asthma among newly diagnosed prostate cancer patients in each year from 2007 to 2014 and identified factors associated with comorbid asthma. The SubAim 1.2 examined 12-month treatment patterns of asthma and prostate cancer management among prostate cancer patients with comorbid asthma after their prostate cancer diagnoses.

3.2.1.1 Rationale: Our preliminary data showed that the proportion of comorbid allergic conditions (mainly asthma) among prostate cancer patients could be as high as 18%;[99] however, patient-level factors associated with having asthma among prostate cancer patients remain unclear. Currently, there are no clear treatment guidelines for patients with prostate cancer and comorbid asthma. These two chronic diseases are still considered as independent with separate treatment guidelines. However, evidence has indicated that systemic inflammatory response, not only prostate inflammation, contributes to prostate cancer etiology.[11] Therefore, asthma, one of the most common inflammation diseases, has been considered an important pathway to cause prostate cancer, and it is possible that males with a long-term inflammatory response of asthma are at an increased risk of prostate cancer.[12-18] For men with prostate cancer, treatments are needed to help control the growth of the prostate. These treatments may include chemotherapy, targeted therapy, ADT, and other types of treatments, such as surgery, radiation therapy, biologic therapy, or a combination of these. The complexity of treatment options can be increased when prostate cancer patients have other chronic conditions such as asthma. In order to provide better understanding in treatment patterns in prostate cancer patients with comorbid asthma, population-based evidence in treatment type, frequency, and dosage for these patients is needed.

<u>3.2.1.2 SubAim 1.1:</u> To examine the proportion of comorbid asthma among prostate cancer patients and treatment patterns among patients with concurrent asthma and prostate cancer.

<u>3.2.1.2.a Data Source</u>

For all three aims, we used the linked two large population-based data sources that provide detailed information about Medicare beneficiaries with cancer claims data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database from 2006-2014. The SEER-Medicare database is a joint effort between the National Cancer Institute (NCI), SEER, and the Centers for Medicare and Medicaid Services (CMS). The SEER program is a population-based cancer registry that collects clinical data (e.g., cancer site, stage, grade, comorbidities), demographics, and cause of death information for persons with cancer. Moreover, the SEER registry captures nearly 26% of the US population and contains information on patient demographics, tumor characteristics, and choice of primary treatment modality.[100] The Medicare program provides claims data which cover health care services from the time of a person's Medicare eligibility until death, including hospital and hospice (Part A), and physician, outpatient, and home health (Part B), as well as prescription drugs (Part D). Linkage to Medicare, which provides benefits to 97% of Americans aged ⩾65 years, offers additional treatment data, including therapies administered in the outpatient setting such as ADT.[101,102] The linkage of persons in the SEER data to their Medicare claims is performed by the NCI, and CMS and research investigators only have access to the de-identified data files.

The SEER-Medicare database provides data for 19 tumor sites, including prostate cancer, and can be used for a variety of cancer research such as cancer screening, treatment, outcomes, patterns of care, and expenditures. The SEER-Medicare database is a unique data resource that makes it possible to conduct longitudinal research as well as derive incidence- and prevalence-based estimates of cancer-related outcomes by site and stage of disease, by treatment approach, and for age and gender strata for individuals older than 65 years and those who received Social Security Disability Insurance (SSDI) and became eligible for Medicare (i.e., those under age 65).

The SEER data files are known as the Patient Entitlement and Diagnosis Summary File (PEDSF). PEDSF contains one record per person for individuals in the SEER database who have been matched with Medicare enrollment records. Necessary SEER diagnostic information is available for up to 10 diagnosed cancer cases for each person. The remaining files are the Medicare files for specific types of service, e.g., hospital, physician, outpatient, etc. Specifically, the Medicare claims data include 1) Medicare enrollment files, which include yearly information on patient demographics, monthly eligibility and enrollment information; 2) carrier files (claims for physician services); 3) outpatient files (claims for hospital outpatient visits); 4) inpatient files (claims for hospital stays); and 5) Part D files (prescription drug events).

There are two cohorts of individuals included in the SEER-Medicare data: those with diagnosed cancer and a random sample of Medicare beneficiaries who did not have a cancer diagnosis. The "non-cancer" group is drawn from a random 5% sample of Medicare beneficiaries residing in the SEER areas. Medicare claims are available for the non-cancer beneficiaries in the same format as for the cancer cases. Information from the non-cancer group can be used for comparative purposes, such as the cost of care or the use of specific tests or procedures among a random sample of Medicare beneficiaries who did not have cancer. Detailed information on the SEER-Medicare database is published and available at http://appliedresearch.cancer.gov/seermedicare/. The Department of Health Outcomes Research and Policy at Auburn University has an active data use agreement with the IMS (NCI's information technology contractor) to support defined research activities among cancer patients. This study among prostate cancer patients was approved by the Auburn University Institutional Review Board (IRB).

3.2.1.2.b Study Population

Medicare beneficiaries were included in the SubAim 1.1 analysis if they were male and newly diagnosed with prostate cancer in the 2007-2014 SEER-Medicare data. We included male beneficiaries who were at least one year continually enrolled in Medicare before the time of their prostate cancer diagnosis to ensure an adequate period of Medicare claims for defining comorbidities based on previous studies.[103] Beneficiaries must be diagnosed with prostate cancer (ICD-9: 185) as primary site cancer (ICD-O site codes: 619)[52,104,105] and had already started reporting to SEER at time of diagnosis; in addition, their month of diagnosis and cancer stage must not be missing in the SEER data. In order to ensure continuous enrollment with Medicare and identifying comorbid asthma before cancer diagnosis and treatment pattern after the prostate cancer diagnosis, beneficiaries must have full coverage in Medicare Parts A, B, and D at least 12 months before and after their first prostate cancer diagnosis. Those beneficiaries who had Medicare Advantage (Medicare Part C) coverage or were Medicare-Medicaid dual eligible at any time the 12 months continuous enrollment period were excluded because Medicare does not fully capture their medical services claims data.

At the same time, we included a sample of non-cancer beneficiaries as the comparison group from the SEER-Medicare "non-cancer" sample. These "non-cancer" beneficiaries should also be male, and they should be continuously enrolled in Medicare Parts A, B, and D in 2007-2014 for at least 12 months before January 1th, 2018, in the year of being included in the study.

<u>3.2.1.2.c Measurements</u>

<u>Outcomes</u>

The main outcomes of interest in SubAim 1.1 were concomitant asthma among SEER-Medicare beneficious with and without prostate cancer from 2007-2014. Asthma was identified by using the ‘Asthma First Ever Occurrence Date’ flag from chronic conditions in the master beneficiary summary file or using ICD-9 diagnosis code (493.xx) from Medicare claim data based on previous studies.[106] The asthma comorbidity flag was created by the CMS to track the beneficiary’s common chronic conditions for research purposes. ICD-9 codes were retrieved from Medicare inpatient, outpatient, and physician claims data. Patients with ICD-9 diagnosis codes that appeared in at least one inpatient claim or two outpatient or physician claims during 12 months before the new diagnosis of prostate cancer (or in the calendar year for non-cancer patients). For physician and outpatient claims, asthma diagnoses must appear on at least two different claims that are more than 30 days apart. This approach has been used in previous studies.[52,104,107]

Predictors and covariates

To identify factors associated with comorbid asthma among patients with prostate cancer included demographics (age and race), geographic region (Northeast, Midwest, West, and South), and residence in urban or rural area, socioeconomic status, tumor characteristics, other comorbid conditions except asthma and prostate cancer. The 5-digit Zipcode of each beneficiary was used to match with the 2010 Urban Area to ZIP Code Tabulation Area (ZCTA). Age was categorized into four categories as less and equal 65, 66-75, 76-85 and 85 and above. Race (white, black, and others) was categorized. Other races include Hispanic, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, and multiple races. Since patient-level data are not available in SEER, we used median household income, education level, poverty level from the census tract variables to represent socioeconomic status. Patient risk group and tumor characteristics, including stage, grade, tumor size, and positive results of bone metastases, were obtained from the SEER database. The clinical staging criteria for prostate cancer were defined by using the American Joint Committee on Cancer (AJCC) Cancer Staging Manual.[108] Patient's risk group was grouped using the National Comprehensive Cancer Network (NCCN) criteria into low risk (T1-T2a or Gleason score 6, or PSA <10 ng/mL), intermediate risk (T2b-T2c or Gleason score 7, or PSA 10-20 ng/mL), high risk and Metastatic (T3a or above, or Gleason score 8-10, or PSA >20 ng/mL).[51] Comorbidities were calculated by Charlson comorbidity index (CCI), which was calculated using the inpatient, outpatient, and physician Medicare claims for specific ICD-9-CM codes (excluding prostate cancer and asthma) during the 12 months before the initial prostate cancer diagnosis. For physician and outpatient claims, a patient's diagnoses must appear on at least two different claims that are more than 30 days apart.

3.2.1.2.d Statistical Analysis

Annual trends in the proportion of asthma were estimated overall among participants with and without cancer, respectively. Descriptive and simple linear regression analyses were used to estimate the trends for asthma proportions in prostate cancer patients in 2007-2014.

To identify factors associated with asthma in Medicare beneficiaries with and without prostate cancer from the 8 years data (2007-2014), both bivariate (chi-square tests) and multivariate analyses were conducted. Chi-square tests were used to compare proportions of asthma between beneficiaries' characteristics among patients with and without prostate cancer, respectively. Multiple logistic regression was used to identify factors associated with asthma in prostate cancer patients, controlling for patient age category, race/ethnicity, cancer stage, comorbidity, region, income level, and metropolitan status. The parameter estimates from logistic regression models were presented as adjusted odds ratio (AOR) and their corresponding 95% confidence intervals (CI) by using the SAS procedure PROC LOGESTIC. All statistical analyses used SAS (version 9.4; SAS Institute, Cary, NC), and the two-sided significance was defined as $P<0.05$.

Statistic Model: To examine the likelihood of having comorbid asthma among prostate cancer patients and non-cancer patients.

Dichotomous response variable (Y): having asthma disease in prostate cancer patients (y=yes/no)

Predictors: demographic (age, sex, race/ethnicity), socioeconomic status, cancer stage, comorbidities, and geographical location

Logit (E(Yi)) =natural log (odds)=$\beta_0+\beta_1$Xdemographic+ β_2Xcancer stage+ β_3Xcomorbidities+ β_4Xsocioecnomic+ β_5Xgeographical location

Dichotomous response variable (Y): having asthma disease in non-cancer patients (y=yes/no)

Predictors: demographic (age, sex, race/ethnicity), socioeconomic status, comorbidities, and geographical location

Logit (E(Yi)) =natural log (odds)=β_0+β_1Xdemographic+ β_2Xcancer stage + β_3Xsocioecnomic+ β_4Xgeographical location

3.2.1.3 SubAim 1.2: To examine 12-month treatment patterns of asthma and prostate cancer management among prostate cancer patients with comorbid asthma after their prostate cancer diagnoses.

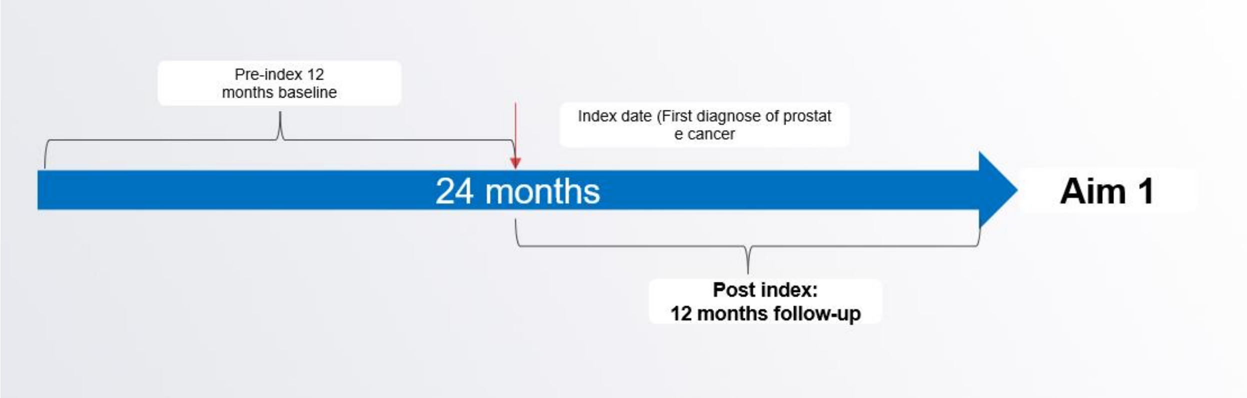
3.2.1.3.a Data Source

The 2007-2013 SEER-Medicare data files were used for SubAim 1.2. The data files were same as SubAim 1.1, please refer to section 3.2.1.2.a for more details about the data source.

3.2.1.3.b Study Sample

Medicare beneficiaries who were included in the SubAim 1.2 analysis fit the same inclusion and exclusion criteria for SubAim 1.1 (described in section 3.2.1.2.b). In addition, prostate cancer patients must be continuously enrolled in the Medicare Parts A, B, and D for 12 months after the index date (first prostate cancer diagnosis) unless they died after the index date. The new user design of SubAim 1.2 is elucidated in Figure 2.

Figure 2. New user study design for Aim 1 – SubAim 1.2



This information regarding prostate cancer definition was obtained from SEER Patient Entitlement and Diagnosis Summary File (PEDSF), using the three digits of the ICD-9, current procedural terminology (CPT) codes, and three digits of the ICD-O primary site codes. (Table 3.1, Table 3.2., Table 3.3)

3.2.1.3.c Measurements

In SubAim 1.2, the patterns of asthma treatments and prostate cancer treatments were identified and examined in the 12 months post-index period.

Receipt of asthma pharmacological treatments

Receipt of asthma pharmacological treatments was defined as at least one medication used for asthma management among long-term control group medications and quick-relief medications. Asthma treatment therapeutic classes were categorized as Anti-leukotrienes or leukotriene modifiers, Cromolyn sodium, Inhaled corticosteroids, Long-acting inhaled beta2-agonists, Methylxanthines, Oral corticosteroids, and Immunomodulators, respectively (see Table 3.1). Treatments were identified using the National Drug Code (NDC) and generic drug names in the Part D event data files.

Table 3.1: All asthma management medications[86]

Drug Class	Generic Name	Brand Name	Usual Dosage
Inhaled Corticosteroids (including combination inhalers)	Beclomethasone Dipropionate	Qvar 40 Redihaler Qvar 80 Redihaler	1-2 puffs twice a day 1-2 puffs of 40 or 80 twice a day
	Beclomethasone Dipropionate HFA	QVAR Inhalation Aerosol 40mcg/puff QVAR Inhalation Aerosol 80 mcg/puff	Children 5 to 11: 40 to 80 mcg twice a day. Adult: 40 to 320 mcg twice a day.
	Budesonide	Pulmicort Flexhaler 90 mcg Pulmicort Flexhaler 180mcg	Children 6 to 17: 180 mcg twice a day. Maximum is 360 mcg twice a day. Age 18 and older: 360 mcg twice a day. Maximum is 720 mcg twice a day.
		Pulmicort Respules 0.25 mg/2mL susp 0.5 mg/2mL susp 1 mg/2 mL susp	12 months to 8 years old: 0.5mg to 1 mg, either once a day or in divided doses.
	Ciclesonide	Alvesco Inhalation Aerosol 80mcg 160mcg	80 or 160 mcg 1 p bid daily
	Flunisolide	Aerobid Aerosol 250 mcg/puff Aerobid-M Aerosol 250 mcg/puff	Age 6 and older: 2 inhalations twice a day. Adult: 2 to 4 inhalations twice a day.
	Fluticasone Furoate	Arnuity Ellipta 100 or 200 mcg	12 and above 1 puff of 100 or 200 mcg
	Fluticasone Propionate	Flovent HFA 44 mcg Inhalation Aerosol Flovent HFA 110 mcg Inhalation Aerosol Flovent HFA 220 mcg Inhalation Aerosol Flovent Diskus 50, 100 and 250 mcg	Age 4 and above. Dosing varies. The dose must be adjusted by physicians. 44 is the weakest. 110 is intermediate. 220 is the strongest. Diskus does 1 or 2 inhalations two times per day.
	Mometasone	Asmanex Twisthaler 220mcg Asmanex Twisthaler 110mcg	Age 12 and older: 220 to 880 mcg. Children 4 to 11:110 mcg in the evening.
	Mometasone furoate HFA	Asmanex HFA 100 or 200 mcg	2 puffs twice a day
	Triamcinolone Acetonide	Azmacort Inhalation Aerosol 75mcg/spray	Age 6 to 12: 2 to 8 puffs a day in divided doses. Adults: 4 to 16 puffs a day in divided doses.
	Budesonide In combination with Formoterol (bronchodilator)	Symbicort 80/4.5 Symbicort 160 /4.5	Symbicort 80/4.5: 2 puffs twice a day. Symbicort 160/4.5: 2 puffs twice a day. Prescriber should designate the exact strength 80/4.5 or 160/4.5.

	Fluticasone Furoate 100 mcg and Vilanterol 25 mcg	Breo Ellipta	1 puff once a day
	Fluticasone furoate, umeclidinium and vilanterol	Trelegy Ellipta	1 puff per day
	Fluticasone in combination with Salmeterol (bronchodilator)	Advair Diskus: 100/50 Advair Diskus: 250/50 Advair Diskus: 500/50 Advair HFA 45/21 Advair HFA 115/21 Advair HFA 230/21	Age 4 to 11: Advair Diskus 100/50 Age 12 and older: Advair Diskus 100/50, 250/50 and 500/50 One inhalation twice daily. Advair HFA (all 3 strengths) Age 12 and older: 2 inhalations twice a day.
	Fluticasone Propionate and Salmeterol	AirDuo Respiclick 55/14, 113/14 and 232/14 and also generic of each	1 puff twice a day
	Mometasone in combination with Formoterol (bronchodilator)	Dulera 100/5 and 200/5	For ages 12 and above. Two puffs two times a day.
Oral Corticosteroids	Cortisone Acetate	Cortisone Acetate	10 mg Tablet 25 mg Tablet
	Dexamethasone	Dexamethasone	0.50 mg Tablet 0.75 mg Tablet 1.00 mg Tablet 1.50 mg Tablet 2.00 mg Tablet 4.00 mg Tablet 6.00 mg Tablet 4 mg/mL solution
	Hydrocortisone	Cortef	10mg/5 mL Suspension 5 mg Tablets 10 mg Tablets 20 mg Tablets
	Methylprednisolone	Medrol	4 gm Tablets 8 mg Tablets 16 mg Tablets 24 mg Tablets 32 mg Tablets
	Prednisolone	Orapred Prelone	15 mg/5 mL solution
		Pediapred	5 mg/ 5 mL solution
		Orapred ODT	10, 15 and 30 mg orally disintegrating tablets
	Prednisone		Tablets come as 1, 2.5, 5, 10 and 20 mg Oral Solution is 5mg/ 5 mL
Long-Acting Beta-Agonists (LABAs) Long-Acting Beta-Agonists (LABAs)	Albuterol Sulfate	VoSpireER Extended-Release Tablets	For relief of bronchospasm. Age 6 to 12: 4 mg every 12 hours Age 12 and older: 4 mg or 8 mg every 12 hours
	Formoterol Fumarate	Foradil Aerolizer	Prevent asthma symptoms (age 5 and older).

	(inhalation powder)	(Foradil is the capsule. Aerolizer is the inhaler)	Prevent exercise-induced asthma (age 5 and older). Occasional use once a day. One capsule is 12mcg; taken every 12 hours (age 5 and older).
	Salmeterol Xinafoate	Serevent Diskus (Serevent is the medication. Diskus is the inhaler)	Prevent asthma symptoms in patients 4 and older. One inhalation every 12 hours. Prevent exercise-induced asthma in patients 4 and older.
	Arformoterol Tartrate	Brovana Inhalation Solution	One 15 mcg vial every 12 hours by compressor/nebulizer. Approved for use in adults. To prevent bronchoconstriction in patients with COPD (chronic bronchitis and emphysema).
	Formoterol Fumarate (inhalation solution)	Perforomist Inhalation Solution	Long-term control of COPD (chronic bronchitis and emphysema). 20 mcg nebule every 12 hours.
	Olodaterol (2.5 mcg)	Striverdi Respimat	2 puffs daily COPD - adults
		Combination	
	Budesonide In combination with Formoterol (bronchodilator)	Symbicort 80/4.5 Symbicort 160 /4.5	Maintenance of asthma. Age 12 and older. Symbicort 80/4.5: 2 puffs twice a day. Symbicort 160/4.5: 2 puffs twice a day. Prescriber should designate the exact strength 80/4.5 or 160/4.5.
	Fluticasone furoate, umeclidinium and vilanterol	Trelegy Ellipta	Maintenance treatment of COPD 1 puff per day
	Fluticasone Propionate and Salmeterol	AirDuo RespiClick	12 and above: 1 puff twice a day
	Fluticasone Propionate and Salmeterol	Authorized generic of AirDuo RespiClick	12 and above: 1 puff twice a day
	Fluticasone Propionate and Salmeterol	AirDuo Respiclick 55/14, 113/14 and 232/14 and also generic of each	12 and over maintenance treatment of asthma 1 puff twice a day
	Fluticasone in Combination with Salmeterol (bronchodilator)	Advair Diskus: 100/50 Advair Diskus: 250/50 Advair Diskus: 500/50 Advair HFA 45/21 Advair HFA 115/21 Advair HFA 230/21	Control/prevent asthma. Age 4 to 11: Advair Diskus 100/50. Age 12 and older: Advair Diskus 100/50, 250/50 and 500/50. One inhalation twice daily. Advair HFA (all 3 strengths) Age 12 and older: 2 inhalations twice a day.

	Fluticasone furoate 100 mcg and Vilanterol 25 mcg	Breo Ellipta	For maintenance treatment and exacerbation reduction in COPD Maintenance of asthma age 18 and above. 1 puff once a day
	Glycopyrrolate/ Formoterol Fumarate	Bevespi Aerosphere	COPD Maintenance Treatment Adults 2 puffs twice a day
	Indacaterol/glycopyrrolate	Utibron Neohaler	COPD 1 dose twice a day
	Mometasone in Combination with Formoterol (bronchodilator)	Dulera 100/5 and 200/5	Control/prevent asthma For ages 12 and above. Two puffs two times a day.
	Tiotropium 2.5 mcg Olodaterol 2.5 mcg	Stiolto Respimat	COPD- adults 2 puffs daily
	Umeclidinium and Vilanterol	Anoro Ellipta 62.5.25 mcg	Maintenance treatment of airflow obstruction in COPD One inhalation once a day
Anticholinergics	Aclidinium Bromide (400 mcg)	Tudorza Pressair	COPD - adults 1 puff 2 times a day
	Glycopyrrolate	Seebri Neohaler	Maintenance treatment of COPD 1 dose twice a day
	Ipratropium Bromide/Albuterol	Combivent® Respimat®	For relief of bronchospasm of COPD. Approved for adults with COPD: 1 puff 4 times daily.
	Ipratropium Bromide HFA	Atrovent HFA Inhalation Aerosol	For relief of bronchospasm of COPD. Age 12 and above: 2 inhalations every 6 hours.
	Tiotropium (1.25 mcg)	Spiriva Respimat	Maintenance treatment of asthma 12 and above. 2 puffs (2.5 mcg) daily Exists as a 2.5 mcg per puff device for COPD in adults 2 puffs (5 mcg) daily
	Tiotropium Bromide Inhalation Powder	Spiriva HandiHaler Spiriva is the capsule of Tiotropium. HandiHaler is the device used to breath in the Spiriva.	For long-term relief of bronchospasm of COPD. Approved for adults with COPD. One capsule once a day taken with the HandiHaler.
	Umeclidinium	Incruse Ellipta	COPD Maintenance Treatment Adults 1 puff per day
	Combination		
	Fluticasone furoate, umeclidinium and vilanterol	Trelegy Ellipta	Maintenance treatment of COPD 1 puff per day
	Glycopyrrolate/ Formoterol Fumarate	Bevespi Aerosphere	COPD Maintenance Treatment Adults 2 puffs twice a day

	Indacaterol/glycopyrrolate	Utibron Neohaler	COPD 1 dose twice a day
	Tiotropium 2.5 mcg and Olodaterol 2.5 mcg	Stiolto Respimat	COPD- adults 2 puffs daily
	Umeclidinium and Vilanterol	Anoro Ellipta 62.5.25 mcg	Maintenance treatment of airflow obstruction in COPD One inhalation once a day
Cromolyn, Theophylline and Phosphodiesterase Inhibitors	Cromolyn Sodium	Generic Cromolyn Nebulizer Solution	One 20 mg unit-dose vial 4 times a day.
	Roflumilast	Daliresp	500 mg once a day
	Theophylline, Sustained release, Tablets and Capsules	Multiple products: Uniphyl as well as generic versions	Variable in each individual based upon weight.
Leukotriene Modifiers	Montelukast	Singulair 10 mg Tablet 5 mg Chewable Tablet 4mg Chewable Tablet 4 mg Oral Granules	Age 12 to 23 months: One packet of 4-mg oral granules daily. Age 2 to 5: One 4 mg tablet once a day. Age 6 to 14: One 5 mg tablet once a day. Age 15 and older: One 10 mg tablet once a day. To prevent exercise-induced asthma take 2 hours before activity.
	Zafirlukast	Accolate 10 or 20 mg Tablets	Age 5 to 11: One 10 mg tablet twice a day. Age 12 and older: One 20 mg tablet twice a day.
	Zileuton	Zyflo CR Tablets 600 mg	Age 12 and older: Two 600 mg tablets twice daily within 1 hour of meals.
Immunomodulator Medications	Benralizumab	Fasenra	Severe asthma age 12 and above. 30 mg subcutaneous injection accessorized pre-filled syringe to be dosed as 30 mg every 4 weeks for the first 3 doses, followed by once every 8 weeks thereafter
	Mepolizumab	Nucala	Severe asthma age 12 and above, with eosinophilic phenotype
	Omalizumab	Xolair	Treat allergic asthma age 6 and older
	Reslizumab	Cinqair	Severe asthma ages 12 and above, with eosinophilic phenotype

*Brovana and Perforomist are LABA medication approved for use in COPD not asthma. They are listed here for informational purposes only.

Prostate cancer treatments were identified and categorized as active surveillance, radical prostatectomy, radiation therapy, brachytherapy, ADT, chemotherapy (Alkylating agents, Antibiotics, Antimetabolites, and Mitotic inhibitors), and others (second-line hormones therapy, immunotherapy) based on the extent of prostate cancer. (Summary see Tables 3.2-3.4)

Table 3.2 Approach to Treatments of Prostate Cancer

Extent of Cancer	Therapeutic Options
Low risk: T1 or T2, GS=7, PSA<10 ng/ml	Active surveillance
	Radical prostatectomy
	Radiation therapy
	Brachytherapy
Intermediate risk: T2, GS=7, PSA=10-20 ng/ml	Active surveillance
	Radical prostatectomy
	Radiation therapy
	Brachytherapy
High risk: T3, GS>7, PSA>20 ng/ml	Radical prostatectomy
	Radiation therapy + ADT
	Brachytherapy + ADT
Node positive	ADT
	Radiation therapy + ADT
Metastatic Castration-Resistance Prostate Cancer (mCRPC)	ADT
	Second-line hormones
	immunotherapy
	Chemotherapy

ADT: androgen deprivation therapy;
GS: Gleason score
PSA: prostate specific antigen

Table 3.3: Medications Used for Treatments of Prostate Cancer and the HCPCS Codes[51,56]

Generic (brand) name	HCPCS code—code description	CPT administration codes
ADT		
1. LHRH Agonists		
leuprolide acetate (Eligard, Lupron Depot)	J9217 - Leuprolide acetate (for depot suspension), 7.5 mg	96402
leuprolide acetate (Lupron)	J9218 - Leuprolide acetate, per 1 mg	96402
Goserelin acetate (Zoladex)	J9202 - Goserelin acetate implant, per 3.6 mg	96372, 96402
Triptorelin (Trelstar Depot, Trelstar)	J3315 - Injection, triptorelin pamoate, 3.75 mg	96372, 96402
Histrelin (Vantas)	J9225 - Histrelin implant (Vantas), 50 mg	11981, 11982, 11983
2. LHRH Antagonist		
Degarelix (Firmagon)	J9155 – Injection, degarelix, 1 mg	96402
3. CYP17 Inhibitor		
Abiraterone acetate (Zytiga)	J8999 - Prescription drug, oral, chemotherapeutic, not otherwise specified	N/A
Abiraterone acetate (Zytiga)	C9399 - Unclassified drugs or biologicals (Hospital outpatient use only)	N/A
4. Anti-androgens		
Flutamide (Eulexin)	J8999 - Prescription drug, oral, chemotherapeutic, not otherwise specified	N/A
Flutamide (Eulexin)	S0175 - Flutamide, oral, 125 mg	N/A
Bicalutamide (Casodex)	J8999 - Prescription drug, oral, chemotherapeutic, not otherwise specified	N/A
Nilutamide (Nilandron)	J8999 - Prescription drug, oral, chemotherapeutic, not otherwise specified	N/A
Enzalutamide (Xtandi)	C9399 - Unclassified drugs or biologicals (Hospital outpatient use only)	N/A
Enzalutamide (Xtandi)	J8999 - Prescription drug, oral, chemotherapeutic, not otherwise specified	N/A
5. Estrogens		
Medroxyprogesterone (Depo-Provera)	J1050 - Injection, medroxyprogesterone acetate, 1 mg	96372, 96402
Megestrol acetate (Megace)	J8999 - Prescription drug, oral, chemotherapeutic, not otherwise specified	N/A
Megestrol acetate (Megace)	S0179 - Megestrol acetate, oral, 20 mg	N/A
estradiol valerate (Delestrogen)	J1380 - Injection, estradiol valerate, up to 10 mg	96372
estrogen (eg, estradiol, conjugated estrogen, esterified estrogen)	J8499 - Prescription drug, oral, nonchemotherapeutic, not otherwise specified	N/A
6. Others		
Ketoconazole (Nizoral)	J8499 - Prescription drug, oral, nonchemotherapeutic, not otherwise specified	N/A
Chemotherapy drugs		
Docetaxel (Taxotere, Docefrez)	J9171 - Injection, docetaxel, 1 mg	96413
Cabazitaxel (Jevtana)	J9043 - Injection, cabazitaxel, 1 mg	96413

Mitoxantrone (Novantrone)	J9293 - Injection, mitoxantrone hydrochloride, per 5 mg	96409, 96413
Estramustine (Emcyt)	J8999 - Prescription drug, oral, chemotherapeutic, not otherwise specified	N/A
Paclitaxel (Taxol)	J9267 - Injection, paclitaxel, 1 mg	96413, 96415
Melphalan (Alkeran)	J8600 - Melphalan, oral, 2 mg	N/A
Melphalan (Alkeran)	J9245 - Injection, melphalan hydrochloride, 50 mg	96409, 96413
Topotecan (Hycamtin)	J9351 - Injection, topotecan, 0.1 mg	96413
Trastuzumab (Herceptin)	J9355 - Injection, trastuzumab, 10 mg	96413, 96415
VinBLAStine (Velban)	J9360 - Injection, vinblastine sulfate, 1 mg	96409
Vinorelbine (Navelbine)	J9390 - Injection, vinorelbine tartrate, per 10 mg	96409
Bevacizumab (Avastin)	J9035 - Injection, bevacizumab, 10 mg	96413, 96415
Cisplatin (Platinol AQ)	J9060 - Injection, cisplatin, powder or solution, per 10 mg	96409, 96413, 96415
Cyclophosphamide (Cytoxan)	J8530 - Cyclophosphamide, oral, 25 mg	N/A
Cyclophosphamide (Cytoxan)	J9070 - Cyclophosphamide, 100 mg	96409, 96413, 96415
Epirubicin (Ellence)	J9178 - Injection, epirubicin hydrochloride, 2 mg	96409, 96413
ixabepilone (Ixempra)	J9207 - Injection, ixabepilone, 1 mg	96413, 96415
Vaccine Treatment		
Sipuleucel-T (Provenge)	Q2043 - Sipuleucel-T, minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF, including leukapheresis and all other preparatory procedures, per infusion (Code Price is per 250 mL)	96413, 96415
Corticosteroids		
Methylprednisolone (Medrol)	J7509 - Methylprednisolone, oral, per 4 mg	N/A
Methylprednisolone (Depo-Medrol)	J1020 - Injection, methylprednisolone acetate, 20 mg	11900, 11901, 20600, 20605, 20610, 96372
Methylprednisolone (Depo-Medrol)	J1030 - Injection, methylprednisolone acetate, 40 mg	11900, 11901, 20600, 20605, 20610, 96372
Methylprednisolone (Depo-Medrol)	J1040 - Injection, methylprednisolone acetate, 80 mg	11900, 11901, 20600, 20605, 20610, 96372
Methylprednisolone (Solu-Medrol)	J2920 - Injection, methylprednisolone sodium succinate, up to 40 mg	96365, 96366, 96372, 96374
Methylprednisolone (Solu-Medrol)	J2930 - Injection, methylprednisolone sodium succinate, up to 125 mg	96365, 96366, 96372, 96374
Prednisolone (eg, Orapred, Millipred)	J7510 - Prednisolone, oral, per 5 mg	N/A
Dexamethasone (Decadron)	J8540 - Dexamethasone, oral, 0.25 mg	N/A
Prednisone (Deltasone)	J7512 - Prednisone, immediate release or delayed release, oral, 1 mg	N/A
Other Adjuvant therapy medicine		
radium Ra dichloride (Xofigo)	A9606 - Radium Ra-223 dichloride, therapeutic, per microcurie	79101
Bacillus Calmette-Guérin (BCG Vaccine)	90585 - Bacillus Calmette-Guérin vaccine (BCG) for tuberculosis, live, for percutaneous use	90471, 90472
Bacillus Calmette-Guérin (Tice BCG)	90586 - Bacillus Calmette-Guérin vaccine (BCG) for bladder cancer, live, for intravesical use	51720
Bacillus Calmette-Guérin (Tice BCG)	J9031 - bCG (intravesical), per installation	51720

Finasteride (eg, Proscar)	S0138 - Finasteride, 5 mg	N/A

Table 3.4: CPT/ICD-9 Codes to Identify Prostate Cancer Treatments

Description: Prostate Cancer Treatment	
Surgery	
CPT Procedure Codes	
55801	Prostatectomy, perineal, subtotal
55810	Extensive Prostate Surgery
55812	Extensive Prostate Surgery
55815	Extensive Prostate Surgery
55821	Removal of Prostate
55831	Removal of Prostate
55840	Extensive Prostate Surgery
55842	Extensive Prostate Surgery
55845	Extensive Prostate Surgery
55859	Percut/Needle Insert - Pros
55860	Surgical Exposure - Prostate
55862	Extensive Prostate Surgery
55865	Extensive Prostate Surgery
ICD-9 Procedure Code	
60.3	Suprapubic prostatectomy
60.4	Retropubic prostatectomy
60.5	Radical prostatectomy
60.6	Other prostatectomy
60.61	Local excision of lesion of prostate
60.62	Perineal prostatectomy
60.69	Other prostatectomy
Radiation	
55866	Laparo Radical Prostatectomy
77750	Infuse Radioactive Materials
77761	Apply Intrcav Radiat Simple
77762	Apply Intrcav Radiat Interm
77776	Apply Interstit Radiat Simpl
77777	Apply Interstit Radiat Inter
77778	Apply Interstit Radiat Compl
77781	High Intensity Brachytherapy
77782	High Intensity Brachytherapy
77783	High Intensity Brachytherapy
77784	High Intensity Brachytherapy
77799	Radium/Radioisotope Therapy

G0256	Prostate brachytherapy implanting Palladium seeds
G0261	Prostate brachytherapy implanting iodine seeds
4200F	Prostate external beam radiotherapy as primary therapy
4201F	Prostate external beam radiotherapy to non-prostate only

3.2.1.3.d Statistical Analysis

Descriptive analyses were conducted to assess demographic, clinical, and treatment characteristics among the cohorts. Chi-squared tests for categorical variables and t-test for continuous variables were used to compare differences in treatment pattern across prostate cancer patients with and without asthma. Also, proportions of receipt of prostate cancer treatment by treatment type (active surveillance, radical prostatectomy, radiation therapy, brachytherapy, ADT, chemotherapy), drug class of ADT and chemotherapy, and drug category (classic, novel, hormone agents) across predictors were examined. The variable types of measurements and analytical plan for SubAim 1.2 are described in Table 3.5

Table 3.5 Summary of Outcome Variables, Measures, and Statistical Methods for SubAim1.2

Outcome variables	**Measures**	**Statistical methods**
Binary variables: Receipt of prostate cancer treatments by treatment category: 1. Observation (1 vs. 0) 2. Surgery or/and radiation (1 vs. 0) 3. ADT (1 vs. 0) 4. Chemo (1 vs. 0) 5. Others	Number of positive response (i.e., 1) to prostate cancer treatment category: 1. Observation, 2. Surgery or/and radiation 3. ADT 4. Chemo 5. Others	Descriptive analyses examining proportion of prostate cancer treatment
Binary variables: Receipt of ADT and Chemo agent for prostate cancer by drug class: 1. Alkylating agents (1 vs. 0) 2. Antibiotics (1 vs. 0) 3. Antimetabolites (1 vs. 0) 4. Hormones (1 vs. 0) 5. Mitotic inhibitors (1 vs. 0)	Number of positive response (i.e., 1) to prostate cancer treatment drug class: 1. Alkylating agents 2. Antibiotics 3. Antimetabolites 4. Hormones 5. Mitotic inhibitors	Descriptive analyses examining proportion of ADT and Chemotherapy agent was prescribed by drug class.
Binary variables: Receipt of **any** ADT and/or Chemo agent for prostate cancer (1 vs. 0)	Number of positive response (i.e., 1) to **any** ADT and/or Chemo agent for prostate cancer	Descriptive analyses examining proportion of any ADT and Chemotherapy gent was

	1. Alkylating agents 2. Antibiotics 3. Antimetabolites 4. Hormones 5. Mitotic inhibitors	prescribed by drug class.
Binary variables: Receipt of asthma treatment by drug class: 1. Anti-leukotrienes or leukotriene modifiers (1 vs. 0) 2. Cromolyn sodium (1 vs. 0) 3. Inhaled corticosteroids (1 vs. 0) 4. Long-acting inhaled beta2-agonists (1 vs. 0) 5. Methylxanthines (1 vs. 0) 6. Oral corticosteroids (1 vs. 0) 7. Immunomodulators (1 vs. 0)	Number of positive response (i.e., 1) to asthma treatment drug class: 1. Anti-leukotrienes or leukotriene modifiers 2. Cromolyn sodium 3. Inhaled corticosteroids 4. Long-acting inhaled beta2-agonists 5. Methylxanthines 6. Oral corticosteroids 7. Immunomodulators	Descriptive analyses examining proportion of asthma management gent was prescribed by drug class.

3.2.2 Aim 2: To assess the associations between comorbid asthma and clinical outcomes for patients with prostate cancer.

The approach for this aim was to conduct a new user cohort analysis to examine the incidences of clinical outcomes (All-cause ED visit, hospitalizations, and mortality; prostate cancer related ED visit, hospitalizations, and mortality) and assess the associations between comorbid asthma with these clinical outcomes among prostate cancer patients.

3.2.2.1 Rationale:

Emerging evidence suggests that inflammation, and more generally, the immune response influence the development of prostate cancer etiology.[10,109,110] For example, TH1 cells are predominant in the inflammatory influence in carcinoma, and some features of a TH2 response are also present.[111] On the other hand, evidence has shown that corticosteroid agents, the preferred treatment for long-term control of persistent asthma and also widely used in management of all types of prostate cancer (including the metastatic castration-resistant prostate cancer (mCRPC)), may promote prostate tumor progression with long-term use.[71] Knowledge gaps exist in the associations between comorbid asthma and its treatments with prostate cancer outcomes.

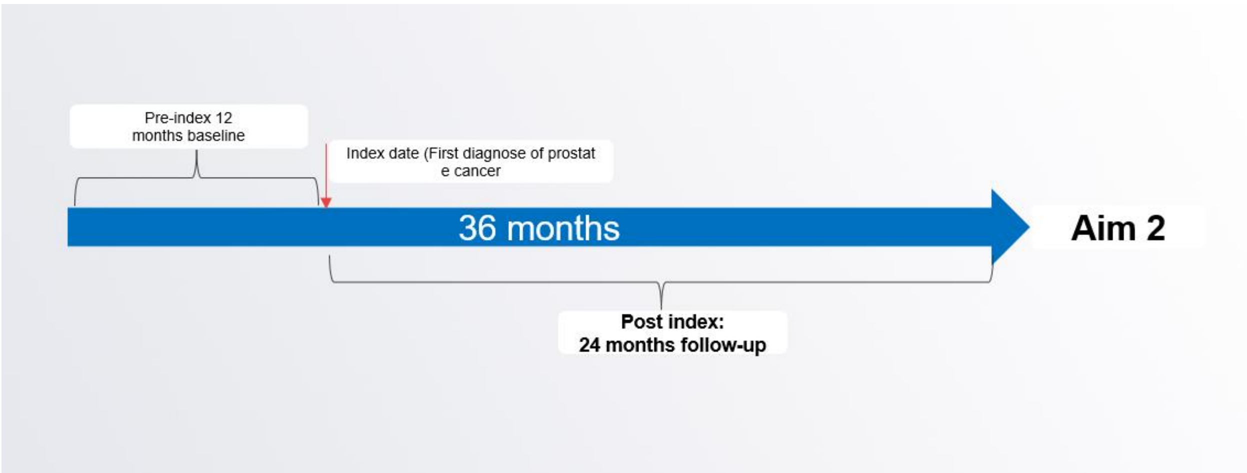
3.2.2.2 Data Source:

The same 2006-2014 SEER-Medicare data files were used for Aim 2. Please refer to section 3.2.1.2.a for more details about the data source.

3.2.2.3 Study Sample

Medicare beneficiaries who were included into the Aim 2 analysis fit the same inclusion and exclusion criteria for SubAim 1.1 (described in section 3.2.1.2.b). In addition, prostate cancer patients must be continuously enrolled in the Medicare Parts A, B, and D for 24 months after the index date (first prostate cancer diagnosis) unless they died after index date. If patients died after diagnosis, they must be continuously enrolled in Medicare fee-for-service Part A or Part B for at least 1 month after the index date, for a total of at least 13 months of continuous enrollment (12+1). The new user design of Aim 2 is elucidated in Figure 3.

Figure 3. New user study design for Aim 2



3.2.2.4 Hypothesis Tested in Aim 2:

H_0: There is no association between comorbid asthma and prostate cancer patients' clinical outcomes controlling for baseline covariates

H_A: There is association between asthma and prostate cancer patients' clinical outcomes controlling for baseline covariates

3.2.2.5 Measurements:

Clinical outcomes

Clinical outcomes assessed in Aim 2 included all-cause ED visits, hospitalizations, mortality, as well as prostate cancer related ED visits, hospitalizations, and mortality in a 24-month follow up period after the index date. All cause ED visit was identified by Revenue Center Code (045x) from Medicare outpatient file (OUTPAT file) and inpatient file (MEDPAR file), and Healthcare Common Procedure Coding System (HCPCS) codes (99281, 99282, 99283, 99284, and 99285) from Carrier Claims file (NCH file) based on previous studies.[112-116] Prostate cancer related ED visit was identified by using the same Revenue Center Code, HCPCS codes, and combine with primary diagnosis of prostate cancer (ICD-9-CM diagnosis code 185) through Medicare inpatient and outpatient claims data files. Both all-cause ED visits and prostate cancer related ED visits will exclude duplicate. To exclude duplicate claims, we considered outpatient or inpatient claims conducted at the same hospital (defined by Medicare provider number) and by the same physician (defined by NPI number) on the same date without use of coding modifier 25 or 27, which indicate unique same day ED visits, to be duplicate claims. Duplicate provider claims were excluded. All-cause hospitalizations and prostate cancer related hospitalization were identified by using the date the beneficiary was admitted for inpatient care or the date that care started and combine with primary diagnosis of prostate cancer (ICD-9-CM diagnosis code 185) from the inpatient file (MEDPAR file). All-cause mortality and prostate cancer mortality were identified using the date of death which is available in both SEER and Medicare PEDSF files by using the variable of "Date of Death Flag" and "Cause of Death ICD-9" (185) respectively.

Predictors and covariates

Comorbid asthma

Prostate cancer patients with comorbid asthma were identified by using the same strategies described in Aim 1 (section 3.2.1.2.c).

Beneficiary's demographic characteristics and comorbidities at baseline

Beneficiary's characteristics included age, ethnicity/race, and region from SEER and Medicare PEDSF files.

Other comorbidities were calculated based on the Charlson comorbidity index[73]. Comorbidities were extracted from inpatient, outpatient, and physician Medicare claims for specific ICD-9-CM codes at any time during 1 year before the prostate cancer diagnosis. For physician and outpatient claims, a patient's diagnoses must appear on at least two different claims that are more than 30 days apart. Asthma and prostate cancer were excluded from comorbidities calculation.

Beneficiary's socioeconomic status at baseline

Since patient-level data regarding socioeconomic status are not available in the SEER-Medicare data files, we used median household income, education level, poverty level from the census tract variables to represent socioeconomic status.[72, 73] The 5-digit Zip code of each beneficiary in the enrollment files was used to match with the 2010 Urban Area to ZIP Code Tabulation Area (ZCTA) Relationship File to determine beneficiary's residence in urban or rural area.

Prostate cancer tumor characteristics and stage, including stage, grade, tumor size, number of positive lymph nodes, and positive results of bone metastases were obtained from the Patient Entitlement and Diagnosis Summary File (PEDSF) in SEER database. The patients' cancer stage was identified based on the American Joint Committee on Cancer (AJCC) 7th edition criteria. Prostate cancer treatment variables, including surgery, radiation, ADT and chemotherapy, were defined using corresponding HCPCS, CPT, and ICD-9 procedure codes in the Medicare claims and/or the SEER database.

- Surgery: We collected data on surgery during 12 months after prostate cancer diagnosis using HCPCS, ICD-9 and CPT procedure cods. Data were retrieved from Medicare inpatient claims, outpatient claims, and Part B bills (Table 3.4).
- Radiation: During 12 months prostate cancer diagnosis using HCPCS, ICD-9, CPT, revenue center codes, and SEER variables (radiation delivery). Data were retrieved from Medicare inpatient claims, outpatient claims, Part B bills, and SEER (radiation delivery variables and codes, Table 3.4).
- Androgen deprivation therapy (ADT): We identified ADT use for 12 months after prostate cancer diagnosis using HCPCS and CPT procedure codes (Table 3.3). Data were retrieved from Medicare inpatient claims, outpatient claims, and Part B bills.
- Chemotherapy exposure: We identified chemotherapy during 12 months after prostate cancer diagnosis using HCPCS and CPT procedure codes (Table 3.3). Data were retrieved from Medicare inpatient claims, outpatient claims, and Part B bills.

3.2.2.6 Statistical analyses

Baseline prostate patient and tumor characteristics were compared using the chi-square test for categorical variables and t-test for continuous variables across asthma and non-asthma groups. The cumulative incidence of all outcome variables was calculated using Kaplan-Meier estimates and was compared using the log-rank test. Time to the outcome was calculated in months from the date of prostate cancer diagnosis to the date of the event. Adjusted Hazard Ratios (AHRs) and 95% confidence intervals (CIs) of outcomes at a given time were compared across asthma vs. non-asthma groups, using multivariate Cox proportional hazards models, adjusting for covariates, including patient demographics, tumor characteristics, socioeconomic status, ADT, chemotherapy, radiation, surgery, and comorbidities. Two multivariable negative binomial models were performed to examine patient factors associated with numbers of all-cause and prostate related hospitalization and ED visits in the 2 years follow up period as sensitivity analyses. Adjusted Relative Risk (ARRs) and 95% confidence intervals (CIs) of outcomes were compared across asthma vs. non-asthma groups by adjusting for covariates, including patient demographics, tumor characteristics, socioeconomic status, ADT, chemotherapy, radiation, surgery, and comorbidities. All the variable types of measurements and analytical plan for aim 2 are described in Table 3.6. All analyses used SAS version 9.4 (SAS Institute Inc., Cary, NC).

Table 3. 6 Summary of Outcome Variables, Measures, and Statistical Methods for Aim 2

Outcome Variables	**Predictors and Covariates**	**Statistical Methods**
Descriptive Analyses		
Binary variables: Clinical outcomes: 1. All-cause ED visit (1 vs. 0) 2. All-cause mortality (1 vs. 0) 3. All-cause hospitalizations (1 vs. 0) 4. Prostate cancer related ED visit (1 vs. 0) 5. Prostate cancer related hospitalization (1 vs. 0) 6. Prostate cancer related mortality (1 vs. 0)	1. Patient characteristics and geographical area, including age in years at prostate cancer diagnosis, ethnicity/race, region (state level), and socioeconomic status 2. Patient tumor characteristics, including stage, grade, tumor size, and number of positive lymph nodes 3. CCI 4. Prostate cancer treatment variables, including surgery, radiation, ADT, and chemotherapy	Descriptive analyses examined proportions of comorbid asthma by all covariates among prostate cancer patients Kaplan-Meier curves was used to describe and compare the cumulative rates of all outcome variables by baseline comorbid asthma status **Cox proportional hazard models was used to** estimat e the risks of outcomes betw een **Exposed group:** Asthma V S. **non-exposed group:** non -asthma controlling for patient characteristic, tumor characteristic, socioeconomic status, chemotherapy, radiation, surgery, and comorbidities

3.2.3 Aims 3: To assess the associations between long-term use of corticosteroids and clinical outcomes for patients with prostate cancer and comorbid asthma. The approach for this aim was to conduct a new user cohort analysis to assess the effect of long-term corticosteroids uses on clinical outcomes among prostate cancer patients with comorbid asthma. The clinical outcomes included all-cause mortality, all-cause ED visits and hospitalizations, prostate cancer related and cardiovascular related ED visits and hospitalizations, and prostate cancer related mortality.

3.2.3.1 Rationale:

Corticosteroid agents, the preferred treatment for long-term control of persistent asthma, also are widely used in the management of all types of prostate cancer, including the metastatic castration-resistant prostate cancer (mCRPC). Emerging evidence has shown that long-term use of corticosteroids may promote prostate tumor progression when long-term use.[71] In addition, patients undergoing long-term corticosteroid use may increase risks of medication related adverse events, such as insulin intolerance, cardiovascular diseases, or fracture.[72,80,82] Knowledge gaps exist in the associations between long-term use of corticosteroid medications and clinical outcomes among prostate cancer patients comorbid with asthma.

3.2.3.2 Data Source

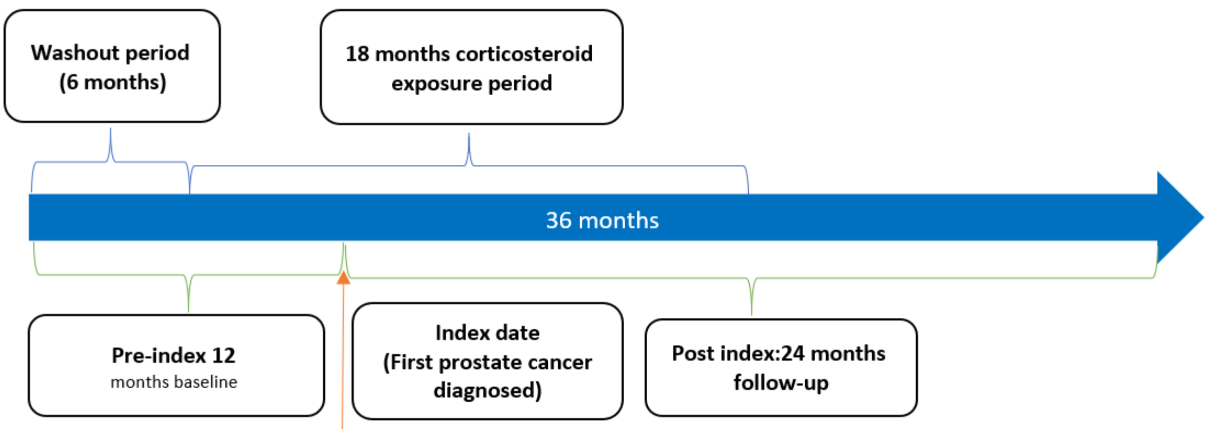
The same 2007-2014 SEER-Medicare data files were used for Aim 3. Please refer to section 3.2.1.2.a for more details about the data source.

3.2.3.3 Study Sample

Medicare beneficiaries who were included in the Aim 3 analysis fit the same inclusion and exclusion criteria for SubAim 1.1 (described in section 3.2.1.2.b). In Aim 3, the use of corticosteroid medications was captured as a continuous exposure both before (12 months) and after (24 months) prostate cancer diagnosis. It was defined as a filled corticosteroid inhaled or oral prescription during this period, and it was incident use since we used a six months washout period to identify new users of corticosteroids. The date of the first corticosteroid prescription observed during the 18 months of pre-post prostate cancer diagnosis (6 months pre and 12 months after) was considered as time zero to measure the duration of corticosteroids use.

In addition, newly diagnosed prostate cancer patients must be continuously enrolled in the Medicare Parts A, B, and D for 24 months after the index date. The new user design of Aim 3 is elucidated in Figure 4. Patients were included in the analysis if they were male who were at the first diagnosis of prostate cancer. (**Figure 4**). Beneficiaries who died before the index date were excluded. Finally, beneficiaries included in Aim 3 must be continuously enrolled in the Medicare fee-for-service Part A, Part B, and Part D for at least 13 months (12 months baseline + 1 months after first prostate cancer diagnosis) if they died, or for a total of at least 36 months of continuous enrollment (12+24) if they were alive till the end of study observation.

Figure 4. New user study design for Aim 3



3.2.3.4 Hypothesis Tested in Aim 3:

H_0: There is no association between long-term corticosteroids use and the clinical outcomes for patients with prostate cancer and comorbid asthma controlling for baseline covariates at a given time

H_A: There is an association between long-term corticosteroids use and the clinical outcomes for patients with prostate cancer and comorbid asthma controlling for baseline covariates at a given time

3.2.3.5 Measurements:

Clinical outcomes

Clinical outcomes assessed in Aim 3 were the same as described in section **3.2.2.5**, including all-cause mortality, all-cause ED visits and hospitalizations, as well as prostate cancer related ED visits and hospitalizations, and prostate cancer related mortality.

In addition, adverse events related to long-term use of corticosteroid medications were also examined, which included the incidence of insulin resistance and cardiovascular diseases ED visit and hospitalization.

Table 3.7 Diagnosis Codes Used to Identify Cardiovascular Related ED Visit and Hospitalizations in Medical Claims[64,66,67]

Disease	ICD-9 Code
Cardiovascular Disease	
Hear Failure	402.01, 402.11,402.91,404.1,404.91,404.93, 428.x
Cardiomyopathy	425.x
Atrial Fibrillation / Flutter	427
Coronary heart disease	410-414
Angina	413
Other form of heart disease	420-429
Hypertension	401-405
Cerebrovascular disease (stroke)	430-438
Disease of arteries, arterioles, and capillaries	440-448
Disease of veins and lymphatics and other diseases	451-459
Congenital cardiovascular anomalies	745-747
Disease of pulmonary circulation	415-417
Renal failure	403-404, 588, V42.0, V45.1, 585.x, 586.x, V56.x
Hyperlipidemia	272.x

Predictors and covariates

In addition to the predictors and covariates in Aim 2, we included long-term corticosteroids exposure in the analysis.

Long term use of corticosteroids exposure

Corticosteroid medication use in the entire exposure period (up to 18 months) was assessed as a time-dependent exposure (monthly flag). In addition, the average daily dosage of corticosteroids use was also measured and categorized as low or intermediate daily dosage (<7.5mg/day) and high daily dosage (≥ 7.5mg/day) based on previous studies.[117,118] Combining both exposure duration and dosage, the exposure of corticosteroid use was further categorized in the following categories: 1) No corticosteroid medication use; 2) Short-term corticosteroid medication use (<6 months) with low or intermediate daily dosage (<7.5mg/day); 3) Short-term corticosteroid medication use (<6 months) with high daily dosage (≥ 7.5mg/day); 4) Long-term corticosteroid medication use (≥ 6 months) with low or intermediate daily dosage (<7.5mg/day); and 5) Long-term corticosteroid medication use (≥ 6 months) with high daily dosage (≥ 7.5mg/day). Patients were defined as treatment discontinuation if they had a refill gap (i.e., >90 days) between two corticosteroid prescriptions.

3.2.3.6 Weighting

Since observational studies are a lacking random assignment, imbalances in confounding factors between treatment and control groups should be adjusted to reduce bias on the effect of the intervention. A propensity scoring technique, which has been used in many observational studies,[119-122] was applied to reduce a potential selection bias that affected both the treatment and the outcome of interest. Approaches such as adjustment weighting, matching, and stratification using propensity scores are widely used techniques to compare groups, usually comparing a treatment group to a non-treatment group. However, selecting a control group using propensity score matching usually reduces sample size dramatically.[123] Therefore, in our study, propensity score weighting was used to balance corticosteroid exposure and non-exposure groups. The propensity score is the conditional probability of each patient receiving a particular treatment based on pretreatment variables. Specifically, the approach is used to estimate the probability (or propensity) that an individual patient under a condition or received treatment (i.e., using inhaled or oral corticosteroids medications). Using the LOGISTIC procedure, propensity scores were calculated based on the 10 covariates listed in Table 4.10. The objective was to balance factors between the corticosteroids exposure and non-exposure groups to reduce the bias of treatment selection and obtain a better idea of treatment effect on the outcome of compliance. Weighting variables for the propensity score included patient's baseline covariates: patient characteristics, including age (in years at prostate cancer diagnosis), race/ethnicity; socioeconomic status; tumor characteristics, including stage, and grade; diagnosis year; Charlson comorbidity index; SEER region.

3.2.3.7 Statistical analyses

Baseline prostate patient and tumor characteristics were compared using the chi-square test for categorical variables and t-test for continuous variables across asthma with long-term use of corticosteroid medications and non/or short-term use groups. The cumulative incidence of outcomes were calculated using Kaplan-Meier estimates and were compared using the log-rank test. Hazard Ratios (HRs) and 95% confidence intervals (CIs) of outcomes at a given time were compared across different corticosteroid exposure groups using multivariate Cox proportional hazards models. The models were adjusted for covariates that were not included in the previous propensity score weighting process, which include prostate cancer treatment patterns (Active surveillance, Surgery or Radiation, ADT, chemotherapy, and multiple treatments). We performed two sensitivity analyses to examine the validity of our findings: (a) limiting to patients without any corticosteroids use at baseline 12 months; and (b) grouping post-prostate cancer diagnosis corticosteroids exposure as long-term, short term, and no use, and add average daily dosage as a time-dependent exposure.

All the variable types of measurements and analytical plan for aim 3 are described in Table3.8. All analyses used SAS version 9.4 (SAS Institute Inc., Cary, NC).

Table 3.8 Summary of Outcome Variables, Measures, and Statistical Methods for Aim 3

Outcome variables	**Covariates**	**Statistical methods**
<u>Binary variables:</u> Clinical outcomes: 1. All-cause ED visit (1 vs. 0) 2. All-cause hospitalizations 3. All-cause mortality (1 vs. 0) 4. Prostate cancer related ED visit (1 vs. 0) 5. Prostate cancer related mortality (1 vs. 0) 6. Cardiovascular related ED visit (1 vs. 0) 7. Cardiovascular related hospitalization (1 vs. 0)	1. Patient characteristics and geographical area, including age in years at prostate cancer diagnosis, ethnicity/race, region (state level), and socioeconomic status 2. Patient tumor stages 3. CCI 4. Prostate cancer treatment variables, including surgery, radiation, ADT, and chemotherapy	Descriptive analyses examining proportion of prostate cancer patients comorbid with asthma who had ED visit event or hospitalizations or die after prostate cancer diagnosis A Cox proportional hazard model estimating the risks of all-cause ED visit, hospitalizations, mortality, cardiovascular related ED visit, hospitalization, and prostate cancer related ED visit, hospitalization, and mortality between **<u>Exposed group</u>:** long-term use of corticosteroids agents **VS. <u>non-exposed group</u>:** non-use or short-term use of corticosteroids agents, controlling for patient characteristic, tumor characteristic, socioeconomic status, chemotherapy, radiation, surgery, and comorbidities

The Cox proportional hazards models:

$h(t|X)$ = a conditional hazard of outcome (yes/no), $h0(t)$= an unspecified baseline hazards, and t=a patient's time of outcome with time measured in months.

$h(t|X) = h_0(t)\exp(\beta_1 X\text{tumor characteristic}+\beta_2 X\text{type of chemotherapy}+ \beta_3 X\text{ADT} +\beta_4 X\text{radiation}+ \beta_5 X\text{surgery}+ \beta_6 X\text{comorbidities})$

Chapter 4 Results

4.1 Results for Aim 1

4.1.1 Annual trends in the proportion of asthma among prostate cancer patients and non-cancer patients

Figure 5.1 describes annual trends in the proportion of asthma among prostate cancer patients and non-cancer patients in 2007-2014. Overall, trends were stable in both prostate cancer and non-cancer cohorts over time (P_{trend}=0.35 and P_{trend}=0.47, respectively). Among patients with prostate cancer, proportion of comorbid asthma was 13.20% (95% CI=14.07, 12.76) in 2007 and 15.71% (95% CI=14.89, 16.21) in 2014. Among non-cancer patients, the proportion of asthma was 12.91 % (95% CI=12.02, 31.86) in 2007 and 14.50% (95% CI=13.22, 15.13) in 2014. Overall, the annual proportion of asthma was slightly higher among prostate cancer patients compared to non-cancer patients.

4.1.2 Patient characteristics and treatment patterns of prostate cancer and asthma

Table 4.1 presents detailed treatment patterns of prostate cancer and asthma in 12 months among patients with prostate cancer and non-cancer patients. Of the 69,803 prostate cancer patients identified between 2007 and 2014, approximately 15.87% of them had asthma compared with 14.35% in non-cancer patients.

Among patients with prostate cancer, the top three prostate cancer management in 12 months after prostate cancer diagnosis were ADT only (25.83% vs. 23.04%), Active Surveillance (12.34% VS. 17.88%), and Radiation only (9.32% vs. 11.45%) in patients with and without comorbid asthma, respectively. Overall, prostate cancer treatment patterns were significantly different between those with and without comorbid asthma ($P<0.0001$). Specifically, the higher proportion of prostate cancer patients with comorbid asthma received ADT only, chemotherapy only, chemotherapy+corticosteroids, chemotherapy+other adjuvant therapy, and multiple managements compared to those without comorbid asthma. However, the proportion of active surveillance among prostate cancer patients with comorbid asthma was lower than those without asthma.

Asthma treatment patterns were also different between prostate cancer patients and non-cancer patients with asthma ($P=0.0178$). In both cohorts, inhaled corticosteroids (62.29% vs. 71.05%) and quick relief agents (14.35% vs. 14.02%) were the top two treatments, respectively. Compared to non-cancer patients, the higher proportion of prostate cancer patients with comorbid asthma received quick relief agents, oral corticosteroids only, long-acting beta-agonists only, and multiple treatments comparing with non-cancer asthma patients. However, the proportion of prostate cancer patients with comorbid asthma who received inhaled corticosteroids only was lower than non-cancer patients.

4.1.3 Factors associated with comorbid asthma among patients with prostate cancer

Table 4.2 summarizes the descriptive characteristics of patients with prostate cancer by asthma status. The higher proportion of prostate cancer patients with asthma were older in age (65-74), black, with more advanced cancer stage, not married, and have more chronic diseases compared to those without asthma (all $P<0.05$). Results from the multivariable logistic regression model found that prostate cancer patients who were older (65-74 vs. <65 (adjusted odds ratio [AOR]=1.27 with 95% CI=1.04-2.09), black (AOR=1.29 with 95% CI=1.04-2.39), were diagnosed in stage IV prostate cancer (AOR=1.27 with 95% CI=1.08-1.49), and had two or more chronic diseases (AOR=1.16 with 95% CI=1.12-1.39) were more likely to have comorbid asthma compared to their counterparts. However, those prostate cancer patients who were currently married were less likely to have comorbid asthma compared to those who were not married (AOR=0.80 with 95% CI=0.61-1.31). Other factors were not statistically associated with the likelihood of having comorbid asthma.

Table 4.1: Prostate Cancer and Asthma Treatment Patterns among Prostate Cancer Patients and Non-cancer Patients

Treatment Patterns	Prostate Cancer Patients N=69,803				P Value	Non-cancer Patients N=89,145				P Value
	Asthma		Non-Asthma			Asthma		Non-Asthma		
	N	%	N	%		N	%	N	%	
	11,078	15.87	58,725	84.93		12,792	14.35	76,353	85.65	
Prostate Cancer					**<0.0001**					
Active surveillance	1367	12.34	10500	17.88						
Surgery only	994	8.98	5878	10.01						
Radiation only	1032	9.32	6724	11.45						
ADT only	2861	25.83	13530	23.04						
Chemotherapy only	706	6.37	3506	5.97						
Immunotherapy only	113	1.02	546	0.93						
ADT[1] + Radiation	688	6.21	3541	6.03						
ADT + Surgery	922	8.32	4710	8.02						
ADT + Corticosteroids	893	8.06	4657	7.93						
Chemotherapy + Corticosteroids	471	4.25	1773	3.02						
Chemotherapy + Other adjuvant therapy	323	2.91	1198	2.04						
Multiple Managements[2]	597	5.39	2537	4.32						
Asthma										**0.0178**
Quick Relief Agents only[3]	1590	14.35				1793	14.02			
Inhaled Corticosteroids only	6900	62.29				9089	71.05			
Oral Corticosteroids only	910	8.21				681	5.32			
Long-Acting Beta-Agonists only	828	7.47				544	4.25			
Anticholinergics only	357	3.22				302	2.36			
Cromolyn, Theophylline and Phosphodiesterase Inhibitors only	267	2.41				165	1.29			
Leukotriene Modifiers only	114	1.03				100	0.78			
Immunomodulator Medications Only	113	1.02				119	0.93			
Multiple Treatments[4]	846	7.64				718	5.61			

1. ADT: Androgen Deprivation Therapy

2. Multiple Managements for prostate cancer include patients who received more than two management agents such as ADT+Surgery/Radiation+Second-line hormones/Vaccine Treatment

3. Quick Relief Agents includes short-acting beta-agonists Albuterol (ProAir HFA, Proventil HFA, Ventolin HFA), Levalbuterol (Xopenex HFA), Metaproterenol, Terbutaline

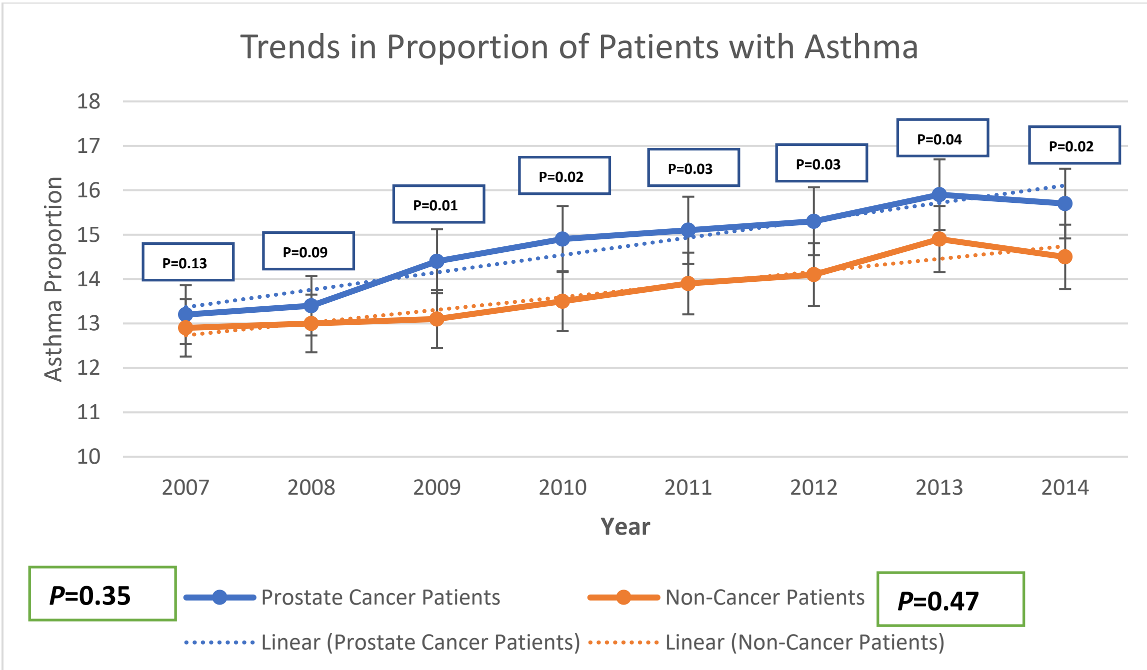
4. Multiple Treatments for asthma include patients who received more than two management agents such as Inhaled corticosteroids + quick relief, Inhaled corticosteroids + Long-Acting Beta-Agonists/Anticholinergics/ Leukotriene Modifiers/ Immunomodulator Medications

Table 4.2: Sample Characteristics and Factors Associated with Comorbid Asthma among SEER-Medicare Prostate Cancer Patients in 2007-2014

Characteristics	Prostate cancer N=70,325			Prostate cancer patients with asthma
	Asthma	Non-asthma	P Value	AOR (95% CI)
	N=11,245 (15.99%)	N=59,080 (84.01%)		
Age at Diagnose			**0.0035**	
<65	494 (4.39%)	1926 (3.26%)		Ref
65-74	5339 (47.48%)	26816 (45.39%)		**1.27 (1.04—2.09)**
75-84	4726 (42.03%)	26184 (44.32%)		1.15 (0.89—1.72)
>84	686 (6.10%)	4153 (7.03%)		0.83 (0.74—1.47)
Race				
White	8132 (72.32%)	45450 (76.93%)	**<0.0001**	Ref
Black	2040 (18.14%)	7834 (13.26%)		**1.29 (1.04—2.39)**
Others*	1073 (9.54%)	5796 (9.81%)		0.87 (0.71—1.25)
Urban vs. rural				
Urban	10347 (92.01%)	54360 (89.33%)	0.3286	1.10 (0.82—1.25)
Rural	898 (7.99%)	4720 (10.67%)		Ref
ESRD				
No	10848 (96.47%)	56221 (95.16%)	0.0587	Ref
Yes	397 (3.53%)	2859 (4.84%)		1.03 (0.87—1.32)
Low income subsidy eligible			0.1275	
No	10720 (95.33%)	56740 (96.04%)		Ref
Yes	525 (4.67%)	558 (3.96%)		0.84 (0.71—1.14)
Stage			**<0.0001**	
I	2139 (19.02%)	12602 (21.33%)		Ref
II	5654 (50.28%)	31005 (52.48%)		0.86 (0.68—1.12)
III	2428 (21.59%)	11863 (20.08%)		1.05 (0.81—1.19)
IV	1024 (9.11%)	3610 (6.11%)		**1.27 (1.08—1.49)**
Marital status			**<0.0001**	
Not married	4641 (41.27%)	23260 (39.37%)		Ref
Currently Married	5956 (52.97%)	33800 (57.21%)		**0.80 (0.61—1.31)**
Unknown	648 (5.76%)	2021 (4.09%)		1.11 (0.72—1.25)
SEER region			0.3064	
Northeast	2316 (20.60%)	11704 (19.81%)		Ref
Midwest	2770 (24.63%)	13984 (23.67%)		0.83 (0.71—1.12)
South	2990 (26.31%)	16861 (28.54%)		1.03 (0.64—1.20)
West	3169 (28.18%)	16531 (27.98%)		1.14 (0.78—1.28)
Median Household income			0.4731	
Quartile 1 (lowest)	2626 (23.35%)	13541 (22.92%)		Ref
Quartile 2	2729 (24.27%)	14386 (24.35%)		1.05 (0.74—1.26)
Quartile 3	2920 (25.97%)	15018 (25.42%)		1.07 (0.78—1.29)
Quartile 4 (high)	2970 (26.41%)	16135 (27.31%)		1.12 (0.81—1.31)
Education (high school graduation rates)			**0.0373**	
Quartile 1 (lowest)	3753 (33.35%)	13541 (22.33%)		Ref
Quartile 2	2506 (22.27%)	14386 (25.79%)		1.02 (0.84—1.14)
Quartile 3	2821 (25.07%)	15018 (26.84%)		0.97 (0.72—1.09)
Quartile 4 (high)	2173 (19.31%)	16135 (25.04%)		0.91 (0.79—1.15)
Comorbidity Score*			**<0.0001**	
0	3107 (28.12%)	17535 (29.68%)		Ref
1	5214 (46.37%)	27986 (47.37%)		0.93 (0.75—1.29)
≥2	2924 (31.20%)	13559 (22.95%)		**1.16 (1.12—1.39)**

*Comorbidity Score was adjusted by excluding asthma and prostate cancer
AOR: adjusted odds ratio; CI: confidence interval; ESRD: end stage renal disease

Figure 5.1. Annual Trends of Proportion of Asthma among Prostate Cancer Patients and Non-Cancer patients in SEER-Medicare from 2007-2014



4.2 Results for Aim 2

4.2.1 Descriptive estimates of clinical outcomes

Between 2007 and 2012, a total of 46,307 prostate patients with and without asthma were included in our study (Table 4.3). Table 4.3 describes the descriptive estimates of all clinical outcomes by comorbid asthma status in prostate cancer patients in the 24 months follow up period. The cohort included 7,046 (15.22%) prostate cancer patients with comorbid asthma and 39,261 (84.78%) without asthma. Among prostate cancer patients with asthma, 3,176 (45.07%) had all-cause hospitalization events, which was higher than 16,627 (42.35%) with all-cause hospitalization in patients without asthma (P=0.0012). In addition, the mean (SD) number of all-cause hospitalizations in patients with asthma was higher than in those without asthma patients (0.68 (1.21) vs. 0.55 (1.01), P<0.0001). Similarly, there were 4,085 (57.97%) patients with asthma who had all-cause ED visits, compared with 17,039 (42.35%) in patients without asthma (P<0.0001), and the mean (SD) number of all-cause ED visit in patients with asthma was also higher than in non-asthma patients (0.81 (1.05) vs. 0.52 (0.79), P<0.0001). For all-cause mortality, the proportion of patients with asthma who passed away in 2 years was not statistically significantly different than those without asthma (6.02% vs. 5.06%, P=0.0551).

For analyses focused on prostate cancer related clinical outcomes, there were 2,116 (30.00%) of prostate cancer patients with asthma who experienced prostate cancer related hospitalization, which was lower than patients without asthma (20.12%). The mean (SD) number of prostate cancer related hospitalizations in patients with asthma was higher than in patients without asthma (0.29 (0.45) vs. 0.14 (0.42), P<0.0001). For prostate cancer related ED visits, there were 351 (4.98%) of patients with asthma and 1,694 (4.31%) of patients without asthma who had prostate cancer related ED visits, but it was not statistically significantly different (p=0.2376). For prostate cancer related mortality, the proportion of patients with asthma who passed away in 2 years was not statistically significantly different than those without asthma (1.87% vs. 1.81%, P=0.1366).

4.2.2 Kaplan-Meier curves

Figure 5.2 depicts the Kaplan-Meier plot for time to first all-cause hospitalization events among patients with prostate cancer. The Kaplan-Meier survival probability estimates for all-cause hospitalization at 24 months were about 0.42 for patients with asthma and 0.58 for patients without asthma, respectively (log-rank P<0.0001). Lower survival probability for all-cause ED visits also exists among patients with asthma compared to those without asthma (Figure 5.3, 0.42 vs. 0.61, respectively, P<0.0001). However, the survival probability for all-cause mortality was similar to prostate cancer patients with and without asthma (Figure 5.4, P=0.1937). For prostate cancer related outcomes, patients with asthma had lower survival probability for prostate cancer related hospitalization compared to those without asthma (Figure 5.5, 0.77 vs. 0.83, respectively, P<0.0001), but they had similar survival probabilities for prostate cancer related ED visits and mortality (Figures 4.6 and 4.7).

4.2.3 Unadjusted differences in comorbid asthma and patient characteristics by clinical outcomes

Tables 4.4 and 4.5 describe and compare patient characteristics of all-cause and prostate cancer related clinical outcomes, respectively. Of the 46,307 prostate cancer patients, after 2 years of prostate cancer diagnosis, 19,803 (42.76%) had at least one all-cause hospitalization event, 21,124 (45.62%) had at least one all-cause ED visit, and 2,411 (5.28%) passed ways for any causes (Table 4.4). Among these prostate cancer patients, 10,016 (21.63%) had prostate cancer related hospitalizations, 2,045 (4.42%) had prostate cancer related reasoned visits, and 843 (1.82%) passed way because of prostate cancer (Table 4.5).

As shown in Table 4.4, higher proportions of patients with all-cause hospitalization events were those who received chemotherapy, surgery, or received multiple treatments in the 2-year follow up period (15.60%, 22.58%, 30.25%, respectively) than patients without all-cause hospitalizations. Compared with corresponding age subgroups who did not have all-cause hospitalization events, prostate cancer patients in 76-85 and >85 years old had higher proportions of all-cause hospitalizations (63.87% and 10.59%, respectively). Those patients who lived in southern regions had a more advanced stage of cancer, and those who had more comorbidities had a higher likelihood of all-cause hospitalizations (all $P<0.05$).

In addition, higher proportions of patients with all-cause ED events were those who received ADT or chemotherapy or multiple treatments than patients without all-cause ED visits. Prostate cancer patients in 66-75 and 76-85 years old had higher proportions of all-cause ED visits. Those patients who lived in urban settings had a more advanced stage of cancer and had more comorbidities had a higher likelihood of all-cause ED visits (all $P<0.05$).

Moreover, higher proportions of patients with all-cause mortality were those who received ADT or chemotherapy combination therapy than patients without all-cause mortality. Those patients who were older had ESRD and more advanced stage of cancer, had lower level of education and more comorbidities had higher likelihood of all-cause mortality (all $P<0.05$).

As shown in Table 4.5, higher proportions of patients with prostate cancer related hospitalization events were those who received surgery, chemotherapy or multiple managements than patients without prostate cancer related hospitalizations. Prostate cancer patients in 76-85 and >85 years old had higher proportions of prostate cancer related hospitalizations (60.14% and 12.21%, respectively). Those patients who were African American, residing in urban settings or in southern regions, had a more advanced stage of cancer and had more comorbidities had a higher likelihood of prostate cancer related hospitalizations (all P<0.05).

In addition, higher proportions of patients with prostate cancer related ED events were those who received surgery, chemotherapy or multiple managements than patients without prostate cancer related ED visits. Compared with other age subgroups, prostate cancer patients in 76-85 and >85 years old had higher proportions of prostate cancer related ED visits. Those patients who were African American resided in urban settings had more advanced stages of cancer, and those who had more comorbidities had a higher likelihood of prostate cancer related ED visits (all P<0.05).

Moreover, higher proportions of patients with prostate cancer related mortality were those who received chemotherapy or multiple managements than patients without prostate cancer related mortality. Those patients who were older in age, had more advanced stage of cancer and more comorbidities had higher likelihood of prostate cancer related mortality (all P<0.05).

4.2.4 Adjusted associations between comorbid asthma and clinical outcomes, controlling for patient characteristics

Results of multivariate Cox proportional hazards models for associations between patient characteristics and all-cause clinical outcomes are presented in Table 4.6. Overall, patients with comorbid asthma had statistically significant higher risks of all-cause hospitalization, ED visit, and mortality compared with those without comorbid asthma. Specifically, patients with asthma had 12% higher risk of hospitalization (adjusted hazard ratio (AHR)=1.12; 95% confidence interval (CI)=1.03, 2.24), 29% higher risk of ED visit (AHR)=1.29; 95% CI=1.02, 1.97), and 13% higher risk of mortality (AHR=1.13; 95% CI=1.04, 1.46) compared to those without asthma. In addition, patient factors associated with higher risk of all-cause hospitalization and ED visit included receiving surgery, chemotherapy, and multiple prostate cancer treatments (vs. active surveillance cancer management), older age (>75 vs. <65 years), being African-American, living in the South region (vs. Northeast), having a higher CCI comorbidity score (≥2 vs. 0), and having advanced prostate cancer stage (II-IV). Regarding all-cause mortality, prostate cancer patients who received chemotherapy only and multiple cancer treatments had higher risk (AHR=1.27; 95%CI=1.16, 1.89; AHR=1.33; 95% CI=1.07, 2.32, respectively) compared with active surveillance management whereas other therapies, including surgery only, radiation only and ADT only regimens, were not associated with mortality compared with active surveillance. Similar to the outcomes of all-cause hospitalization and ED visit, patient's sociodemographic and tumor characteristics were also associated with a higher risk of all-cause mortality, including being African-American, older age (> 75 vs. <65 years), having advanced cancer stage, and having a higher comorbidity score (≥2 vs. 0).

Results of multivariate Cox proportional hazards models for associations between patient characteristics and prostate cancer related outcomes are presented in Table 4.7. Similar to all-cause clinical outcomes, prostate cancer patients with comorbid asthma had statistically significant higher risks of prostate cancer related hospitalization and ED visits (AHR=1.07, 95% CI=1.02, 1.94; AHR=1.12, 95% CI=1.04, 1.29, respectively). However, comorbid asthma was not associated with the risk of prostate cancer related mortality (AHR=1.02, 95% CI=0.82, 1.15). In terms of patient cancer treatment, sociodemographic and tumor characteristics, factors associated with higher risks of prostate cancer related hospitalization and ED visit included receiving chemotherapy only and multiple cancer treatments, older age (>75 vs. <65 years), being African-American, living in the South region (vs Northeast), having a higher comorbidity score (≥2 vs. 0), and having advanced cancer stage. Having chemotherapy, and multiple treatments as cancer managements were associated with higher risk of prostate cancer related hospitalization (AHR=1.47, 95% CI=1.21, 2.16) and ED visits (AHR=1.36, 95% CI=1.28, 1.60). Regarding prostate cancer related mortality, patients who received chemotherapy and multiple cancer treatments (HR, 1.35; 95%CI 1.21 to 2.20; HR, 1.38; 95% CI 1.15 to 1.98, respectively) compared with active surveillance were associated with higher risk compared with those under active surveillance. Similar to prostate cancer related hospitalization and ED visits, patient's sociodemographic and tumor characteristics were also associated with a higher risk of prostate cancer related mortality, including being African-American, older age (>75 vs. <65 years), living in urban settings having advanced cancer stage, and having a higher comorbidity score (≥2 vs. 0).

Sensitivity analyses using multivariable negative binomial models

Two multivariable negative binomial models were performed to examine patient factors associated with numbers of all-cause and prostate related hospitalization and ED visits in the 2 years follow up period as sensitivity analysis (Tables 4.8 and 4.9). Similarly, prostate cancer patients with comorbid asthma had higher risks of all-cause hospitalization and ED visits compared to those without asthma (Adjusted Relative Risk (ARR)=1.46; 95%CI=1.09, 1.84; ARR=1.68; 95%CI=1.19, 2.21). Prostate cancer patients with comorbid asthma also had higher risk of prostate cancer related hospitalization (ARR=1.24; 95%CI=1.16, 1.87) but similar risk of prostate cancer related ED visits (ARR=0.75, 95%CI=0.47, 1.15).

Table 4.3. Descriptive Estimates of All Clinical Outcomes

	Prostate Cancer Patient Cohort N=46,307		
	Asthma N (%)	**Non-Asthma N (%)**	**P***
	7046 (15.22%)	39261 (84.78%)	
All-Cause Hospitalization			**0.0012**
Yes	3176 (45.07%)	16627 (42.35%)	
No	3870 (54.93%)	22634 (57.65%)	
Number, mean, SD	4764, 0.68, 1.21	21615, 0.55, 1.01	**<0.0001**
All-Cause ED			**<0.0001**
Yes	4085 (57.97%)	17039 (43.40%)	
No	2961 (42.03%)	22222 (56.60%)	
Number, mean, SD	5719, 0.81, 1.05	20447, 0.52, 0.79	**<0.0001**
All-Cause Mortality			0.0566
Yes	424 (6.02%)	1987 (5.06%)	
No	6622 (93.98%)	37274 (94.94%)	
Prostate Cancer Related Hospitalization			**<0.0001**
Yes	2116 (30.00%)	7900 (20.12%)	
No	4930 (70.00%)	31361 (79.88%)	
Number, mean, SD	2022, 0.29, 1.02	8244, 0.14, 0.89	**<0.0001**
Prostate Cancer Related ED			0.2376
Yes	351 (4.98%)	1694 (4.31%)	
No	6695 (95.02%)	37567 (95.69%)	
Number, mean, SD	621, 0.09, 0.42	1859, 0.05, 0.53	0.0978
Prostate Cancer Related Mortality			0.1366
Yes	132 (1.87%)	711 (1.81%)	
No	6914 (98.13%)	38550 (98.19%)	

*Chi-square and t-tests at P<0.05

Table 4.4. Patient Characteristics by All-cause Clinical Outcomes

	Prostate Cancer Patient Cohort N=46,307								
	Hospitalization		**P***	**ED**		**P***	**Mortality**		**P***
	Yes	**No**		**Yes**	**No**		**Yes**	**No**	
	19803 (42.76%)	26504 (57.24%)		21124 (45.62%)	25183 (54.38%)		2411 (5.28%)	43896 (94.72%)	
Asthma			**0.0243**			**<0.0001**			**0.0296**
Yes	3176 (16.04%)	3870 (14.59%)		4085 (20.01%)	2961 (15.01%)		424 (18.78%)	6622 (15.25%)	
No	16627 (83.96%)	22634 (85.41%)		17039 (42.03%)	22222 (56.60%)		1987 (81.22%)	37274 (84.75%)	
First Prostate Treatment Pattern			**<0.0001**			**<0.0001**			**<0.0001**
Active surveillance	4218 (21.30%)	11622 (43.85%)		6874 (32.54%)	8872 (35.23%)		846 (35.09%)	15276 (34.80%)	
Surgery only	2753 (13.90%)	50 (0.19%)		879 (4.16%)	1503 (5.97%)		50 (2.08%)	2585 (5.89%)	
Radiation only	3963 (20.01%)	3056 (11.53%)		2704 (12.80%)	5054 (20.07%)		157 (6.53%)	8626 (19.65%)	
ADT only	4472 (22.58%)	6554 (24.73%)		5463 (25.86%)	4724 (18.76%)		871 (36.14%)	8310 (18.93%)	
Multiple Treatments and Other*	5990 (30.25%)	1333 (5.03%)		5205 (24.64%)	5029 (19.97%)		486 (20.16%)	9100 (20.73%)	
Age at Diagnose			**<0.0001**			**<0.0001**			**<0.0001**
<65	710 (3.57%)	1398 (5.27%)		1145 (5.42%)	963 (3.82%)		49 (2.03%)	2059 (4.69%)	
66-75	4351 (21.97%)	14376 (54.24%)		4087 (19.35%)	14640(58.13%)		381 (15.79%)	18346 (41.80%)	
76-85	12648 (63.87%)	8461 (31.92%)		11859(56.14%)	9250 (36.73%)		922 (38.23%)	20187 (45.99%)	
>85	2094 (10.59%)	2269 (8.56%)		4033 (19.09%)	330 (1.31%)		1060(43.95%)	3303 (7.52%)	
Race			0.0917			0.0577			0.1426
White	13592 (68.64%)	18555 (70.01%)		14829(70.20%)	17318(68.77%)		1717(71.20%)	30430 (69.32%)	
Black	3910 (19.17%)	4735 (17.87%)		4041 (19.13%)	4604 (17.87%)		423 (17.56%)	8222 (18.73%)	
Other	2301 (11.62%)	3214 (12.13%)		2254 (10.67%)	3216 (12.59%)		271 (11.24%)	5244 (11.95%)	
Urban vs. rural			0.1045			**<0.0001**			**0.0249**
Urban	17698 (89.37%)	23387 (88.24%)		19882(94.12%)	21203(84.20%)		2195(91.03%)	38890 (88.60%)	
Rural	2105 (10.63%)	3117 (11.76%)		1242 (5.88%)	3980 (15.80%)		216 (8.97%)	5006 (11.40%)	
ESRD			0.2765			0.1478			0.2679
Yes	553 (2.79%)	936 (3.53%)		1029 (1.58%)	460 (1.83%)		88 (3.63%)	1401 (3.19%)	
No	19250 (97.21%)	25568 (96.98%)		20095(98.42%)	24723 (98.17)		2323(96.37%)	42495 (96.81%)	
Low income subsidy eligible			0.1746			0.3147			0.2413
No	19546 (98.70%)	26109 (98.51%)		20786(98.40%)	24869(98.75%)		2346(97.35%)	43309 (98.51%)	
Yes	257 (1.30%)	395 (1.49%)		338 (1.60%)	314 (1.25%)		65 (2.65%)	587 (1.49%)	
Prostate Cancer Stage			**<0.0001**			**<0.0001**			**<0.0001**
I	3972 (20.06%)	13605 (51.33%)		3308 (15.66%)	14270(56.67%)		249 (10.31%)	17329 (39.48%)	
II	9757 (49.27%)	7458 (28.14%)		8718 (41.27%)	8497 (33.74%)		298 (12.35%)	16917 (38.54%)	
III	3594 (18.15%)	4585 (17.30%)		6200 (29.35%)	1979 (7.86%)		906 (37.56%)	7273 (16.57%)	
IV	2479 (12.52%)	856 (3.23%)		2898 (13.72%)	437 (1.74%)		959 (39.78%)	2376 (5.41%)	

Marital status			0.0875			0.5129			**0.0483**
Not married	5582 (28.19%)	7755 (29.26%)		6065 (28.71%)	7272 (28.88%)		778 (32.66%)	12559 (28.61%)	
Currently Married	13379 (67.56%)	17421 (65.73%)		14045(66.49%)	16755(66.53%)		1522(63.14%)	29278 (66.70%)	
Unknown	842 (4.25%)	1328 (5.01%)		1014 (4.80%)	1156 (4.59%)		111 (4.60%)	2059 (4.69%)	
SEER region			0.0577			0.0643			0.0719
Northeast	4470 (22.57%)	6215 (23.45%)		4751 (22.49%)	5934 (23.56%)		560 (23.24%)	10125 (23.07%)	
Midwest	4646 (23.46%)	6499 (24.52%)		4814 (22.79%)	6331 (25.14%)		582 (24.14%)	10563 (24.52%)	
South	5769 (29.13%)	7193 (27.14%)		6153 (29.13%)	6809 (27.04%)		705 (29.26%)	12257 (27.92%)	
West	4919 (24.84%)	6597 (24.89%)		5406 (25.59%)	6110 (24.26%)		564 (23.37%)	10952 (24.95%)	
Median Household income			0.2677			0.1942			0.0984
Quartile 1 (lowest)	4438 (22.41%)	6104 (23.03%)		4911 (23.25%)	5631 (22.36%)		635 (26.35%)	9907 (22.57%)	
Quartile 2	5014 (25.32%)	6406 (24.17%)		5744 (27.19%)	5676 (22.54%)		604 (25.05%)	10814 (24.64%)	
Quartile 3	5163 (26.07%)	6971 (26.30%)		5158 (24.42%)	6976 (27.70%)		608 (25.23%)	11528 (26.26%)	
Quartile 4 (highest)	5188 (26.20%)	7024 (26.50%)		5311 (25.14%)	6901 (27.40%)		563 (23.37%)	11649 (26.54%)	
Education (high school graduation rates)			**0.0267**			**0.0389**			**0.0477**
Quartile 1 (lowest)	5052 (25.51%)	6268 (23.65%)		5249 (24.85%)	6071 (24.11%)		646 (26.79%)	10674 (24.32%)	
Quartile 2	5404 (27.29%)	6531 (24.64%)		5539 (26.22%)	6396 (25.40%)		602 (24.97%)	11333 (25.82%)	
Quartile 3	4854 (24.51%)	7188 (27.12%)		5249 (24.85%)	6793 (26.97%)		587 (24.34%)	11455 (26.10%)	
Quartile 3 (highest)	4493 (22.69%)	6517 (24.59%)		5087 (24.08%)	5923 (23.52%)		576 (23.90%)	10434 (23.76%)	
Comorbidity score*			**0.0004**			**0.0009**			**<0.0001**
0	1766 (8.92%)	14649 (55.27%)		1572 (7.44%)	14843(58.94%)		67 (2.77%)	16348 (37.24%)	
1	3416 (17.25%)	5714 (21.56%)		3462 (16.39%)	5668 (22.51%)		201 (8.35%)	8929 (20.34%)	
2	5814 (29.36%)	4272 (16.12%)		6595 (31.22%)	3491 (13.86%)		1187(49.25%)	8899 (20.27%)	
≥3	8806 (44.47%)	1869 (7.05%)		9495 (44.955)	1180 (4.69%)		955 (39.63%)	9720 (22.14%)	

*Chi-square tests at P<0.05

^ Multiple Treatments indicated patients received more than two management agents

*****CCI didn't include asthma and prostate cancer

Table 4.5. Patient Characteristics by Prostate Cancer Related Clinical Outcomes

	Prostate Cancer Patient Cohort N=46,307								
	Hospitalization		P*	ED		P*	Mortality		P*
	Yes	No		Yes	No		Yes	No	
	10016 (21.63%)	36291 (78.37%)		2045 (4.42%)	44262 (95.58%)		843 (1.82%)	45464 (98.18%)	
Asthma			**<0.0001**			0.1046			0.1366
Yes	2116 (21.13%)	4930 (13.58%)		351(16.77%)	6695 (15.01%)		132 (15.43%)	6914(15.48%)	
No	7900 (81.65%)	31361(86.42%)		1694 (83.23%)	37567(84.94%)		711 (84.57%)	38550 (84.52%)	
Prostate Treatment Pattern			**<0.0001**			**<0.0001**			**<0.0001**
Active surveillance	1053 (10.51%)	15576 (42.92%)		386 (18.87%)	15416 (34.83%)		212 (25.12%)	15885 (34.94%)	
Surgery only	2169 (21.66%)	127 (0.35%)		386 (18.87%)	2510 (5.67%)		4 (0.48%)	2614 (5.75%)	
Radiation only	2368 (23.64%)	3883 (10.70%)		482 (23.58%)	8379 (18.93%)		22 (2.58%)	8710 (19.16%)	
ADT only	2400 (23.96%)	9134 (25.17%)		347 (16.98%)	8795 (19.87%)		441 (52.34%)	8833 (19.43%)	
MultipleTreatments and Others*	2026 (20.23%)	7570 (20.86%)		444 (21.70%)	9162 (20.70%)		164 (19.48%)	9420 (20.72%)	
Age at Diagnose			**<0.0001**			**<0.0001**			**<0.0001**
<65	413 (4.12%)	1695 (4.67%)		101 (4.93%)	2007 (4.53%)		16 (1.92%)	2092 (4.60%)	
66-75	2357 (23.53%)	16370 (45.10%)		375 (18.34%)	18352 (41.46%)		118 (13.98%)	18609 (40.93%)	
76-85	6024 (60.14%)	15085 (41.57%)		1263 (61.78%)	19846 (44.84%)		334 (39.59%)	20775 (45.70%)	
>85	1222 (12.21%)	3141 (8.66%)		306 (14.95%)	4057 (9.17%)		375 (44.51%)	3988 (8.77%)	
Race			**<0.0001**			0.1579			0.2478
White	6704 (66.93%)	25443 (70.11%)		1445 (70.67%)	30702 (69.36%)		585 (69.37%)	31562 (69.42%)	
Black	2087 (20.84%)	6558 (18.07%)		391 (19.13%)	8254 (18.65%)		170 (20.12%)	8475 (18.64%)	
Other	1225 (12.23%)	4290 (11.82%)		209 (10.20%)	5306 (11.99%)		89 (10.51%)	5426 (11.93%)	
Urban vs. rural			**<0.0001**			**<0.0001**			**<0.0001**
Urban	9242 (92.27%)	31843 (87.74%)		1923 (94.03%)	39162 (88.48%)		790 (93.76%)	40295 (88.64%)	
Rural	774 (10.63%)	4448 (12.26%)		122 (5.97%)	5100 (11.52%)		56 (6.65%)	5166 (11.36%)	
ESRD			0.2765			0.1478			0.2679
Yes	312 (2.79%)	1177 (3.24%)		59 (2.87%)	1430 (3.23%)		58 (2.83%)	1431 (3.23%)	
No	9704 (97.21%)	35114 (96.76%)		1986 (97.13%)	42832 (96.77%)		1987 (97.17%)	42831 (96.77%)	
Low income subsidy eligible			0.1746			0.3147			0.2413
No	9868 (98.52%)	35787 (98.51%)		2007 (98.12%)	43648 (98.61%)		818 (97.04%)	44837 (98.62%)	
Yes	148 (1.48%)	210 (1.49%)		38(1.88%)	614 (1.39%)		25 (2.96%)	627 (1.38%)	
Prostate Cancer Stage			**<0.0001**			**<0.0001**			**<0.0001**
I	924 (9.23%)	16654 (45.89%)		210 (10.25%)	17368 (39.24%)		26 (3.14%)	17552 (38.61%)	
II	3731 (37.25%)	13484 (37.16%)		331 (16.17%)	16884 (38.15%)		112 (13.25%)	17103 (37.62%)	
III	2941 (29.36%)	5238 (14.43%)		537 (26.24%)	7642 (17.27%)		317 (37.66%)	7862 (17.29%)	
IV	2420 (24.16%)	915 (2.52%)		967 (47.34%)	2368 (5.35%)		388 (45.95%)	2948 (6.48%)	

Marital status			0.1245			0.4948			0.5104
Not married	2476 (24.72%)	10861 (29.93%)		537 (26.25%)	12800 (28.92%)		246 (29.13%)	13091 (28.79%)	
Currently Married	6625 (66.14%)	24175 (66.61%)		1383 (67.61%)	29417 (66.46%)		526 (62.53%)	30274 (66.59%)	
Unknown	915 (9.14%)	1255 (3.46%)		125 (6.14%)	2045 (4.62%)		72 (8.52%)	2098 (4.61%)	
SEER region			0.4812			**<0.0001**			**0.0246**
Northeast	2242 (22.38%)	8443 (23.26%)		372 (18.21%)	10313 (23.30%)		178 (21.14%)	10507 (23.11%)	
Midwest	2314 (23.10%)	8831 (24.33%)		510 (24.95%)	10635 (24.03%)		212 (25.20%)	10933 (24.05%)	
South	2909 (29.04%)	10053 (27.70%)		601 (29.39%)	12361 (27.93%)		247 (29.34%)	12715 (27.97%)	
West	2552 (25.48%)	8964 (24.71%)		561 (27.45%)	10955 (24.75%)		205 (24.32%)	11311 (24.88%)	
Median Household income			**<0.0001**			**<0.0001**			**<0.0001**
Quartile 1 (lowest)	2849 (28.44%)	7693 (21.20%)		596 (29.14%)	9946 (22.47%)		222 (26.35%)	10320 (22.70%)	
Quartile 2	2694 (26.90%)	8726 (24.04%)		563 (27.52%)	10857 (24.53%)		229 (27.13%)	11191 (24.61%)	
Quartile 3	2325 (23.21%)	9809 (27.03%)		454 (22.21%)	11680 (26.39%)		205 (24.32%)	11929 (26.24%)	
Quartile 4 (high)	2148 (21.45%)	10064 (27.73%)		432 (21.13%)	11780 (26.61%)		187 (22.20%)	12025 (26.45%)	
Education (high school graduation rates)			**0.0128**			**0.0329**			**0.0032**
Quartile 1 (lowest)	2372 (23.68%)	8948 (24.66%)		455 (22.27%)	10865 (24.55%)		223 (26.44%)	11097 (24.41%)	
Quartile 2	2352 (23.48%)	9583 (26.41%)		493 (24.09%)	11442 (25.85%)		220 (26.14%)	11715 (25.77%)	
Quartile 3	2823 (28.18%)	9219 (25.40%)		595 (29.09%)	11447 (25.86%)		205 (24.32%)	11837 (26.04%)	
Unknown	2470 (24.66%)	8540 (23.53%)		502 (24.55%)	10508 (23.74%)		195 (23.10%)	10815 (23.79%)	
Comorbidity score*			**<0.0001**			**<0.0001**			**<0.0001**
0	604 (6.03%)	15811 (43.57%)		107 (5.24%)	16308 (36.85%)		35 (4.16%)	16380 (36.03%)	
1	2238 (22.34%)	6892 (18.99%)		405 (19.82%)	8725 (19.71%)		151 (17.86%)	8979 (19.75%)	
2	2565 (25.61%)	7521 (20.72%)		498 (24.35%)	9588 (21.66%)		232 (27.47%)	9854 (21.68%)	
≥3	4609 (46.02%)	6066 (16.72%)		1035 (50.59%)	9640 (21.78%)		426 (50.51%)	10249 (22.54%)	

*Chi-square significant at P<0.05

^ Multiple Treatments indicated patients received more than two management agents

***** CCI didn't include asthma and prostate cancer

Table 4.6. Adjusted Patient Factors Associated with All-cause Clinical Outcomes in Prostate Cancer Patients

Factor	Hospitalization (AHR^, 95% CI)	ED Visit (AHR^, 95 % CI)	Mortality (AHR^, 95%CI)
Asthma			
Yes	**1.12 (1.03—2.23)**	**1.29 (1.02—1.58)**	**1.13 (1.04—1.31)**
No	Ref	Ref	Ref
Prostate Cancer Treatment			
Active surveillance	Ref	Ref	Ref
Surgery only	**1.52 (1.17—2.03)**	1.21 (0.78 – 1.85)	1.37 (0.87 – 1.84)
Radiation only	1.18 (0.84—1.57)	1.04 (0.73—1.21)	1.12 (0.92—1.49)
ADT only	1.23 (0.92—2.11)	**1.21 (1.05—1.37)**	**1.31 (1.04 – 1.72)**
Multiple Treatments and Others*	**2.78 (1.34—3.96)**	**1.83 (1.31—2.17)**	1.14 (0.82 – 1.33)
Age at Diagnose			
<65	Ref	Ref	Ref
66-76	1.08 (0.79—1.35)	0.90 (0.68—1.28)	1.17 (0.76—1.79)
76-85	**1.21 (1.02—1.55)**	**1.14 (1.06—1.23)**	**1.13 (1.04—1.20)**
>85	**2.46 (1.55—3.27)**	**1.31 (1.01—1.71)**	**1.44 (1.05—1.87)**
Urban vs. rural			
Urban	1.18 (0.78—1.25)	1.08 (0.81—1.39)	1.10 (0.91—1.29)
Rural	Ref	Ref	Ref
Race			
White	Ref	Ref	Ref
Black	**1.18 (1.03—1.89)**	**1.31 (1.15—1.82)**	**1.21 (1.14—2.01)**
Other	0.93 (0.68—1.28)	0.93 (0.56—1.53)	0.68 (0.36—1.26)
Prostate Cancer Stage			
I	Ref	Ref	Ref
II	**1.74 (1.24—2.64)**	**1.19 (1.03—1.52)**	**1.36 (1.12—1.67)**
III	**1.12 (1.04—1.69)**	**2.20 (1.93—2.54)**	**1.20 (1.02—1.43)**
IV	**2.20 (1.76—2.89)**	**3.18 (2.89—3.55)**	**2.34 (2.15—3.27)**
Marital status			
Not married	Ref	Ref	Ref
Currently Married	0.95 (0.73—1.25)	0.62 (0.31—1.24)	0.95 (0.87—1.03)
Unknown	0.93 (0.75—1.13)	0.59 (0.34—1.04)	0.71 (0.33—1.56)
SEER region			
Northeast	Ref	Ref	Ref
Midwest	0.91 (0.79—1.33)	0.92 (0.84--1.78)	1.07 (0.79—1.35)
South	**1.21 (1.06—2.04)**	**1.27 (1.04--1.96)**	0.94 (0.73—1.23)
West	1.04 (0.77—1.23)	0.94 (0.67--1.31)	1.10 (0.85—1.46)
Median Household income			
Quartile 1 (lowest)	Ref	Ref	Ref
Quartile 2	0.75 (0.63--1.65)	0.89 (0.71—1.13)	0.91 (0.70—1.19)
Quartile 3	0.87 (0.58--1.42)	0.90 (0.71—1.13)	1.11 (0.90—1.38)
Quartile 4 (highest)	0.87 (0.58—1.29)	0.85 (0.67—1.10)	1.05 (0.79—1.31)
Education (high school graduation rates)			
Quartile 1 (lowest)	Ref	Ref	Ref
Quartile 2	1.00 (0.83—1.20)	0.90 (0.77 – 1.41)	0.81 (0.58 – 1.11)
Quartile 3	1.18 (0.74—1.54)	0.86 (0.70 – 1.38)	0.99 (0.92 – 1.29)
Quartile 4 (highest)	1.03 (0.77—1.26)	0.76 (0.57—1.24)	0.85 (0.63—1.47)
Comorbidity score			
0	Ref	Ref	Ref
1	0.93 (0.75—1.13)	0.73 (0.58 – 1.21)	0.82 (0.71 --1.94)
2	**1.22 (1.03—2.13)**	**1.25 (1.08 – 2.34)**	**1.29 (1.13 – 2.97)**
≥3	**1.38 (1.09 – 1.91)**	**1.58 (1.31 – 2.10)**	**1.79 (1.25 – 2.19)**

***** Multiple Treatments indicated patients received more than two management agents

^All covariance variables that had Chi-square test P≥0.05 or small cell size (<20) were removed from the Cox regression models; adjusted hazard ratios (AHR) and 95% confidence intervals (CI) were reported

Table 4.7. Adjusted Patient Factors Associated with Prostate Cancer Related Clinical Outcomes in Prostate Cancer Patients

Factor	Hospitalization (AHR^, 95% CI)	ED Visit (AHR^, 95 % CI)	Mortality (AHR^, 95%CI)
Asthma			
Yes	**1.07 (1.02—1.94)**	**1.12 (1.04—1.29)**	1.02 (0.81—1.14)
No	Ref	Ref	Ref
Prostate Cancer Treatment			
Active surveillance	Ref	Ref	Ref
Surgery only	**1.24 (1.06—1.54)**	**1.29 (1.05—1.53)**	1.31 (0.57 – 1.98)
Radiation only	**1.12 (1.04—1.27)**	**1.13 (1.02—1.27)**	1.13 (0.64—1.79)
ADT only	1.06 (0.66—1.39)	1.17 (0.73—1.85)	**2.11 (1.09 – 3.02)**
Multiple Treatments and Others*	1.14 (0.83—1.39)	1.05 (0.89—1.14)	1.14 (0.82 – 1.33)
Age at Diagnose			
<65	Ref	Ref	Ref
66-76	1.10 (0.90—1.84)	1.05 (0.75—1.73)	0.95 (0.73—1.25)
76-85	**1.18 (1.09—1.58)**	**1.08 (1.01—1.79)**	**1.28 (1.08—1.41)**
>85	**2.19 (1.23—2.46)**	**1.32 (1.11—2.38)**	**1.27 (1.04—1.41)**
Urban vs. rural			
Urban	1.09 (0.78—1.39)	1.05 (0.81—1.39)	**1.21 (1.01—2.28)**
Rural	Ref	Ref	Ref
Race			
White	Ref	Ref	Ref
Black	**1.11 (1.01 –1.94)**	**1.16 (1.02—1.99)**	**1.28 (1.04—2.13)**
Other	0.80 (0.64—1.12)	0.91 (0.74-- 1.87)	0.75 (0.57—1.94)
Prostate Cancer Stage			
I	Ref	Ref	Ref
II	1.02 (0.72—1.95)	1.04 (0.81—1.83)	1.10 (0.65—2.23)
III	**1.43 (1.20—2.13)**	**1.10 (1.28--2.60)**	**1.27 (1.15—2.08)**
IV	**3.65 (2.09—5.67)**	**3.86 (3.27--5.06)**	**1.35 (1.05—2.87)**
Marital status			
Not married	Ref	Ref	Ref
Currently Married	0.89 (0.71—1.17)	0.64 (0.47—1.09)	0.88 (0.63—1.29)
Unknown	0.95 (0.81—1.25)	0.61 (0.52—1.14)	0.75 (0.59—1.32)
SEER region			
Northeast	Ref	Ref	Ref
Midwest	0.92 (0.72—1.76)	0.90 (0.69—1.67)	1.04 (0.72—1.15)
South	**1.16 (1.05—1.89)**	**1.27 (1.02—1.79)**	0.95 (0.72—1.29)
West	1.05 (0.85—1.95)	0.96 (0.80—1.84)	1.09 (0.73—1.32)
Median Household income			
Quartile 1 (lowest)	Ref	Ref	Ref
Quartile 2	0.74 (0.53—1.35)	0.87 (0.63—1.15)	0.93 (0.73—1.20)
Quartile 3	0.83 (0.62—1.47)	0.95 (0.74—1.28)	1.10 (0.82—1.34)
Quartile 4 (high)	**0.74 (0.59—0.90)**	0.94 (0.70—1.31)	1.12 (0.85—1.42)
Education (high school graduation rates)			
Quartile 1 (lowest)	Ref	Ref	Ref
Quartile 2	1.01 (0.82—1.25)	0.92 (0.78 – 1.36)	0.80 (0.67 – 1.23)
Quartile 3	1.15 (0.69—1.53)	0.84 (0.72 – 1.41)	0.93 (0.89 – 1.32)
Quartile 4 (highest)	1.04 (0.78—1.25)	0.79 (0.62—1.57)	0.89 (0.62—1.49)
Comorbidity score			
0	Ref	Ref	Ref
1	0.84 (0.46 – 1.54)	0.74 (0.59 – 1.30)	0.83 (0.68 –2.03)
2	**1.25 (1.02 – 1.83)**	**1.28 (1.11 – 1.89)**	**1.24 (1.03 – 1.79)**
≥3	**1.28 (1.05 – 1.56)**	**1.69 (1.35 – 2.12)**	**1.85 (1.35 – 2.53)**

***** Multiple Treatments indicated patients received more than two management agents

^All covariance variables that had Chi-square test P≥0.05 or small cell size (<20) were removed from the Cox regression models; adjusted hazard ratios (AHR) and 95% confidence intervals (CI) were reported

Table 4.8. Adjusted Patient Factors Associated with All-cause Clinical Outcomes in Prostate Cancer Patients (sensitivity analysis using multivariable negative binomial models)

Factor	Hospitalization (ARR^, 95%CI)	ED Visit (ARR^, 95%CI)
Asthma		
Yes	**1.46 (1.09—1.84)**	**1.68 (1.19—2.21)**
No	Ref	Ref
Prostate Cancer Treatment		
Active surveillance	Ref	Ref
Surgery only	**1.81 (1.15—3.21)**	1.11 (0.82—1.31)
Radiation only	1.39 (0.89—1.33)	1.61 (0.82—2.07)
ADT only	1.04 (0.79—1.21)	**1.47 (1.28—1.91)**
Multiple Treatments and Others*	1.10 (0.76—1.42)	0.86 (0.71—1.08)
Age at Diagnose		
<65	Ref	Ref
66-76	1.32 (0.67—1.73)	1.27 (0.79—1.91)
76-85	**1.41 (1.05—1.99)**	**1.44 (1.13—1.93)**
>85	**1.66 (1.27—2.31)**	**1.61 (1.31—2.03)**
Race/ethnicity		
White	Ref	Ref
Black	**1.28 (1.01—1.89)**	**1.31 (1.15—2.14)**
Other	1.09 (0.92—1.37)	1.13 (0.98—1.73)
Prostate Cancer Stage		
I	Ref	Ref
II	1.11 (0.87—1.63)	1.09 (0.81—1.96)
III	**1.22 (1.08—1.79)**	**1.20 (1.10—1.84)**
IV	**1.31 (1.13—1.92)**	**1.54 (1.21—2.31)**
Marital status		
Not married	Ref	
Currently Married	0.77 (0.34—1.21)	0.69 (0.59—1.21)
Unknown	0.69 (0.39—1.29)	0.67 (0.47—1.93)
SEER region		
Northeast	Ref	
Midwest	0.81 (0.59—0.92)	0.73 (0.59—0.94)
South	**1.09 (1.01—1.43)**	**1.11 (1.06—1.48)**
West	1.28 (0.93—1.69)	1.39 (0.94—1.84)
Median Household income		
Quartile 1 (lowest)	Ref	
Quartile 2	0.57 (0.48—1.03)	0.77 (0.55—1.22)
Quartile 3	0.67 (0.50—1.13)	0.64 (0.47—1.09)
Quartile 4 (high)	0.47 (0.39—1.02)	0.53 (0.42—1.23)
Education (high school graduation rates)		
Quartile 1 (lowest)	Ref	
Quartile 2	1.12 (0.83—1.31)	1.15 (0.95—1.29)
Quartile 3	1.18 (0.79—1.33)	1.21 (0.82—1.27)
Quartile 4 (highest)	1.17 (0.69—1.92)	1.53 (0.62—2.14)
Comorbidity score		
0	Ref	
1	1.13 (0.95—1.73)	1.14 (0.89—1.72)
2	**1.33 (1.03—1.87)**	**1.29 (1.01—1.91)**
≥3	**1.48 (1.22—2.40)**	**1.28 (1.14—1.71)**

*Multiple Treatments indicated patients received more than two management agents

^ All covariance variables that had Chi-square test P⩾0.05 or small cell size (<20) were removed from the negative binomial models; adjusted Relative Risk (ARR) and 95% confidence intervals (CI) were reported

Table 4.9. Adjusted Patient Factors Associated with Prostate Cancer Related Clinical Outcomes in Prostate Cancer Patients (sensitivity analysis using multivariable negative binomial models)

Factor	Hospitalization (ARR^, 95%CI)	ED Visit (ARR^, 95%CI)
Asthma		
Yes	**1.24 (1.16—1.87)**	0.75 (0.47—1.25)
No	Ref	Ref
Prostate Cancer Treatment		
Active surveillance	Ref	Ref
Surgery only	**1.09 (1.02—1.14)**	**1.17 (1.04—1.23)**
Radiation only	**1.17 (1.03—1.32)**	**1.10 (1.03—1.19)**
ADT only	1.10 (0.87—1.27)	1.03 (0.72—1.36)
Multiple Managements and Others*	1.02 (0.76—1.41)	1.21 (0.74—1.73)
Age at Diagnose		
<65	Ref	Ref
66-76	1.04 (0.63—1.25)	1.13 (0.88—1.92)
76-85	**1.57 (1.25—2.14)**	**1.46 (1.23—1.96)**
>85	**1.71 (1.37—2.75)**	**1.69 (1.21—2.20)**
Race/ethnicity		
White	Ref	Ref
Black	**1.21 (1.11—1.74)**	**1.39 (1.16—1.90)**
Other	1.17 (0.87—1.49)	1.21 (0.71—1.71)
Prostate Cancer Stage		
I	Ref	Ref
II	**1.39 (1.18—1.90)**	**1.31 (1.22—1.92)**
III	**1.41 (1.22—2.13)**	**1.39 (1.25—1.99)**
IV	**1.49 (1.24—2.09)**	**1.53 (1.30—2.31)**
Marital status		
Not married	Ref	
Currently Married	0.82 (0.41—1.32)	0.71 (0.52—1.70)
Unknown	0.73 (0.50—1.23)	0.69 (0.43—1.64)
SEER region		
Northeast	Ref	
Midwest	**0.73 (0.30—0.94)**	**0.71 (0.51—0.97)**
South	**1.11 (1.02—1.72)**	**1.13 (1.04—1.80)**
West	1.29 (0.91—1.58)	**1.32 (1.11—1.99)**
Median Household income		
Quartile 1 (lowest)	Ref	
Quartile 2	**0.71 (0.61—0.84)**	0.78 (0.59—1.32)
Quartile 3	**0.79 (0.59—0.91)**	0.84 (0.73—1.64)
Quartile 4 (high)	**0.85 (0.69—0.98)**	0.96 (0.69—1.79)
Education (high school graduation rates)		
Quartile 1 (lowest)	Ref	
Quartile 2	1.22 (0.97—1.76)	1.21 (0.65—1.45)
Quartile 3	1.17 (0.89—1.82)	1.32 (0.79—1.69)
Quartile 4 (high)	1.25 (0.74—2.98)	1.16 (0.77—1.96)
Comorbidity score		
0	Ref	
1	1.23 (0.85—1.93)	1.11 (0.78—1.46)
2	1.31 (0.74—1.87)	1.36 (0.69—1.83)

*

*****Multiple Treatments indicated patients received more than two management agents

^ All covariance variables that had Chi-square test P⩾0.05 or small cell size (<20) were removed from the negative binomial models; adjusted Relative Risk (ARR) and 95% confidence intervals (CI) were reported

Figure 5.2. Kaplan-Meier Curve of All-cause Hospitalization

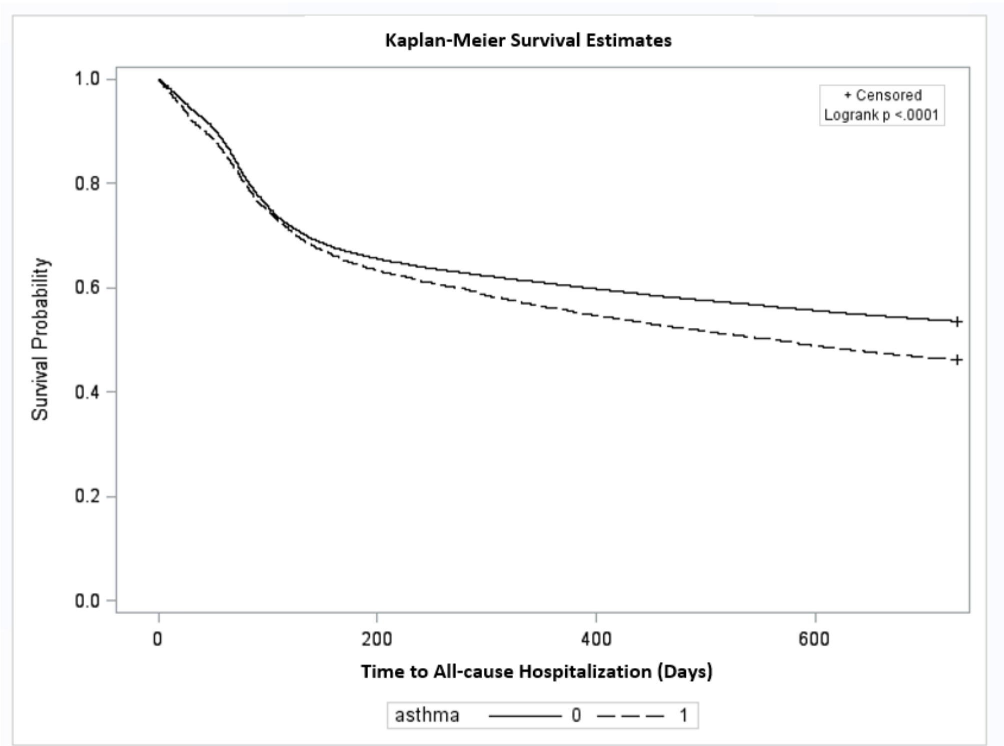


Figure 5.3. Kaplan-Meier Curve of All-cause ED

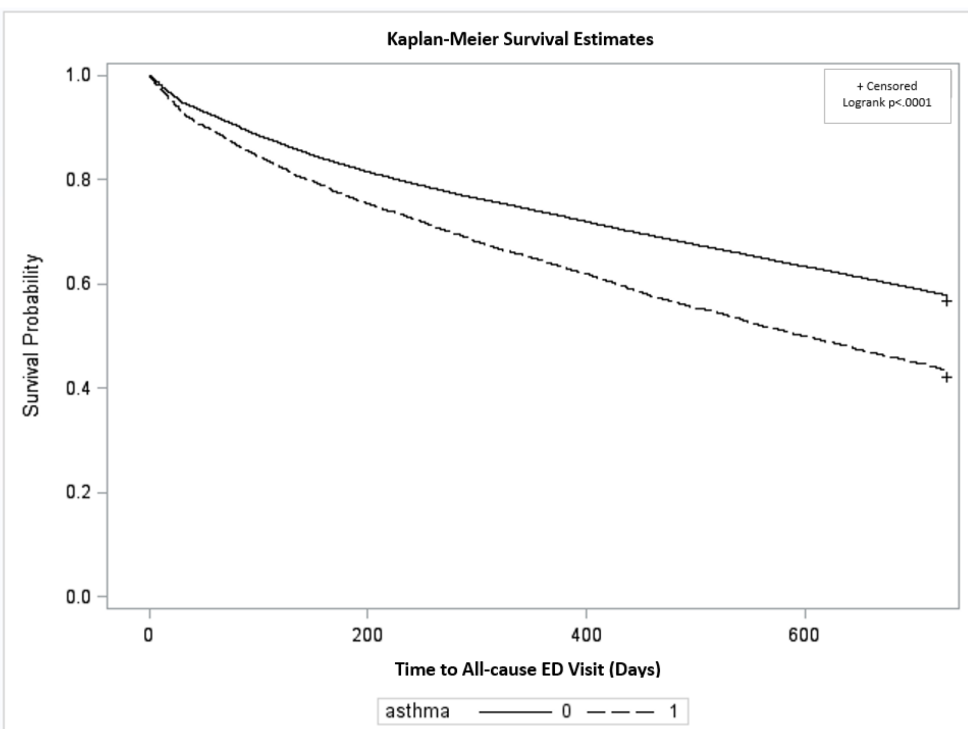


Figure 5.4. Kaplan-Meier Curve of All-cause Mortality

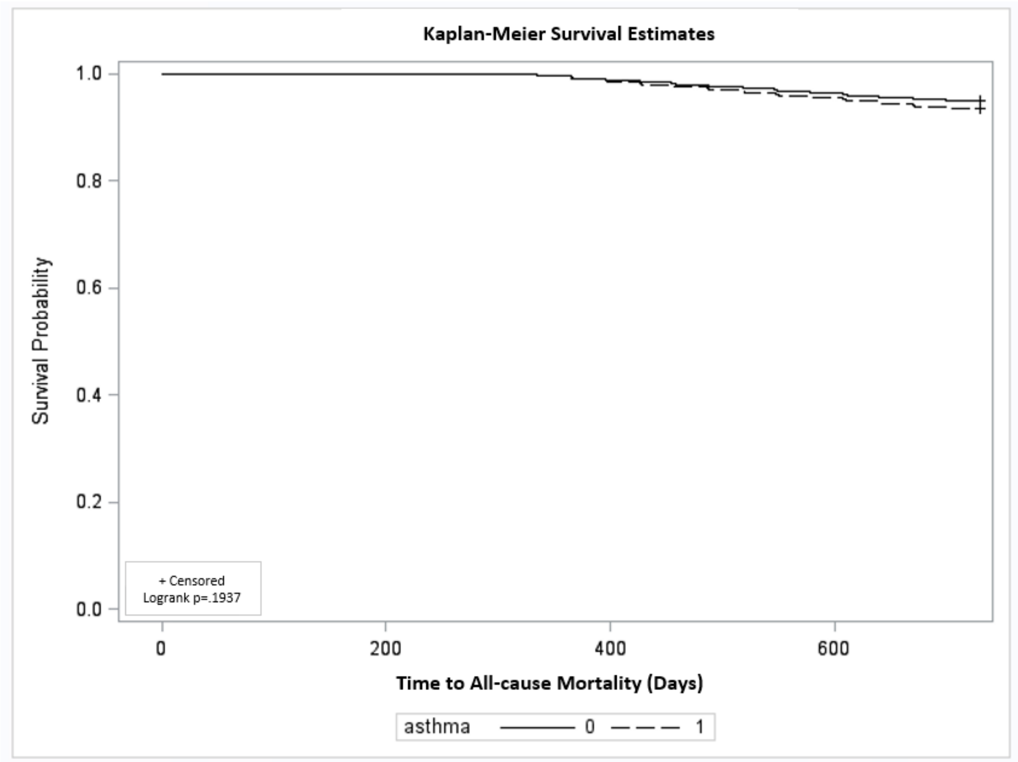


Figure 5.5. Kaplan-Meier Curve of Prostate Cancer Related Hospitalization

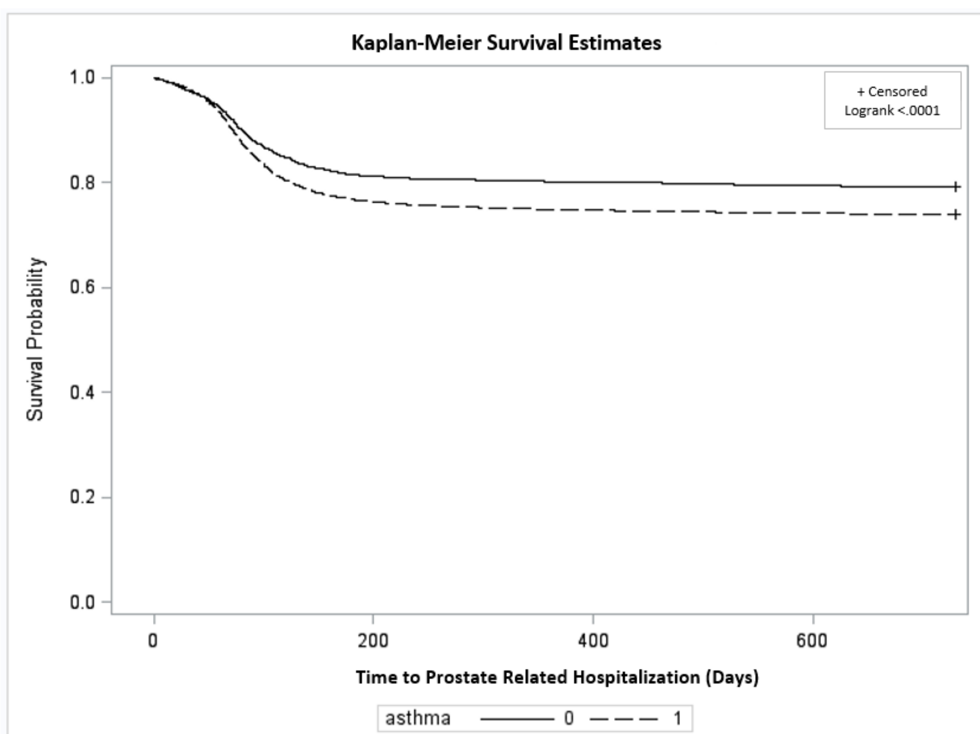


Figure 5.6. Kaplan-Meier Curve of Prostate Cancer Related ED

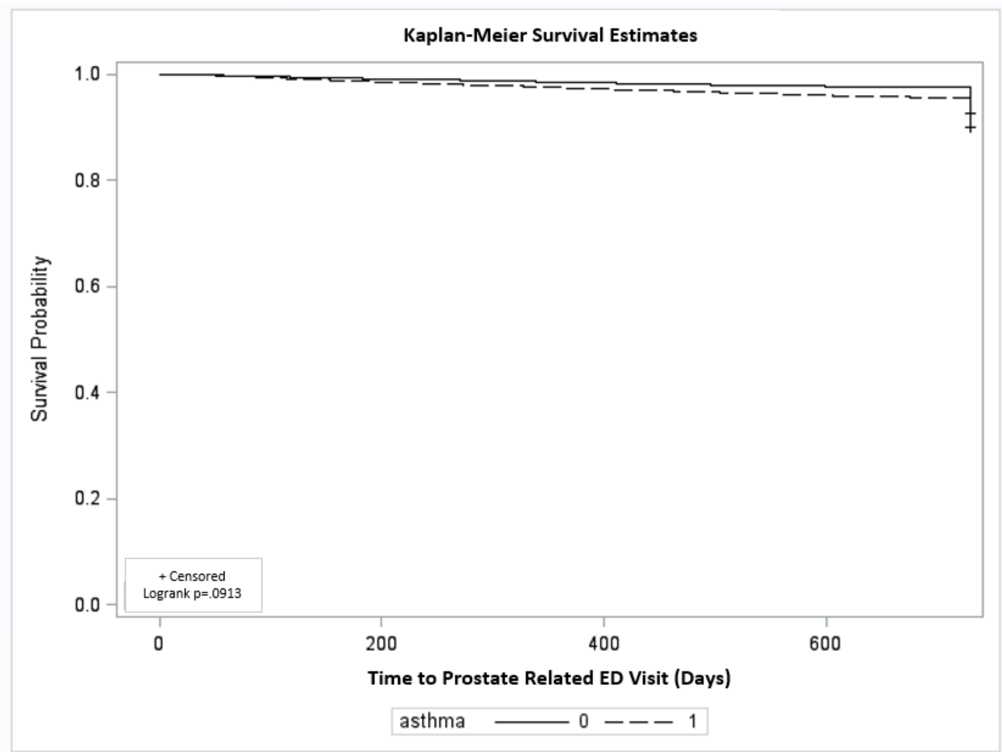
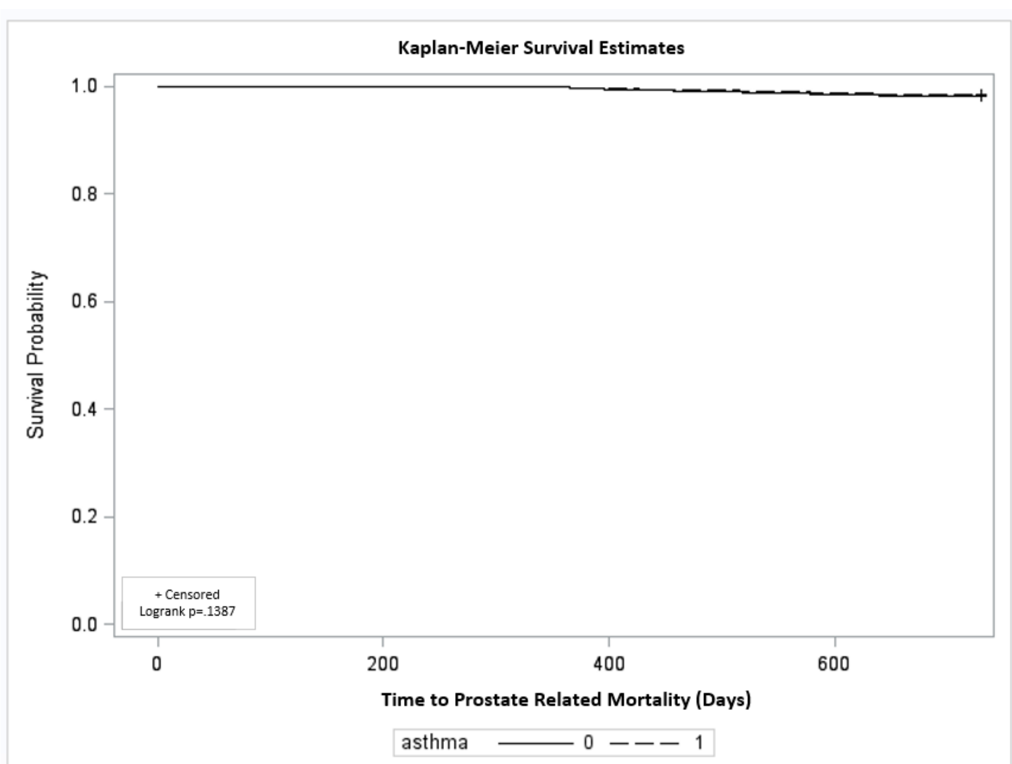


Figure 5.7. Kaplan-Meier Curve of Prostate Cancer Related Mortality



4.3 Results for Aim 3

4.3.1 Sample characteristics before and after propensity score weighting

Between 2008 and 2012, a total of 6,351 newly diagnosed prostate patients with asthma were included in this aim (Table 4.10). There were 2,843 (44.76%) patients who used corticosteroids (inhaled or oral) before and after their prostate cancer diagnosis. Before applying propensity score weighting, corticosteroids users were tend to be older, in African Americans, having advanced prostate cancer stage, and more co-morbidities than the corticosteroids non-users (all P<0.05). After applying propensity score weighting, the weights were adjusted among subgroups of the corticosteroids non-users. Therefore, the differences in patient characteristics between the corticosteroids user and non-user groups became balanced and no covariate had a statistical difference between the two groups.

4.3.2 Descriptive estimates of clinical outcomes by different corticosteroid exposure groups

Table 4.11 describes the descriptive estimates of all clinical outcomes by corticosteroid use status among prostate cancer patients in the 24 months follow up period. The cohort included 6,351 prostate cancer patients with comorbid asthma who had long-term corticosteroid use (1785, 28.11%), short-term corticosteroids use (1058, 16.65%), and non-users (3508, 55.24%). Among prostate cancer patients comorbid asthma with long-term corticosteroids, 967 (54.17%) had all-cause hospitalization events, of which the percentage was higher than 492 (46.50%) and 1206 (34.38%) with all-cause hospitalization in patients with short-term and non-users, respectively (P=0.0031). In addition, the mean (SD) number of all-cause hospitalizations in patients with long-term corticosteroids was also higher than in those with short-term and non-users (0.95 (1.13) vs 0.82 (1.03) vs 0.53 (0.42), respectively, P=0.0103). Similarly, there were 939 (52.61%) patients with long-term corticosteroids who had all-cause ED visits, compared with 563 (53.21%) and 1589 (4.30%) in patients with short-term corticosteroids and non-users respectively (P=0.0216), and the mean (SD) number of all-cause ED visit in patients with long-term corticosteroids use was also higher than those with short-term and non-users (0.89 (1.15) vs 0.91 (1.17) vs 0.81 (0.52), respectively, P=0.0202). For all-cause mortality, the proportion of patients with long-term corticosteroids exposure who passed away in 24 months was not statistically significantly different than those with short-term corticosteroids or non-users (7.28% vs. 7.75% vs. 7.07%, P=0.0635).

For prostate cancer related clinical outcomes, there were 635 (35.57%) of prostate cancer patients with long-term corticosteroid use who experienced prostate cancer related hospitalization, which was higher than patients with short-term use (382, 36.11%) or non-users (323, 9.21%). The mean (SD) number of prostate cancer related hospitalizations in patients with long-term corticosteroid use was also higher than in patients with short-term use and no use (0.78 (1.01) vs. 0.69 (0.92) vs. 1.15 (0.24), P<0.0001). For prostate cancer related ED visit, there were 118 (6.61%) of patients with long-term corticosteroid use, 79 (7.47%) of patients with short-term use, and 114 (3.25%) of patients with no use who had prostate cancer related ED visits, and the mean (SD) number of prostate cancer related ED visits in patients with long-term corticosteroid use was higher than in patients with short-term use and no use (0.08 (0.42) vs. 0.06 (0.36) vs. 0.04 (0.41), P=0.0037). For prostate cancer related mortality, the proportion of patients with long-term corticosteroids who passed away in 2 years was not statistically significantly different than those with short-term or non-users (2.58% vs. 2.17% vs. 1.60%, P=0.1472).

Regarding cardiovascular related clinical outcomes, there were 357 (20.00%) of prostate cancer patients with long-term corticosteroid use who experienced cardiovascular related hospitalization, which was higher than patients with short-term use (199, 18.18%) or non-users (576, 16.42%). The mean (SD) number of cardiovascular related hospitalizations in patients with long-term corticosteroid use was also higher than in patients with short-term use or no use (0.42 (0.51) vs. 0.35 (0.42) vs. 0.28 (0.51), P=0.0396). For cardiovascular related ED visit, there were 695 (38.94%) of patients with long-term corticosteroid use, 275 (25.99%) of patients with short-term use, and 493 (14.05%) of patients with no use who had the outcome events, and the mean (SD) number of cardiovascular related ED visits in patients with long-term corticosteroid use was also higher than in patients with short-term use and no use (0.66 (1.05) vs. 0.58 (0.52) vs. 0.38 (0.37), P=0.0135).

4.3.3 Adjusted associations between corticosteroid exposure and clinical outcomes, controlling for types of patient's prostate cancer treatments

Results of multivariate Cox proportional hazards models for adjusted associations between patients' corticosteroid exposure (by duration and dosage) and all-cause clinical outcomes are presented in Table 4.12. Overall, patients with long-term use (≥6 months) combined with high daily dosage (≥7.5 mg/day) of corticosteroids exposure had the highest statistically significant risks of all-cause hospitalization (hazard ratio (HR)=2.41, 95% CI=1.47-3.82), ED visit (HR=2.25, 95% CI=1.34-3.58), and mortality (HR=1.76, 95% CI=1.23-2.74) compared with non-users. In addition, patients with long-term use (≥6 months) combined with low or intermediate daily dosage (<7.5 mg/day) of corticosteroids exposure also had statistically significant risks of all-cause hospitalization (HR=2.14, 95% CI=1.34-3.59), ED visit (HR=1.85, 95% CI=1.32-3.62), and mortality (HR=1.53, 95% CI=1.17-2.98) compared with non-users. Moreover, patients with short-term (<6 months) and high daily dosage (≥7.5 mg/day) of corticosteroids exposure had significantly higher risks of all-cause hospitalization and ED events (HR=2.07; 95% CI=1.29-3.06; HR=1.31, 95% CI=1.22-2.93; respectively) compared to those without corticosteroids exposure. Finally, patients with short-term and low or intermediate daily dosage of corticosteroids exposure had no significant change in risk of all-cause hospitalization, ED, and mortality.

Similarly, as described in Table 4.13, patients with long-term and high daily dosage of corticosteroids exposure had the highest statistically significant risks of prostate cancer related hospitalization (HR=2.36, 95% CI=1.52-2.96) and ED visit (HR=2.29, 95% CI=1.41-3.57). Patients with long-term and low or intermediate daily dosage exposure also had statistically significant higher risks of prostate cancer related hospitalization (HR=2.04, 95% CI=1.13,-2.97) and ED visits (HR=1.61, 95% CI=1.14-2.83). Patients with short term and high daily dosage exposure also had statistically significant higher risks of prostate cancer related hospitalization (HR=1.27, 95% CI=1.09-2.67) and ED visit (HR=1.09, 95% CI=1.02-1.91) compared to those without corticosteroids exposure. But there was no significant difference in risks of prostate cancer related hospitalization and ED visits between patients with short term and low or intermediate daily dosage exposure with non-users.

Results of associations between corticosteroids exposure and cardiovascular related hospitalization and ED visit are displayed in Table 4.14. Only patients with long-term exposure to corticosteroids had statistically significantly higher risks of cardiovascular related hospitalization and ED visits. Specifically, patients exposed to long-term and high daily dosage of corticosteroids had 98% higher risk of cardiovascular related hospitalization (HR=1.98; 95%

CI=1.32-3.71) and 82% higher risk of cardiovascular related ED visits (HR=1.82; 95% CI=1.14-2.87). Patients exposed to long-term and low or intermediate daily dosage of corticosteroids had 67% higher risk of cardiovascular related hospitalization (HR=1.67; 95% CI=1.09-3.02) and 76% higher risk of cardiovascular related ED visits (HR=1.76; 95% CI=1.07-2.91) compared to those without corticosteroids exposure.

4.3.4 Results from sensitivity analyses

Two sets of sensitivity analyses were performed to compare with our main results: (a) limiting to patients without any corticosteroids use at baseline 12 months; and (b) grouping post-prostate cancer diagnosis corticosteroids exposure as long-term, short term, and no use, and add average daily dosage as a time dependent exposure.

Sensitivity a: Table 4.15 describes the descriptive estimates of all clinical outcomes by corticosteroids exposure status among prostate cancer patients without any baseline corticosteroids use (n=2,721). Of those, approximately 32.78% had all-cause hospitalization, 34.29% had all-cause ED visit, and 6.54% were dead for any reason in 2 years. Three multivariate Cox proportional hazards models were performed to examine the associations between corticosteroids exposure and all-cause hospitalization, ED visits, and mortality (Table 4.16). Similar as the main results, patients with long-term use and high daily dosage of corticosteroids exposure had the highest statistically significant risks of all-cause hospitalization, ED visit, and mortality compared with non-users. Patients with long-term use and low/intermediate daily dosage as well as those with short term use and high daily dosage of corticosteroids exposure also had significantly higher risks of all-cause hospitalization, ED visit, and mortality compared with non-users.

Sensitivity b: when we simply grouping post-prostate cancer diagnosis corticosteroids exposure as long-term, short term, and no use, and adding average daily dosage as a time dependent exposure, both duration and dosage exposures were associated with higher risks of all-cause, prostate cancer related, and cardiovascular related outcomes (Tables 4.17 and 4.18).

Table 4.10 Patients Characteristics Before and After Propensity Score Weighing±

Prostate cancer patients with asthma N=6,351						
	Before Propensity Score Weighting			**After Propensity Score Weighting**		
	Corticosteroids	**Non-Corticosteroids**	**P***	**Corticosteroids**	**Non- Corticosteroids**	**P***
	N=2,843 (44.76%)	N=3,508 (55.24%)		N=2,843		
Age at Diagnose			**0.0004**			0.5382
<65	195 (6.87%)	251 (7.16%)		195 (6.87%)	7.05%	
66-76	1147 (40.36%)	1658 (47.25%)		1147 (40.36%)	41.11%	
76-85	1076 (37.84%)	1185 (33.77%)		1076 (37.84%)	37.18%	
>85	427 (15.02%)	415 (11.82%)		427 (15.02%)	14.66%	
Race			**0.0096**			0.1397
White	2232 (78.51%)	2854 (81.35%)		2232 (78.51%)	79.03%	
Black	348 (12.24%)	332 (9.47%)		348 (12.24%)	12.12%	
Other	263 (9.25%)	322 (9.18%)		263 (9.25%)	8.85%	
Urban vs. rural			0.1482			0.6458
Urban	2645 (93.02%)	3232 (92.14%)		2645 (93.02%)	92.93%	
Rural	198 (6.98%)	276 (7.86%)		198 (6.98%)	7.07%	
ESRD			0.0791			0.3219
Yes	56 (1.98%)	77 (2.19%)		56 (1.98%)	2.02%	
No	2787 (98.02%)	3431 (97.81%)		2787 (98.02%)	97.98%	
Stage			**0.0144**			0.7235
I	541 (19.03%)	1415 (40.35%)		541 (19.03%)	19.11%	
II	1360 (47.82%)	1307 (37.26%)		1360 (47.82%)	47.46%	
III	607 (21.35%)	553 (15.77%)		607 (21.35%)	21.33%	
IV	335 (11.80%)	232 (6.62%)		335 (11.80%)	12.10%	
Marital status			0.5146			0.6783
Not married	636 (22.37%)	722 (20.58%)		636 (22.37%)	22.16%	
Currently Married	1946 (68.46%)	2433 (69.35%)		1946 (68.46%)	68.02%	
Unknown	261 (9.17%)	353 (10.07%)		261 (9.17%)	9.82%	
SEER region			0.2873			0.4852
Northeast	691 (24.32%)	889 (25.33%)		691 (24.32%)	24.24%	
Midwest	715 (25.15%)	848 (24.17%)		715 (25.15%)	25.07%	
South	847 (29.78%)	1090 (31.06%)		847 (29.78%)	30.12%	
West	590 (20.75%)	682 (19.44%)		590 (20.75%)	20.57%	
Median Household income			0.1782			0.8674
Quartile 1 (lowest)	617 (21.72%)	719 (20.51%)		617 (21.72%)	21.64%	
Quartile 2	730 (25.67%)	923 (26.32%)		730 (25.67%)	25.43%	
Quartile 3	772 (27.14%)	928 (26.44%)		772 (27.14%)	27.08%	

Quartile 4 (high)	724 (25.47%)	938 (26.73%)		724 (25.47%)	25.85%	
Education (high school graduation rates)			0.6139			0.6139
Quartile 1 (lowest)	668 (23.39%)	801 (22.84%)		668 (23.39%)	22.84%	
Quartile 2	691 (24.29%)	905 (25.79%)		691 (24.29%)	25.79%	
Quartile 3	667 (23.45%)	797 (22.71%)		667 (23.45%)	22.71%	
Quartile 4 (high)	818 (28.77%)	1005 (28.66%)		818 (28.77%)	28.66%	
Comorbidity score			**<0.0001**			0.0745
0	604 (21.25%)	1977 (56.35%)		604 (21.25%)	23.31%	
1	850 (29.87%)	737 (21.02%)		850 (29.87%)	29.04%	
2	942 (33.14%)	552 (15.74%)		942 (33.14%)	32.56%	
≥3	447 (15.74%)	242 (6.89%)		447 (15.74%)	15.09%	

*Chi-square significant at P<0.05
±Logistic regression model was used for propensity score weighting

Table 4.11. Descriptive Estimates of Study Outcomes by Post-Prostate Cancer Diagnosis Corticosteroids Exposure

Clinical Outcomes	Prostate Cancer Patients with Asthma N=6,351			
	Long-term Corticosteroids N (%)	Short-term Corticosteroids N (%)	No Corticosteroids Use N (%)	P*
	1785 (28.11%)	1058 (16.65%)	3508 (55.24%)	
All-Cause Hospitalization				**0.0031**
Yes	967 (54.17%)	492 (46.50%)	1206 (34.38%)	
No	818 (57.03%)	566 (53.50%)	2302 (65.62%)	
Mean, SD	0.95, 1.13	0.82, 1.03	0.53, 0.42	**0.0103**
All-Cause ED				**0.0216**
Yes	939 (52.61%)	563 (53.21%)	1589 (45.30%)	
No	846 (47.39%)	495 (91.44%)	1919 (54.70%)	
Mean, SD	0.89, 1.15	0.91, 1.17	0.81, 0.52	**0.0202**
All-Cause Mortality				0.0635
Yes	130 (7.28%)	82 (7.75%)	248 (7.07%)	
No	1655 (92.72%)	976 (92.25%)	3260 (92.93%)	
Prostate Cancer Related Hospitalization				**<.0001**
Yes	635 (35.57%)	382 (36.11%)	323 (9.21%)	
No	1150 (64.43%)	676 (63.89%)	3185 (90.79%)	
Mean, SD	0.78, 1.01	0.69, 0.92	0.15, 0.24	**<.0001**
Prostate Cancer Related ED				**0.0037**
Yes	118 (6.61%)	79 (7.47%)	114 (3.25%)	
No	1667 (93.39%)	979 (92.53%)	3394 (96.75%)	
Mean, SD	0.08, 0.42	0.06, 0.36	0.04, 0.41	**0.0112**
Prostate Cancer Related Mortality				0.1472
Yes	46 (2.58%)	23 (2.17%)	56 (1.60%)	
No	1739 (97.42%)	1035 (97.83%)	3452 (98.40%)	
Cardiovascular Related Hospitalization				**0.0396**
Yes	357 (20.00%)	199 (18.18%)	576 (16.42%)	
No	1428 (80.00%)	859 (81.19%)	32932 (83.58%)	
Mean, SD	0.42, 0.51	0.35, 0.42	0.28, 0.51	**0.0347**
Cardiovascular Related ED				**0.0273**
Yes	695 (38.94%)	275 (25.99%)	493 (14.05%)	
No	1090 (61.06%)	783 (74.01%)	3015 (85.95%)	
Mean, SD	0.66, 1.05	0.58, 0.52	0.38, 0.37	**0.0135**

SD, Standard Deviation

*Chi-square and t-tests at P<0.05

Table 4.12. Adjusted Associations between Post-Prostate Cancer Diagnosis Corticosteroids Exposure and All-cause Clinical Outcomes (n=6,351)^

Factor	Hospitalization (HR, 95% CI)	ED Visit (HR, 95 % CI)	Mortality (HR, 95%CI)
Corticosteroids Use After Cancer Diagnosis			
Non-exposure	**Ref**	**Ref**	**Ref**
Short-term exposure (<6 months) with low or intermediate daily dosage (<7.5mg/day)	1.44 (0.77—2.12)	1.34 (0.85—2.81)	1.52 (0.97—2.38)
Short-term exposure (<6 months) with high daily dosage (≥7.5mg/day)	**2.07 (1.29—3.06)**	**1.31 (1.22—2.93)**	1.72 (0.95—3.06)
Long-term exposure (≥6 months) with low or intermediate daily dosage (<7.5mg/day)	**2.14 (1.34—3.55)**	**1.85 (1.32—3.62)**	**1.53 (1.17—2.98)**
Long-term exposure (≥6 months) with high daily dosage (≥7.5mg/day)	**2.41 (1.47—3.82)**	**2.25 (1.34—3.58)**	**1.76 (1.23—2.74)**
Prostate Cancer Treatment			
Active surveillance	**Ref**	**Ref**	**Ref**
Surgery/ Radiation only	1.73 (0.93—2.01)	1.46 (0.83—2.39)	1.04 (0.82—1.93)
ADT/ Chemotherapy only	**1.47 (1.32—2.73)**	**1.23 (1.14—3.21)**	1.14 (0.79—2.19)
Multiple Managements and Others*	**2.14 (1.49—3.26)**	**2.47 (1.19—3.87)**	**1.85 (1.13—2.80)**

***** Multiple Treatments indicated patients received more than two management agents
^All covariance variables that were used in propensity weighting were removed from the Cox regression models; adjusted hazard ratios (HR) and 95% confidence intervals (CI) were reported

Table 4.13. Adjusted Associations between Post-Prostate Cancer Diagnosis Corticosteroids Exposure and Prostate Cancer Related Clinical Outcomes (n=6,351)^

Factor	Hospitalization (HR, 95% CI)	ED Visit (HR, 95 % CI)
Corticosteroids Use After Cancer Diagnosis		
Non-exposure	**Ref**	**Ref**
Short-term exposure (<6 months) with low or intermediate daily dosage (<7.5mg/day)	1.51 (0.83—2.04)	1.29 (0.77—2.68)
Short-term exposure (<6 months) with high daily dosage (≥7.5mg/day)	**1.27 (1.09—2.67)**	**1.09 (1.02—1.91)**
Long-term exposure (≥6 months) with low or intermediate daily dosage (<7.5mg/day)	**2.04 (1.13—2.97)**	**1.61 (1.14—2.83)**
Long-term exposure (≥6 months) with high daily dosage (≥7.5mg/day)	**2.36 (1.52—2.96)**	**2.29 (1.41—3.57)**
Prostate Cancer Treatment		
Active surveillance	**Ref**	**Ref**
Surgery/ Radiation only	1.47 (0.89—2.75)	1.48 (0.84—2.30)
ADT/ Chemotherapy only	**1.54 (1.03—2.56)**	**1.33 (1.08—2.92)**
Multiple Managements and Others*	**2.09 (1.38—3.17)**	**2.08 (1.29—3.41)**

***** Multiple Treatments indicated patients received more than two management agents
^All covariance variables that were used in propensity weighting were removed from the Cox regression models; adjusted hazard ratios (HR) and 95% confidence intervals (CI) were reported

Table 4.14. Adjusted Associations between Post-Prostate Cancer Diagnosis Corticosteroids Exposure and Prostate Cancer Related Clinical Outcomes (n=6,351)^

Factor	Cardiovascular Hospitalization (HR, 95%CI)	Cardiovascular ED Visit (HR, 95%CI)
Corticosteroids Use After Cancer Diagnosis		
Non-exposure	**Ref**	**Ref**
Short-term exposure (<6 months) with low or intermediate daily dosage (<7.5mg/day)	1.47 (0.75—2.32)	1.39 (0.88—1.97)
Short-term exposure (<6 months) with high daily dosage (≥7.5mg/day)	1.52 (0.84—3.08)	1.75 (0.75—2.96)
Long-term exposure (≥6 months) with low or intermediate daily dosage (<7.5mg/day)	**1.67 (1.09—3.02)**	**1.76 (1.07—2.91)**
Long-term exposure (≥6 months) with high daily dosage (≥7.5mg/day)	**1.98 (1.32—3.71)**	**1.82 (1.14—2.87)**
Prostate Cancer Treatment		
Active surveillance	**Ref**	**Ref**
Surgery/ Radiation only	1.77 (0.93—3.02)	1.35 (0.73—2.34)
ADT/ Chemotherapy only	**1.92 (1.21—3.49)**	**1.45 (1.18—3.02)**
Multiple Managements and Others*	**2.21 (1.23—4.02)**	**1.94 (1.26—3.36)**

***** Multiple Treatments indicated patients received more than two management agents
^All covariance variables that were used in propensity weighting were removed from the Cox regression models; adjusted hazard ratios (HR) and 95% confidence intervals (CI) were reported

Table 4.15. Sensitivity Analysis A: Descriptive Estimates of Clinical Outcomes by Post-Prostate Cancer Diagnosis Corticosteroids Exposure (n=5,286)^

Factor	Prostate Cancer Patients without Baseline Corticosteroid Use N=5,286								
	Hospitalization N (%)		P	ED Visit N (%)		P	Mortality N (%)		P
	Yes	No		Yes	No		Yes	No	
	2325 (43.98%)	2961 (56.02%)		1292 (24.44%)	3994 (75.56%)		364 (6.89%)	4922 (93.11%)	
Corticosteroids Use After Cancer Diagnosis			**<0.0001**			**0.0006**			**<0.0001**
Non-exposure	118 (13.26%)	580 (31.73%)		124 (13.27%)	574 (32.10%)		1519 (65.33%)	2273 (76.76%)	
Short-term exposure (<6 months) with low or intermediate daily dosage (<7.5mg/day)	114 (12.79%)	278 (15.24%)		275 (15.02%)	252 (14.09%)		167 (7.18%)	206 (6.96%)	
Short-term exposure (<6 months) with high daily dosage (≥7.5mg/day)	178 (19.97%)	262 (14.31%)		329 (18.00%)	272 (15.21%)		175 (7.53%)	174 (5.88%)	
Long-term exposure (≥6 months) with low or intermediate daily dosage (<7.5mg/day)	230 (25.74%)	371 (20.26%)		441 (24.13%)	376 (21.03%)		215 (9.25%)	154 (5.20%)	
Long-term exposure (≥6 months) with high daily dosage (≥7.5mg/day)	252 (28.24%)	338 (18.40%)		541 (29.85%)	314 (17.56%)		249 (10.71%)	154 (5.20%)	
Prostate Cancer Treatment			**<0.0001**			**<0.0001**			**<0.0001**
Active surveillance	533 (22.92%)	1110 (37.49%)		379 (29.33%)	1264 (31.65%)		22 (6.04%)	1515 (30.78%)	
Surgery/ Radiation only	743 (31.90%)	289 (9.76%)		159 (12.31%)	873 (21.86%)		71 (19.51%)	1418 (28.81%)	
ADT/ Chemotherapy only	510 (21.94%)	1051 (35.49%)		471 (36.46%)	1090 (27.29%)		128 (35.16%)	1010 (20.52%)	
Multiple Managements and Others [2]	539 (23.18%)	511 (17.26%)		283 (21.90%)	767 (19.20%)		143 (36.29%)	979 (19.89%)	

SD, Stander Deviation

*Chi-square and t-tests at P<0.05

Table 4.16. Sensitivity Analysis A: Adjusted Associations between Post-Prostate Cancer Diagnosis Corticosteroids Exposure and All-cause Clinical Outcomes (n=5,286)^

Factor	Hospitalization (HR, 95% CI)	ED Visit (HR, 95 % CI)	Mortality (HR, 95%CI)
Corticosteroids Use After Cancer Diagnosis			
Non-exposure	**Ref**	**Ref**	**Ref**
Short-term exposure (<6 months) with low or intermediate daily dosage (<7.5mg/day)	1.31 (0.73—1.89)	1.24 (0.76—2.39)	1.42 (0.81—1.94)
Short-term exposure (<6 months) with high daily dosage (≥7.5mg/day)	**1.89 (1.08—1.76)**	**1.29 (1.08—2.93)**	1.53 (0.85—2.96)
Long-term exposure (≥6 months) with low or intermediate daily dosage (<7.5mg/day)	**2.08 (1.34—2.95)**	**1.62 (1.14—3.29)**	**1.76 (1.07—3.08)**
Long-term exposure (≥6 months) with high daily dosage (≥7.5mg/day)	**2.23 (1.52—3.42)**	**1.93 (1.33—3.58)**	**1.94 (1.23—3.61)**
Prostate Cancer Treatment			
Active surveillance	**Ref**	**Ref**	**Ref**
Surgery/ Radiation only	**1.24 (0.81—1.37)**	1.06 (0.78—1.94)	1.01 (0.59—1.32)
ADT/ Chemotherapy only	1.02 (0.74—1.29)	**1.13 (1.09—1.65)**	**1.06 (1.02—1.11)**
Multiple Managements and Others*	**1.32 (1.03—1.72)**	**1.25 (1.03—1.74)**	1.25 (0.79—1.83)

***** Multiple Treatments indicated patients received more than two management agents

^All covariance variables that were used in propensity weighting were removed from the Cox regression models; adjusted hazard ratios (HR) and 95% confidence intervals (CI) were reported

Table 4.17. Sensitivity Analysis B: Adjusted Associations between Post-Prostate Cancer Diagnosis Corticosteroids Exposure and All-cause Clinical Outcomes (n=6,351)^

Factor	Hospitalization (HR, 95% CI)	All-cause ED Visit (HR, 95 % CI)	Mortality (HR, 95%CI)
Corticosteroids Use After Cancer Diagnosis			
Non-exposure	**Ref**	**Ref**	**Ref**
Short-term exposure (<6 months)	**1.56 (1.07—3.08)**	**1.25 (1.03—2.91)**	**1.19 (1.01—2.44)**
Long-term exposure (≥6 months)	**2.61 (1.44—4.17)**	**2.19 (1.35—3.92)**	**1.45 (1.23—3.24)**
Prostate Cancer Treatment			
Active surveillance	**Ref**	**Ref**	**Ref**
Surgery/ Radiation only	1.45 (0.89—2.74)	1.14 (0.75—2.06)	1.29 (0.61—1.87)
ADT/ Chemotherapy only	**1.94 (1.03—3.25)**	**1.14 (1.01—1.98)**	1.24 (0.84—1.79)
Multiple Managements and Others*	**2.12 (1.57—3.89)**	**1.98 (1.23—3.42)**	**1.35 (1.12—2.47)**
Daily Dosages (Mean, SD)	**1.13 (1.05—1.89)**	**1.04 (1.01—1.82)**	**1.01 (1.00--1.45)**

***** Multiple Treatments indicated patients received more than two management agents
^All covariance variables that were used in propensity weighting were removed from the Cox regression models; adjusted hazard ratios (HR) and 95% confidence intervals (CI) were reported

Table 4.18. Sensitivity Analysis B: Adjusted Associations between Post-Prostate Cancer Diagnosis Corticosteroids Exposure and Prostate Cancer and Cardiovascular Related Clinical Outcomes (n=6,351)^

Factor	Prostate Cancer Related Hospitalization (HR, 95% CI)	Prostate Cancer Related ED Visit (HR, 95 % CI)	Cardiovascular Related Hospitalization (HR, 95% CI)	Cardiovascular Related ED Visit (HR, 95 % CI)
Corticosteroids Use After Cancer Diagnosis				
Non-exposure	**Ref**	**Ref**	**Ref**	**Ref**
Short-term exposure (<6 months)	1.14 (0.69—1.69)	1.26 (0.89—2.41)	**1.77 (1.21—2.95)**	**1.19 (1.01—2.44)**
Long-term exposure (≥6 months)	**1.51 (1.05—3.59)**	1.3 (0.91—2.42)	**2.15 (1.74—3.64)**	**1.45 (1.23—3.24)**
Prostate Cancer Treatment				
Active surveillance	**Ref**	**Ref**	**Ref**	**Ref**
Surgery/ Radiation only	1.31 (0.77—1.98)	1.09 (0.84—1.71)	1.42 (0.81—2.17)	1.29 (0.61—1.87)
ADT/ Chemotherapy only	1.21 (0.79—2.11)	1.06 (0.74—2.12)	**1.94 (1.14—3.19)**	1.24 (0.84—1.79)
Multiple Managements and Others*	**2.04 (1.26—3.36)**	**1.45 (1.13—2.89)**	**1.92 (1.52—3.39)**	**1.35 (1.12—2.47)**
Daily Dosages (Mean, SD)				
6.15, 1.98	**1.08 (1.04—2.19)**	1.09 (0.65—1.97)	**1.22 (1.09--2.41)**	**1.01 (1.00--1.45)**

***** Multiple Treatments indicated patients received more than two management agents
^All covariance variables that were used in propensity weighting were removed from the Cox regression models; adjusted hazard ratios (HR) and 95% confidence intervals (CI) were reported

Chapter 5 Discussion and Conclusions

5.1 Discussion, Limitations and Strengths, and Conclusions for Aim 1

5.1.1 *Discussion*

Overall, the annual proportion of asthma was slightly higher among prostate cancer patients compared to non-cancer patients, and trends were stable in both prostate cancer and non-cancer cohorts over time. In 2007-2014, the proportion of asthma among prostate cancer patients has increased from 13.20% to 15.71%. However, among non-cancer patients, the proportion of asthma has increased from 12.91% in 2007 to 14.50% in 2014. In this large cohort study, our findings indicated that the proportion of asthma among prostate cancer patients was slightly higher than non-cancer patients. Compared with the fact that overall 11% asthma prevalence in the US adults, the higher proportions of asthma among prostate cancer populations are worthy of attention from healthcare providers. The higher proportion of asthma found among prostate cancer patients in this study is similar with Severi et al., which found that 12% of prostate cancer patients had asthma. In this study, Severi et al concluded that a history of asthma or the use of asthma medications is associated with the risk of developing prostate cancer.[15] It is important for healthcare providers to screen and understand the burden and needs of managing comorbidities such as asthma among patients with prostate cancer.

Although in recent decades the prevalence of asthma has been increasing in the US,[75,124] findings of our analysis showed that the trend in comorbid asthma among prostate cancer patients was stable in 2007-2014. This is the first study, to our knowledge, to provide trend estimates in proportion of comorbid asthma in prostate cancer patients over time. Because inflammation is commonly found in association with prostate cancer, as one of systematic inflammation diseases, asthma has been examined for an association with prostate cancer in a few studies.[13-15] Our results of higher proportion of asthma among prostate cancer patients than non-cancer patients may help explain the possible association between inflammation and prostate cancer Furthermore, it is important to consider the age of the participants in SEER-Medicare dataset. Due to the heterogeneity of the clinical and functional presentations of the disease in the aged population (including the poor perception of symptoms and the tendency to lose the airway reversibility), for older patients at risk of comorbidity, an asthma diagnosis may be difficult to differentiate from other diseases causing breathlessness, especially chronic obstructive pulmonary disease (COPD), and heart failure. In addition, several studies focusing on the European and US populations have shown that prevalence of asthma among individuals aged over 65 years ranges from 4.5% to 15%,[98,125-130] and existing evidence indicated that asthma in the elderly is still been underdiagnosed and undertreated.[96,98,131,132] Compared with prevalence of asthma in younger adults (ranging from 4% to 9%),[133,134] prevalence of asthma is higher in older adults, with up to 15% found in a study by Wilson et al.[135] The higher prevalence of asthma in older adults may put them on greater risks in hospitalizations, ED visits, or mortality.[136-138] For example, in the US, asthma related hospitalization rate was 272 per 100,000 in the adults 65 years and older, which was higher than younger asthma patients.[139] Overall, due to the high prevalence of asthma in older adult population and its potential risks in adverse outcomes in costs, quality of life, hospitalization and mortality,[75,96,132,140] comorbid asthma in older adults should be properly screened, diagnosed, and treated to improve patient outcomes, especially for patients living with cancer.

This study also provides new evidence in the patterns of treatment of prostate cancer and asthma for patients with both diseases. Among patients with prostate cancer with and without comorbid asthma, the top three prostate cancer management in 12 months after prostate cancer diagnosis were ADT only, active surveillance, and Radiation only, respectively. ADT appeared to be the most common treatment, which is consistent with a previous study of prostate cancer patients using SEER Medicare data,[141] despite no available clinical trial data or practice guidelines to support this practice. Indeed, while ADT has been traditionally used for patients with advanced prostate cancer, it is increasingly being used in patients with early stage cancer, such as in patients with biochemical relapse who have no evidence of metastatic disease.[142] More importantly, findings also indicate that proportions of patients with both prostate cancer and asthma who received advanced cancer treatments were higher among those without asthma. The higher utilization of advanced cancer treatments among prostate cancer patients with asthma is consistent with what we found that cancer severity (stage) in prostate cancer patients with comorbid asthma was higher than those without asthma (e.g., 13.11% stage IV prostate cancer among those with asthma vs. 9.35% among those without asthma). Although there is a lack of evidence in the contribution of comorbid asthma in prostate cancer outcomes, chronic conditions such as cancer and asthma have substantial impact on daily functioning and well-being.[143] For example, high prevalence of comorbid anxiety disorders has been found in patients with asthma: up to 30% in children and adolescents and 34% in adults.[144,145] Moreover, existing evidence shows that asthma patients have a higher risk of developing other comorbid conditions, including rhinitis, nasal polyposis, gastro-esophageal reflux disease, vocal cord dysfunction, bronchiectasis, and some autoimmune diseases.[146-148] In addition, cancer patients with asthma usually have worse prognosis compared with those without asthma.[149] Therefore, these patients may require a multidisciplinary approach to manage the comorbidity, and a similar approach has been introduced in patients with diabetes and cancer to improve their prognosis.[150]

Regarding patterns of treatments of asthma, majority of patients in both prostate cancer cohort and non-cancer cohort received inhaled corticosteroids, which is broadly consistent with guidelines.[78,86,87,151] However, the proportion of receipt of inhaled corticosteroids treatment was lower among prostate cancer patients. This lower proportion of inhaled corticosteroids use in our findings is consistent with the evidence of underutilization of inhaled corticosteroids in older adult patients,[97,98,152] and can be explained by the fear of corticosteroid related side effects such as increased frequencies of cataracts and osteoporosis.[95] One obvious explanation to support this observation is that in our study sample, prostate cancer patients were more likely to receive ADT, either as single agents or combination of corticosteroids. Consideration of drug-drug interaction with cancer management, it may be reasonable to reduce the use of inhaled corticosteroids for asthma management. Likewise, a relatively higher proportion of quick relief agents utilization might indicate that inhaled corticosteroids therapy is not the first choice of treatment by prostate cancer patients who received advanced cancer treatments due to the consideration of side effects or reduced quality of life.[153,154] On the other hand, due to the consideration of comorbidity management and adherence to inhaled corticosteroids medication, asthma management for older adults are different from younger patients, in which quick relief medications are commonly used.[153,154] .

In this large cohort study, similar proportions of prostate cancer patients with comorbid asthma were observed across subgroups defined by sociodemographic characteristics such as residence settings (i.e., urban vs. rural), and SEER regions. Our results showed that prostate cancer patients who were older in age and African Americans were more likely to have comorbid asthma, which is consistent with published studies investigating factors associated with asthma in general population.[155] A few studies indicated that asthma is more prevalent among nonwhites than whites.[156] In addition, we found beneficiaries with more advanced prostate cancer stage (i.e., stage III, IV vs. stage I) were more likely to have asthma compared to those with lower cancer stage. Findings in this study were similar to a previously published study of cancer patients identified in the New Zealand Cancer Registry, which indicated that number of comorbid conditions among cancer patients was associated with advanced cancer stage at diagnosis.[157] Last but not least, findings reported in this study also demonstrated that prostate cancer patients with more comorbidities were more likely to have asthma. Indeed, a population-based study using the SEER dataset found that 30.5% of prostate cancer patients had comorbidities, and the second most common comorbidity was chronic lung diseases (15%).[44]

Findings in this study have a number of clinical and public health implications. First, findings based on encounter level data may help to understand practice variation and the effectiveness of practice guideline dissemination. A better understanding of asthma variability in practice may heighten awareness of the importance of linking clinical research to routine practice, which can result in better treatment outcomes in prostate cancer patients. In addition, this study calls attention to future research to examine treatment patterns and variation among prostate cancer patients with comorbid asthma because evidence suggests that treatment of these comorbid conditions in cancer patients are often inadequate.[158] Overall, the use of inhaled corticosteroids treatment is expected to be relatively lower in prostate cancer patients. However, given the variation in the clinical practice patterns relative to the older adult population, it is likely that evidence of treatment differences related to physician preference, patients' overall health status, or consideration of aging is associated with pharmacokinetic changes that are primarily due to the decline in the function of the liver and the kidneys.[159] Further research is needed to investigate these treatment differences.

Second, although this study suggested that trend in proportion of asthma in prostate cancer patients was stable from 2007 to 2014, it showed a higher proportion of asthma among prostate cancer patients compared to non-cancer patients. Hence, the findings provide evidence to health care providers and policymakers for recognizing the burden of comorbid asthma among prostate cancer patients and achieving better care for prostate cancer patients in the US. Health care providers may screen history of asthma and asthma symptoms among prostate cancer patients and optimize both asthma and prostate cancer treatment to improve patient outcomes. Also, policymakers and practitioners may also pay attention to integrate education initiatives and team based care to improve asthma self-management knowledge and skills to better help patients manage their comorbidities.

Third, this study also identified factors associated with asthma among prostate cancer patients, which will help healthcare providers to screen and identify patients for optimizing treatments and disease management coordination. Specifically, attention should be paid to prostate cancer patients who are older, African Americans, and with more comorbidities, in order to identify potentially undertreated patients and initiate appropriate treatments sooner and safely.

5.1.2 *Limitations and Strengths*

Several limitations and strengths in this study should be noted. First, the SEER-Medicare database mainly consists of patients equal or older than 65 years of age, with only a part of patients less than 65 years old with some specific eligibilities (e.g. ESRD, or disability), and hence these results may not be broadly generalizable to the general prostate cancer patient population. However, consideration of the low incidence rate of prostate cancer among younger adults, our results can still, to some extent, reflect a population-based estimation. Second, other limitations of the data include asthma severity and prostate cancer progress after diagnosis, were not available in SEER-Medicare data. For example, clinical information such as biological characteristics, PSA level, or genetic biomarkers of the tumor (e.g., hormone receptor status) in SEER are limited, preventing possible inferences about the appropriateness of treatment. Consequently, this study did not intend to imply whether the receipt of ADT or receipt of an inhaled corticosteroids was appropriate or not. Finally, critical variables that might impact prostate cancer or asthma, including behavior factors (e.g smoking, alcohol use, or diet behaviors), family history, occupational exposures, or air pollution situation, were not available. Taken together, selection bias may be driving the conclusions about factors associated with asthma among patients with prostate cancer, reflecting residual confounding due to the lack critical variables that can be measured. In addition, reliability, misclassification, and quality of measurements also need to be considered, such as comorbidity from claims-based data.[160] However, study findings are not subject to recall bias because relevant medical information from the SEER registry was collected by physicians/staff, rather than from cancer patients.[101,161]

Despite the limitations of claims data, strengths of this current study included its large sample size and longitudinal trend observations that provided nationally representative estimates of comorbid asthma, asthma and prostate cancer treatment patterns among prostate cancer patients in the US.

5.1.3 *Conclusions*

The proportion of asthma in prostate cancer patients remains stable across time, but higher than non-cancer patients and general population. ADT is the primary treatment in prostate cancer patients with and without asthma. Prostate cancer patients with comorbid asthma appeared to have advanced cancer stage and receive advanced cancer treatments. Factors associated with asthma in prostate cancer patients included sociodemographic characteristics including older age and black race, advanced cancer stage, and more comorbidities. These findings serve as the first step to help practitioners and policymakers understand the prevalence and burdens of comorbid asthma among patients with prostate cancer. Findings highlight future research on treatment access and quality in order to improve clinical outcomes for prostate cancer patients with comorbid asthma.

5.2 Discussion, Limitations and Strengths, and Conclusions for Aim 2

5.2.1 *Discussion*

In this large, new user cohort of prostate cancer patients with and without comorbid asthma, we found the adjusted risks of hospitalization (both all-cause and prostate cancer related) and ED (both all-cause and prostate cancer related) visits were statistically significantly higher in those with comorbid asthma than those without asthma. The results suggested asthma as a common comorbidity and an independent risk factor for both all-cause and prostate related hospitalizations and ED visits. To our knowledge, the present study is among the first large, population-based study to examine the association between comorbid asthma and clinical outcomes among prostate cancer patients. Only one published study evaluated quality of life (QoL) among prostate cancer patients who were treated with radiotherapy and found that patients with coronary heart disease or COPD or asthma had a significantly but small worse course in QoL.[162]

Our results are consistent with existing evidence demonstrating that cancer patients with comorbid asthma are associated with risk of similar clinical outcomes, such as increased mortality, hospitalizations, or ED visits.[163] Indeed, plenty of evidence has indicated that due to underdiagnose and undertreatment of asthma in older adults, risks in hospitalizations and ED visits are higher than younger individuals.[95-98] In addition, it should be noted that our study focused on prostate cancer patients and cancer therapies, especially higher use of ADT in prostate cancer patients with asthma. Although ADT has been shown to have beneficial effects on prostate cancer progression, serious adverse events can occur during treatment,[164,165] such as hyperlipidemia, insulin resistance, cardiovascular disease, anemia, osteoporosis, sexual dysfunction, and cognitive deficits.[166] A few studies also indicated asthma is one of risk factors of prostate cancer.[13,15-17,167,168] Our results already demonstrated that prostate cancer patients with comorbid asthma had advanced cancer stage than those without asthma. In our study, the higher risks of all-cause and prostate cancer related hospitalizations and ED visits due to comorbid asthma might be explained by the impact of asthma on both overall health status and cancer severity, respectively.

In addition, we found that comorbid asthma was associated with all-cause mortality, but not with prostate cancer related mortality. Several studies have indicated that older adults with asthma are at higher risk of mortality.[169-171] Aging is one of key risk factors of mortality, which is not only associated with a mechanical disadvantage of lung functions, such as restricted chest wall,[172] or loss of elastic recoil leads to small airways collapse,[173] but also related to poor medication adherence due to taking multiple medications.[174] On one hand, due to lower use of inhaled corticosteroids,[175,176] and the need for treatment with systemic corticosteroid or theophylline[177] among older asthma patients, they are likely to have higher mortality than younger patients. On the other hand, due to the increased risks for side effects and comorbidities among prostate cancer patients who undergo long-term ADT treatment such as diabetes mellitus

(DM), coronary heart disease, and myocardial infarction (MI), patients may experience an increased risk of coronary heart disease and cardiovascular mortality.[66] In this study, we did not observe the association between comorbid asthma and prostate cancer related mortality. Actually, due to the relatively high 5-year survival rate among prostate cancer patients, two years follow up period in our study might be too short to observe mortality, especially prostate cancer related mortality. Therefore, such association may be further investigated using longer follow up period and larger sample size.

Finally, in our study, we also found socioeconomics, demographics, tumor characteristics, prostate cancer treatment patterns, and comorbidities have an impact on the risk of both all-cause and prostate cancer related hospitalizations and ED visits. Similar to previous studies,[178-180] being older, Africa-American, with comorbidity, and advanced cancer stage were associated with an increased risk of having hospitalization and ED visits, both all-cause and cancer related reasons. The associations between black race and adverse clinical outcomes among prostate cancer patients might be partially explained by the evidence that African American men are more likely to be diagnosed with advanced stage and more severe disease because African American men have prostate cancers that are more biologically aggressive, which has contributed to their higher hospitalizations, ED visits, and mortality rates.[181-184] Our study also supported that comorbidity, as one of a central factor in survival rate for prostate cancer patients, has long been known to have a strong association of non-prostate cancer related death,[185,186] and has even been incorporated into prostate cancer-specific estimation of long-term outcomes.[187]

5.2.2 *Limitations and Strengths*

A number of limitations and strengths of our study should be noted. First, an observational study may introduce selection bias or unmeasurable confounding factors. For instance, we were not able to measure other factors potentially associated with hospitalizations, ED visits, or mortality such as genetic biomarkers that might affect a provider's decision regarding treatment modality,[188,189] or smoking, alcohol use, diet, physical activity, other possible unmeasured confounders (e.g., body-mass index) may affect cancer prognosis. Second, the nature of registry and claims data might introduce some measurement biases. For example, there may be an issue of ascertainment of clinical outcomes such as prostate cancer related hospitalizations, ED visits, or mortality. However, diagnosis and procedure codes reflecting clinical practice have been well documented and utilized in previous studies.[190-192] Third, our scope was limited to Medicare beneficiaries in SEER geographic areas; therefore, our results may not be generalized to other non-SEER populations or with other types of health insurance. In addition, we only included patients newly diagnosed with prostate cancer as the initial primary tumor. This method helps reduce confounding of clinical and mortality bias from patients who underwent cancer treatments for prior cancer, but limits generalizability to those patient who have multiple types of cancer with non-prostate cancer as primary tumor.

Our study also has some strengths. Previous studies that investigated the association between asthma and prostate cancer have included small sample sizes, hospital-based recruitment, limited control for confounding, and potential biases associated with participant selection and exposure measurement.[13-15,167] Although the current study did not focus on the association between asthma and prostate cancer, we evaluated the effect of comorbid asthma on clinical outcomes among newly diagnosed prostate cancer patients using a new user study design, including large sample size, and fully assessing associations of both all-cause and cancer specific clinical outcomes. Quantifying the impact of important comorbidity such as asthma on all-cause and prostate cancer related clinical outcomes, adjusting for patient's cancer treatment, demographics, socioeconomics, tumor characteristics, and other comorbidities, provides practitioners new and empirical evidence in developing appropriate interventions to reduce risk of adverse outcomes and improve overall survival.

5.2.3 Conclusion

In conclusion, our findings indicate that among male Medicare beneficiaries with prostate cancer, comorbid asthma is independently associated with increased risks of all-cause and prostate cancer related hospitalizations and ED visits, as well as all-cause mortality. Patient's characteristics, tumor characteristics, prostate cancer treatment patterns, and other comorbidity are also associated with these clinical outcomes Findings help practitioners recognize the impact of comorbid asthma on clinical outcomes among prostate cancer patients and intervene with timely and appropriate treatment and disease management approach to improve patient outcomes.

5.3 Discussion, Limitations and Strengths, and Conclusions for Aim 3

5.3.1 *Discussion*

In this large population-based study, we observed the adverse effects of long-term ($\geq$ 6 months) corticosteroids use on hospitalizations, ED visits, and mortality among prostate cancer patients with comorbid asthma. These effects remained after categorizing corticosteroids treatment dosage, and controlling for patient's characteristics, tumor characteristics, prostate cancer treatments, and comorbidities. To our knowledge, this is the first study to evaluate the effects of corticosteroids use on clinical outcomes among prostate cancer patients with comorbid asthma, considering corticosteroids treatment duration and dosage.

Most of the therapeutic regimens commonly applied among cancer patients require the concomitant use of corticosteroids to counteract the adverse effects of prescribed chemotherapeutic drugs. In addition, corticosteroids are widely used in the palliative setting, predominantly due to their anti-inflammatory activity or to relieve both specific and non-specific symptoms associated with advanced prostate cancer.[193-197] Since treatment with corticosteroids in prostate cancer, especially in mCRPC, is usually prolonged over several years, most of these patients are exposed to corticosteroids related adverse events and, in the long term, present several clinical manifestations of corticosteroid excess. In our study, patients with long-term use (≥6 months) combined with high daily dosage (≥7.5 mg/day) of corticosteroids exposure had the highest statistically significant risks in all clinical outcomes that we evaluated, including all-cause, prostate cancer related, and cardiovascular related hospitalization and ED visits, as well as all-cause mortality. In addition, patients with long-term use (≥6 months) combined with low or intermediate daily dosage (<7.5 mg/day) of corticosteroids exposure also had statistically significant risks of all of these clinical events compared to those with no exposure of corticosteroids use after prostate cancer diagnosis. Even patients with short-term (<6 months) and high daily dosage (≥7.5 mg/day) of corticosteroids exposure had significantly higher risks of all-cause and prostate cancer related hospitalization and ED events compared to those without corticosteroids exposure. But there was no significant difference in risks of any evaluated clinical outcomes for patients with short term and low or intermediate daily dosage exposure of corticosteroids compared with non-users. Our findings demonstrated the significant and critical impact of corticosteroids use, especially in long-time and high daily dosage, on patient outcomes including hospitalizations, ED visits, and mortality among prostate cancer patients with asthma.

Our findings in prostate cancer patients comorbid asthma can be supported by a number of studies that have indicated chronic use of steroids are associated with the development of multiple toxicities, including adrenal insufficiency, osteoporosis, osteonecrosis, hyperglycemia, hypokalemia, edema, dyspepsia, thrush, hypertension, cataract, glaucoma, insomnia, myopathy, immunosuppression,[67,72] and even a significantly worse survival than those who did not have exposure.[198] Myopathy and hypokalemia induced from corticosteroids may also aggravate fatigue for patients from the malignancy, ADT and chemotherapy. Therefore, a potential mechanism underneath may be that corticosteroid induces the development of multiple toxicities. Moreover, corticosteroids use with concurrent ADT treatment also induces bone loss and muscle atrophy and chemotherapy induced immunosuppression, which may all contribute to the adverse effects of corticosteroids.[72,199] Although the immunosuppressive effects of chronic low dose corticosteroids have not been studied systematically in patients with malignancies, even patients with bronchial asthma exposed to chronic, low dose daily corticosteroids have found to experience a blunting of both humoral and cellular immune responses.[199] Therefore, the vulnerable patients with both asthma and prostate cancer are likely to be exposed to two sources of corticosteroids: one from asthma management (e.g., inhaled corticosteroids) and the other from palliative cancer treatments. Based on the empirical findings of our study, these patients need to be monitored closely for both duration and dosage of corticosteroids treatment in order to prevent adverse clinical outcomes such as hospitalization, ED, and mortality.

In addition, we found patients exposed to long-term corticosteroids also had higher risks of cardiovascular related hospitalization and ED visits. Indeed, based on the guideline, prostate cancer patients with advanced cancer stage receive corticosteroids in order to reduce anti-inflammatory activities[194] or tumor-induced pain.[200] However, because of the mechanism of the action of corticosteroids and their associated side-effects, caution is warranted when using these agents in cancer patients. Evidence has shown that hyperglycemia and hypertension events after corticosteroids exposure may accentuate the risk of cardiovascular disease owing to insulin resistance and hyperlipidemia associated with long-term use corticosteroids.[64,66,67,201] On the other hand, the use of corticosteroids in men with prostate cancer who were receiving ADT may lead to an elevated risk of cardiovascular and metabolic diseases that could be exacerbated further.[67] Therefore, prostate cancer patients may have an increased risk of cardiovascular diseases following long-term treatment of ADT and corticosteroids.[165,202]

Recent clinical and preclinical studies have provided evidence indicating that corticosteroids themselves are likely to promote tumor progression in particular populations of patients with mCRPC, suggesting that this kind of treatment may have a detrimental effect on cancer outcome.[72] For example, analysis of patients receiving enzalutamide in the AFFIRM trial identified that men receiving corticosteroids at baseline had a significantly worse survival than those who did not.[203] Our findings of higher risks of all-cause mortality among exposure of corticosteroids are consistent with previous studies. However, we made extra efforts in looking into the corticosteroids treatment duration and dosage and found that long-term exposure of 6 months and longer of corticosteroids had significant impact on patient’s mortality. Due to the small sample size for patients with prostate cancer related mortality, we could not exam if and how the use of corticosteroids may affect prostate cancer mortality. Moreover, due to the difficulty of determining patient’s prostate cancer stage progress in the SEER Medicare data, we could not investigate the relationship between corticosteroids use and cancer stage progress for our study sample. Even though we are lack of evidence in the effect of corticosteroids on cancer progress, the decision to long-term administer corticosteroids in prostate cancer patients with comorbid asthma should be carefully weighed and, when contraindicated, corticosteroids treatment should be withdrawn.

5.3.2 *Limitations and Strengths*

A number of limitations and strengths of our study should be noted. First, an observational study may introduce selection bias or unmeasurable confounding factors. For instance, we were not able to measure other factors potentially associated with mortality such as smoking or genetic biomarkers that might affect a provider's decision regarding treatment modality. However, we applied propensity score weighting to adjust for patient characteristics, number of comorbidities, and cancer stage and ensure the balanced distribution of observed confounding factors between corticosteroids user and non-users. This approach has been used in many population-based studies to reduce the effects of confounding in observational studies.[204] Second, the nature of registry and claims data might introduce some biases such as ascertainment of clinical outcomes. However, diagnosis codes and procedure of clinical practice are widely accepted in previous studies focused on prostate cancer patients.[52,205,206] Third, potential confounders of corticosteroids use before prostate cancer diagnosis, with various durations and dosages, may exist. However, we addressed this issue by conducting sensitivity analyses limiting to patients without any corticosteroids use in baseline 12 months (Table 4.16). Similar as the main results, patients with long-term and high daily dosage of corticosteroids exposure still had the highest statistically significant risks of all-cause hospitalization, ED visit, and mortality compared with non-users. Finally, our study sample was limited to fee-for-service Medicare beneficiaries in SEER geographic areas; therefore, results may not be generalized to other populations not included in this study.

Our study has a number of strengths. To our knowledge, this is the first population-based study examining the relationship of corticosteroids treatment exposure and clinical outcomes in prostate cancer patients with comorbid asthma. We used a new user cohort including large sample of newly diagnosed prostate cancer patients. We included patients with pre-exposure of corticosteroids before cancer diagnosis to increase generalizability and conducted sensitivity analysis to evaluate potential impact from this baseline factor. Most importantly, we were able to examine the effects of both duration and dosage of corticosteroids exposure on risk of clinical outcomes among prostate cancer patients with comorbid asthma. A better understanding of how long-term and higher dosage of corticosteroids use may contribute to risk of all-cause, prostate cancer related, and cardiovascular related hospitalizations and ED visits, as well as all-cause mortality may lead to the development of timely and effective strategies to reduce adverse clinical events and improve overall prostate cancer survival for this vulnerable cancer patient population.

5.3.3 Conclusion

In conclusion, our study found that among male Medicare beneficiaries with prostate cancer and comorbid asthma, patients who were receiving long-term and higher dosage of corticosteroids after prostate cancer diagnosis had the highest risks in all-cause, prostate cancer related, and cardiovascular related hospitalizations and ED visits, and all-cause mortality. The decision of long-term administration of corticosteroids in prostate cancer patients with comorbid asthma should be carefully weighed to avoid potential adverse outcomes.

5.4 Summary

5.4.1 Overall findings

In this dissertation study, we found the proportion of comorbid asthma in prostate cancer patients was higher than non-cancer patients, and the trend in proportion of asthma in prostate cancer patients was stable across time (Aim 1). In addition, the findings demonstrated that prostate cancer treatment patterns differed between patients with asthma and without asthma. Specifically, although the top three prostate cancer management in 12 months after prostate cancer diagnosis were similar in patients with and without comorbid asthma, higher proportion of prostate cancer patients with comorbid asthma had advanced stage cancer and received advanced cancer therapy (Aim 1). Third, we found that men with prostate cancer with comorbid asthma had statistically significantly increased risks of all-cause and prostate cancer related hospitalizations and ED visits, as well as all-cause mortality, controlling for patient's characteristics, tumor characteristics, prostate cancer treatments, and comorbidities (Aim 2). Finally, our findings demonstrated that the use of corticosteroids in prostate cancer patients with comorbid asthma, especially in long-term and higher dosage use, was associated with increased risks of all-cause, prostate cancer related, and cardiovascular related hospitalizations and ED visits, as well as all-cause mortality. Specifically, patients with long-term use (≥6 months) combined with high daily dosage (≥7.5 mg/day) of corticosteroids exposure after prostate cancer diagnosis had the highest statistically significant risks of these clinical outcomes (Aim 3).

5.4.2 Implication of findings and future research

Findings in this study have a number of implications. First, findings help practitioners and policymakers systematically understand the burden of comorbid asthma in prostate cancer patients, treatment variations, and the effectiveness of clinical practice guideline dissemination. Specifically, this study underscores that treatment differences exist among prostate cancer patients with and without asthma, specifically in terms of ADT, chemotherapy, and corticosteroids. These findings highlight future research on treatment access (e.g., benefit design, health insurance coverage, treatment disparities) and quality (e.g., evidence-based medicine, prescribing patterns) in order to improve clinical outcomes for prostate cancer patients with comorbid asthma. In addition, factors associated with comorbid asthma in prostate cancer patients could be considered to help identify potentially underdiagnosed patients for comorbid asthma.

Second, our study also provides new and empirical evidence regarding the risk factor of comorbid asthma for adverse outcomes including hospitalizations, ED visits, and mortality. Findings help practitioners recognize the impact of comorbid asthma on clinical outcomes among prostate cancer patients and intervene with timely and appropriate treatment and disease management approach to improve patient outcomes. Future research can utilize longer follow up period to observe patient’s clinical outcomes and strategies to migrate risks of patient outcomes among prostate cancer patients with asthma. In addition, educational outreach and interventions can be designed and developed to help patients better manage their asthma symptoms and improve wellbeing.

Finally, most importantly, our study highlights the risk of using corticosteroids, particularly in long-term and with high dosage, on adverse clinical outcomes among prostate cancer with asthma. This finding may support health care providers in planning for prostate cancer patients with asthma. A thorough assessment of a patient's corticosteroids use history, goals of therapy, overall health situation through an assessment, and cooperation with multiple health care specialists will guide treatment decision making. The treatment of advanced prostate cancer is likely to continue to change with ongoing exploration of additional agents; these should be offered to fit those patients with asthma, and considered in those with some vulnerabilities. The dissemination and implementation of these findings into clinical practice will be a step forward to improve the delivery of prostate cancer patients with asthma care.

Consequently, our findings call for primary care physicians' and oncologists' attention on the needs for careful consideration of corticosteroids use, for the assessment and monitoring of side effects and adverse events when initiating these regimens among prostate cancer patients with asthma. Future research can focus on investigating heterogeneity in patient outcomes, the relationship between corticosteroids use and cancer progression, and strategies to optimize treatment outcomes among prostate cancer patients with asthma. In addition, our findings also provide evidence regarding how patient demographic and socioeconomic factors, geographic region, and comorbidities might affect patients' outcomes, which might be helpful for practitioners evaluate plans for precision medicine for individual patients.

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