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Amitkumar Dineshchandra Raval

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**Impact of Chronic Conditions on Treatment, Cancer-and Non-Cancer Outcomes among Elderly
Men with Incident Prostate Cancer**

Amitkumar Dineshchandra Raval

Dissertation submitted
to the School of Pharmacy
at West Virginia University

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy in
Health Outcomes Research

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ABSTRACT

Impact of Chronic Conditions on Treatment, Cancer-and Non-Cancer Outcomes among Elderly Men with Incident Prostate Cancer

Amitkumar Dineshchandra Raval

Prostate Cancer is the most commonly observed non-skin cancer among the elderly men aged 65 years and older in the United States. Nearly one third of elderly men diagnosed with incident prostate cancer have pre-existing chronic conditions. Therefore, among elderly men with prostate cancer, management for cancer and chronic conditions should be optimized to improve healthcare outcomes. Previous literature majorly focused on the risk and management of cancer in the presence of number of conditions, although, it is known that more than 70% of chronic conditions among men diagnosed with prostate cancer were either cardio-metabolic, respiratory or mental health conditions. Lack of evidence persists regarding the impact of common types of chronic conditions and their conditions among elderly men with prostate cancer and vice-versa. The current study is an attempt to shrink the knowledge gap to provide actionable strategies to better management of chronic conditions and prostate cancer among elderly men. The three specific aims of the study were to: (1) examine the associations between the types of pre-existing chronic conditions and cancer stage at diagnosis, initial cancer treatment and clinical outcomes after initial cancer treatment; 2) examine the relationship between metformin use and cancer stage at diagnosis, and the initial cancer-treatment; 3) analyze the impact of cancer diagnosis on the risk of non-cancer hospitalizations and evaluate whether the impact of cancer diagnosis on the risk of non-cancer hospitalizations vary by the types of pre-existing chronic conditions among fee-for-service elderly Medicare beneficiaries with incident prostate cancer. The study used a retrospective cohort design, using multiple years (2002-2010) of the cancer registry data from the Surveillance, Epidemiology and End Results (SEER) program linked with the Medicare administrative claims data and the Area Health Resource Files (AHRF). In the first aim, among elderly men with incident prostate cancer (N = 103,820), the cardio-vascular conditions were the most common chronic condition. 1 in 10 elderly men had advanced prostate cancer at diagnosis. Elderly men without cardio-metabolic, respiratory or mental health conditions were more likely to be diagnosed with advanced prostate cancer as compared to those with all the three types of chronic conditions. 3 in 4 elderly men with localized prostate cancer received either radical prostatectomy (RP), radiation therapy (RT) or hormone therapy during the first six-month after cancer diagnosis. As compared to all three types of chronic conditions, those with single types of chronic conditions were less likely to develop bowel, and urinary dysfunctions. In the second aim, the use of metformin was associated with a reduction in the risk of advanced prostate cancer among elderly men diagnosed with prostate cancer and pre-existing diabetes (N=2, 652). In the third study, elderly men diagnosed with prostate cancer had an increase in the risk of non-cancer hospitalizations during the post-cancer period as compared to the pre-cancer period in both unadjusted and adjusted analyses. The highest rates of non-cancer hospitalizations were observed during first four months after the diagnosis of prostate cancer. To summarize, our study confirms that elderly men with incident prostate cancer and multiple types of pre-existing chronic conditions would pose a different degree of risk for the development of advanced prostate cancer. Although the management of chronic conditions such diabetes with metformin may reduce the risk of advanced prostate cancer among elderly men. An overuse of RT/RP in men with different types of chronic conditions and an increase in the non-cancer hospitalizations in the initial period after diagnosis of prostate cancer suggest the scope of optimum use of RT and RP and improvement in the care of chronic conditions.

DEDICATION

This dissertation is dedicated to my late father Dineshchandra Ratilal Raval (20/5/1952-4/12/1989)
who was a victim of cancer.

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Table of Contents

LIST OF TABLES	ix
LIST OF FIGURES	x
LIST OF APPENDIX	x
LIST OF ABBREVIATIONS	xi
Chapter 1 Introduction	1
1.1 BACKGROUND	1
1.1.2 Epidemiology of Prostate Cancer in the US	2
1.1.3 Cancer Stage at Diagnosis.....	2
1.1.4 Prostate Cancer Treatment	3
1.1.5 Prognosis of Prostate Cancer	3
1.1.6 Chronic Conditions in Prostate Cancer	3
1.1.7 Chronic Conditions and Cancer Stage at Diagnosis, Initial Cancer Treatment and Outcomes	4
1.1.8 Case of Metformin: Risk of Advanced Stage of Cancer and Cancer Treatment in Prostate Cancer and Diabetes	4
1.1.9 Impact of Prostate Cancer Diagnosis on Non-cancer Hospitalizations.....	5
1.3 SPECIFIC AIMS	6
1.4 DATA SOURCES	8
1.4.1 Surveillance Epidemiology and End-Results Registry	8
1.4.2 Medicare	9
1.4.3 Medicare Part-D Data	10
1.4.4 Area Health Resources Files	10
1.5 CONCEPTUAL FRAMEWORK	10
1.6 REFERENCES	12
Chapter 2 Types of Chronic Conditions and Cancer Stage at Diagnosis, Initial Cancer Treatment and Clinical Outcomes among Elderly Medicare Beneficiaries with Prostate Cancer	16
2.1 ABSTRACT.....	16
2.2 INTRODUCTION	19
2.2.1 Pre-existing Chronic Conditions and Cancer Stage at Diagnosis	19
2.2.2 Pre-existing Chronic Conditions and Prostate Cancer Treatment.....	20
2.2.3 Number or Weighted Score of Chronic Conditions	21
2.2.4 Presence of a Specific Chronic Condition	21
2.2.5 Preexisting Chronic Conditions and Clinical outcomes.....	22
2.2.5.2 Presence of a Specific Chronic Condition	22
2.3 CONCEPTUAL FRAMEWORK	23
2.4 METHOD	23
2.4.1 Study Design	23
2.4.2 Data Sources	24
2.4.3 Study Cohort	25

2.4.4 Key Dependent Variables 2.4.4.1 Prostate Cancer Stage at Diagnosis (Localized and Advanced Stage)	25
2.4.4.2 Initial Cancer Treatment	25
2.4.4.3 Clinical Outcomes-Urinary, bowel, and sexual dysfunction.....	26
2.4.5 Key Independent Variable	26
2.4.5.1 Types of pre-existing chronic conditions	26
2.4.6 Other Independent Variables	27
2.4.6.1 Predisposing Characteristics	27
2.4.6.2 Enabling Characteristics	27
2.4.6.3 Need Characteristics	27
2.4.6.4 External environment characteristics	28
2.5 STATISTICAL ANALYSES	28
2.6 RESULTS	29
2.6.1 Study Population	29
2.6.2 Study Population by Types of Chronic Conditions.....	29
2.6.3 Types of Chronic Conditions and Cancer Stage at Diagnosis	30
2.6.4 Types of Chronic Conditions and Initial Cancer Treatment Type	30
2.6.5 Types of Chronic Conditions and Clinical Outcomes.....	31
2.7 DISCUSSION	31
2.7.1 Types of Chronic Conditions and Cancer Stage at Diagnosis	32
2.7.2 Types of Chronic Conditions and Initial Cancer Treatment	32
2.7.3 Types of Chronic Conditions and Clinical Outcomes.....	34
2.8 CONCLUSION	35
2.9 REFERENCES	36
Chapter 3 Association between Metformin Use and Cancer Stage at Diagnosis and Initial Cancer Treatment among Elderly Medicare Beneficiaries with Diabetes and Prostate Cancer	51
3.1 ABSTRACT.....	51
3.2 INTRODUCTION	53
3.2.1 Diabetes and Prostate Cancer Risk and Stage at Diagnosis	53
3.2.2 Anti-diabetes Drugs (Metformin) and Cancer Stage at Diagnosis.....	53
3.2.3 Metformin Use and the Initial cancer treatment	54
3.3 CONCEPTUAL FRAMEWORK	55
3.4 METHODS	55
3.4.1 Study Design	55
3.4.2 Data Source	56
3.4.3 Study Cohort	56
3.4.3 Key Dependent Variable.....	57
3.4.3.1 Cancer Stage at Diagnosis.....	57
3.4.3.2 The initial cancer treatment.....	57
3.4.4 Key Independent Variable	57

3.4.4.1 Metformin Use	57
3.4.5 Other Independent Variables	58
3.4.5.1 Predisposing characteristics	58
3.4.5.2 Enabling characteristics	58
3.4.5.3 Need characteristics	58
3.4.5.4 External environment characteristics	59
3.5 STATISTICAL ANALYSES	59
3.6 RESULTS	60
3.6.1 Description of the Study Cohort	60
3.6.2 Description of the Study Cohort by Metformin Use	60
3.6.3 Metformin and Cancer Stage at Diagnosis.....	60
3.6.4 Metformin and the Initial Cancer Treatment	61
3.5 DISCUSSION	62
3.7 CONCLUSIONS.....	64
3.8 REFERENCES	65
Chapter 4 Impact of Prostate Cancer Diagnosis on Non-Cancer Hospitalizations by Types of Chronic Conditions among Elderly Medicare Beneficiaries with Incident Prostate Cancer	75
4.1 ABSTRACT.....	75
4.2 INTRODUCTION	78
4.3 CONCEPTUAL FRAMEWORK	80
4.4 METHODS	80
4.4.1 Study Design.....	80
4.4.2 Data Sources	81
4.4.3 Study Cohort	81
4.4.4 Key Dependent Variable: Non-cancer hospitalizations	81
4.4.5 Key Independent Variable: Types of co-occurring chronic condition (One of the need factors)	82
4.4.6 Other Independent Variables	82
4.4.6.1 Predisposing Characteristics	82
4.4.6.2 Enabling Characteristics	83
4.4.6.3 External environment characteristics	83
4.5 STATISTICAL ANALYSES	84
4.6 RESULTS	86
4.6.1 Study Population	86
4.6.2 Non-cancer-Hospitalizations during the pre- and post-cancer period.....	86
4.6.3 Probabilities of Non-cancer hospitalizations by Pre and Post-Cancer Period.....	87
4.7 DISCUSSION	87
4.8 CONCLUSION	90
4.9 REFERENCES	91
Chapter 5	102

Discussion of Findings and Research Implications	102
5.1 SUMMARY OF FINDINGS & DISCUSSION.....	102
5.2 IMPLICATIONS FOR FUTURE RESEARCH	104
5.3 STUDY LIMITATIONS	105
5.4 REFERENCES	107

LIST OF TABLES

Table 1.1 American Joint Committee on Cancer (AJCC) Clinical TNM Classification of Prostatic Tumors	14
Table 1.2 Details of Variables for Each Study Objectives-classified based on ABM	15
Table 2.1 Characteristics of Elderly Medicare Beneficiaries with Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database-2002-2010.....	39
Table 2.2 Characteristics of Elderly Medicare Beneficiaries with Prostate Cancer by Types of Chronic Conditions	41
Table 2.3 Number and Percent with Advanced Prostate Cancer and Adjusted Odds Ratios (AOR) and 95% Confidence Intervals from Logistic Regressions for Advanced Stage Diagnosis among Elderly Medicare Beneficiaries with Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database 2002-2010	43
Table 2.4 Number and Percentage with Initial Cancer Treatment by Types of Chronic Conditions Unadjusted and Adjusted Odds Ratios and 95% Confidence Intervals from Multinomial Logistic Regressions among Elderly Medicare Beneficiaries with Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database 2002-2010.....	44
Table 2.5 Number and Percentage with Poor Clinical Outcomes Unadjusted and Adjusted Odds Ratios and 95% Confidence Intervals from Logistic Regressions of Clinical Outcomes among Elderly Men with Prostate Cancer by Types of Chronic Conditions Surveillance, Epidemiology and End Results-Medicare Linked Database 2002-2010	45
Table 3.1 Characteristics of the Study Cohort Elderly Medicare Beneficiaries with Diabetes and Incident Prostate Cancer by Metformin Use SEER-Medicare-linked Database 2007- 2010.....	67
Table 3.2 Adjusted Odds Ratios and 95% Confidence Intervals from Logistic Regressions On Metformin Use among Elderly Medicare Beneficiaries with diabetes Incident Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Data-2007-2010	69
Table 3.3 Number and IPTW-Adjusted Percentage of Men with Localized Versus and Advanced Stage of Prostate Cancer by Metformin Use Elderly Medicare Beneficiaries with Diabetes and Incident Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database-2007-2010	70
Table 3.4 Numbers and IPTW-Adjusted Percentages of the Initial Cancer Treatment Categories	71
Table 4.1 Characteristics of Elderly Medicare Beneficiaries with Incident Prostate Cancer Surveillance, Epidemiology and End Results (SEER)- Medicare Linked Database 2000 – 2010.....	93
Table 4.2 Number and Percentage with Non-Cancer Related Hospitalizations during the Pre- and Post-Cancer Period.....	95
Table 4.3 Adjusted Odds Ratios and 95% Confidence Intervals (CI) of Cancer Diagnosis Period From GEE models on Non-Cancer Related Hospitalizations Elderly Men with Incident Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database-2000-2010	96
Table 4.4 Predicted Probabilities with 95% Confidence Intervals for Types of Chronic Conditions From GEE analysis on Non-Cancer Related Hospitalizations Elderly Medicare Beneficiaries with Incident Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database-2000-2010	97

LIST OF FIGURES

Figure 2.1 Study Theoretical Framework: Adaptation of Andersen Behavioral Model for Aim 1	23
Figure 2.2 Schematic diagram of study design for Aim 1	24
Figure 3.1: Study Theoretical Framework: Adaptation of Andersen Behavioral Model for Aim 2	55
Figure 3. 2 Schematic Presentation of Study Design for Aim 2	56
Figure 4. 1 Study Theoretical Framework: Adaptation of Andersen Behavioral Model for Aim 3	80
Figure 4. 2 Schematic Presentation of Study Design for Aim 3	81

LIST OF APPENDIX

Appendix 2.1 Study Cohort Development Flow diagram for Study Population of Elderly Medicare Beneficiaries diagnosed with Prostate Cancer	46
Appendix 2.2 Codes to Identify Radiation Therapy, Surgery, Hormonal and Chemotherapy Utilization Among Elderly Medicare Beneficiaries with Prostate Cancer Using Surveillance, Epidemiology and End Results-Medicare Linked Data 2002-2010	47
Appendix 2.3 Diagnostic and Procedure codes used to Identify Clinical Outcomes-Bowel, Sexual and Urinary Dysfunctions Among Elderly Men with Prostate cancer using SEER-Medicare data from the year 2002 to 2010.....	48
Appendix 2.4 Codes Used to Identify the Types of Chronic Conditions and List of Other Chronic Conditions Among Elderly Medicare Beneficiaries with Incident Prostate Cancer Surveillance, Epidemiology, End-Results-Medicare Linked Data of 2002 to 2009	50
Appendix 3.1 Study Cohort Development Flow diagram for Study Population of Elderly Medicare Beneficiaries diagnosed with Prostate Cancer and Diabetes	72
Appendix 3.2 Codes and Algorithms to Identify Diabetes Severity Diabetes Complication Severity Index (DCSI) developed by Young <i>et al.</i> and modified by Chang <i>et al.</i>	73
Appendix 4. 1 Study Cohort Development Chart for Study Population of Elderly Medicare Beneficiaries diagnosed with Prostate Cancer	98
Appendix 4. 2 Sensitivity Analysis: Non-cancer hospitalization definition 2-Number and Percentage with Non-Cancer Related Hospitalizations during the Pre- and Post-Cancer Period Elderly Medicare beneficiaries with Incident Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database-2002-2010.....	99
Appendix 4. 3 Sensitivity Analysis: Non-cancer hospitalization definition 2-Adjusted Odds Ratios and 95% Confidence Intervals (CI) of Cancer Diagnosis Period From GEE models on Non-Cancer Related Hospitalizations Elderly Men with Incident Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database-2000-2010.....	100
Appendix 4. 4 Sensitivity Analysis: Non-cancer hospitalization definition 2-Predicted Probabilities with 95% Confidence Intervals for Types of Chronic Conditions From GEE analysis on Non-Cancer Related Hospitalizations Elderly Medicare Beneficiaries with Incident Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database-2000-2010.....	101

LIST OF ABBREVIATIONS

ADT	Androgen Deprivation Therapy
AHRF	Area Healthcare Resource File
AJCC	American Joint Committee on Cancer
AMPK	Adenosine Monophosphate-activated Protein Kinase
ASCVD	Atherosclerotic Cardiovascular Disease
AUA	American Urology Association
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CM	Cardii-metabolic (conditions)
CMS	Center for Medicare and Medicaid
COPD	Chronic Obstructive Pulmonary Disease
CSME	Cystoid Macular Edema/Degeneration
DCSI	Diabetes Complications Severity Index
DHHS	Department of Health and Human Services
DME	Durable Medical Equipment
FIPS	Federal Information Processing Standard
GEE	Generalized Estimating Equations
HHA	Home Health Agencies
HMO	Health Maintenance Organizations
ICD-9 CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IHD	Ischemic Heart Disease
IOM	Institute of Medicine
IPTW	Inverse Probability Treatment Weights
LE	Lower Extremity
LHRH	Luteinizing Hormone Releasing hormone
MEDPAR	Medicare Provider Analysis and Review
MH	Mental Health (conditions)
mTOR	Mammalian Target of Rapamycin
NCCN	National Cancer Comprehensive Network
NDC	National Drug Codes
NOS	Not Otherwise Specified
OCS	Office of Cancer Survivorship
OR	Odds Ratio
OUTPT	Outpatient
Pca	Prostate Cancer
PCP	Primary Care Physician
PDE	Part D Event
PEDSF	Patient Entitlement and Diagnosis Summary File
PSA	Prostate Specific Antigen
PVD	Peripheral Vascular Disease
QIC	Quasi-likelihood Information Criterion
RESP	Respiratory (conditions)
RP	Radical Prostatectomy
RT	Radiation Therapy
SAS	Statistical Analysis System
SEER	Surveillance Epidemiology End-Results
Sig.	Level of Significance
T2DM	Type 2 Diabetes Mellitus
TIA	Transient Ischemic Attack
TNM	Tumor, Nodes, and Metastasis Staging System
US	United States

Chapter 1

Introduction

1.1 BACKGROUND

Many elderly men (age ≥ 65 years) in the United States (US) have pre-existing chronic conditions when diagnosed with cancer. The presence of pre-existing chronic conditions is associated with poor quality of life and cancer-related outcomes. But limited evidence exists on how particular types of chronic conditions affect the risk of aggressive cancer, cancer treatment and clinical outcomes among elderly men with cancer. The management of some of the pre-existing chronic conditions may have beneficial effects on cancer care. For example, the management of pre-existing diabetes with metformin may not only improve the outcomes of diabetes, but also reduce the risk of cancer incidence or prevent aggressive cancers. Conversely, the diagnosis of cancer can eclipse the management of pre-existing chronic conditions and affect non-cancer outcomes such as hospitalizations not related to the cancer. To date, no population-based study has addressed this issue among elderly men with cancer.

Therefore, the overall goal of the dissertation is to analyze the influence of pre-existing chronic conditions on cancer stage, cancer treatment, cancer-related clinical outcomes, and non-cancer outcomes (example: hospitalizations), and analyze the impact of pharmacological agents (example: metformin) used to manage pre-existing conditions (example: diabetes) on the cancer stage and the treatment for cancer. For the purposes of this dissertation, elderly men with prostate cancer was selected because of it is the leading cancer in men accounting for one fourth of all cancer cases diagnosed in the US.

The dissertation is organized as follows: Chapter 1 briefly describes the epidemiology of prostate cancer in the US, the prevalence of pre-existing chronic conditions among men with prostate cancer, the need for the study, conceptual framework for the study, and data sources for the study. Chapter 2 focuses on the association between the types of chronic conditions and stage of diagnosis, the treatment for prostate cancer and clinical outcomes. Chapter 3 emphasizes on the relationship management of pre-existing condition, specifically type 2 diabetes mellitus (T2DM) on the stage of cancer diagnosis and the treatment for cancer. In this chapter, the management of type 2 diabetes

mellitus (T2DM) with metformin, as the first-line treatment for diabetes on the stage of cancer and the cancer treatment is analyzed. The chapter 4 highlights the relationship between pre-existing chronic conditions and non-cancer hospitalizations. Chapter 5 summarizes the study findings from the chapters 2, 3, and 4, and includes a discussion of the findings, implications and recommendations for future research. The advantages and limitations of the study findings are also included.

1.1.2 Epidemiology of Prostate Cancer in the US

Prostate cancer is a cancer of a gland surrounding the neck of the urinary bladder in men. It is the most common non-cutaneous (non-skin) cancer among men in the US. As of 2015, nearly 2.9 million prostate cancer survivors are alive, and about 222,800 new cases of prostate cancer are expected in 2015. Prostate cancer accounts for 24% of all cancer cases (1). Nearly two thirds of prostate cancer cases are diagnosed among the elderly men aged 65 years and older (2).

1.1.3 Cancer Stage at Diagnosis

Prostate cancer is often diagnosed at an earlier stage. The American Joint Committee on Cancer (AJCC) defines the stage of Prostate cancer by the Tumor, Nodes, and Metastasis (TNM) Staging System. The TNM system classifies a stage based on the spread of tumors to the local area, node, or metastases to other organs. “T” denotes for the extent of tumors in the prostate gland, “N” denotes spread of cancer to lymph nodes and “M” indicates the absence or presence of distant metastasis to bone, lung, liver or brain. Early stage tumors are confined to the prostate gland with no spread of cancer to the seminal vesicles or the lymph nodes or metastases (T1-T2, N0, M0). These types of cancers are also termed as localized or organ-confined cancer. Four in every five incident prostate cases (80%) are diagnosed at the localized stage of prostate cancer.

Locally advanced prostate cancer, i.e. aggressive types of prostate cancer usually spreads to nearby regions of the prostate, including seminal vesicles, pelvic nodes, neck of the bladder or back passage or metastasis in bone or other organs (T3-T4, N1, M1). Less than one in every five incident prostate cancer cases are diagnosed as advanced prostate cancer. Details of the TNM staging for the prostate cancer are provided in Table 1.1 (3).

1.1.4 Prostate Cancer Treatment

Treatment options for prostate cancer vary depending on age, cancer stage, and the presence of serious chronic conditions. Traditional treatment modalities for prostate cancer include surgery to remove the tumors (radical prostatectomy - RP), radiation therapy (RT), and hormone therapy. The use of aggressive therapies such as RP or RT can lead to adverse clinical outcomes such as the bowel, sexual, urinary dysfunction. Further, due to a prolonged survival and early stage diagnosis of prostate cancer, men with prostate cancer can survive up to 10 years without even any aggressive treatment. Therefore, the treatment guideline recommends no use of aggressive treatment among those with limited survival benefits to avoid risk of adverse effects of treatment (4).

1.1.5 Prognosis of Prostate Cancer

With an estimated 27,540 deaths in 2015, prostate cancer is the second-leading cause of cancer death in men. However, in the last decade, the mortality rates among men with prostate cancer have declined. (1). In fact, men diagnosed with prostate cancer have a good survival profile with 10-year relative survival rates (compared to non-cancer cases) range: 90-100%, even without aggressive treatments (RP/RT) if diagnosed as localized prostate cancer. However, men with advanced prostate cancer have a very poor survival profile with 5-year survival rate of only 23% (1). Therefore, there are needs to develop the strategy to reduce the risk of advanced prostate cancer.

1.1.6 Chronic Conditions in Prostate Cancer

Nearly one-third (30.5%) of elderly men with prostate cancer had at least one pre-existing chronic conditions. Among those with pre-existing chronic conditions 30% had 2 or more chronic conditions (5). Among elderly men with prostate cancer, the commonly prevalent chronic condition was diabetes (13.1%). Other highly prevalent conditions were: chronic obstructive pulmonary disease (COPD) (9.8%), depression (8.0%), congestive heart failure (5.7%), and coronary artery disease (2.9%).

An overwhelming majority of elderly men (84%) died due to causes other than cancer; in the US, between 1973 and 2008, chronic conditions were the leading causes of death in men with prostate

cancer (6). Therefore, an understanding the role of particular types of chronic conditions in prostate cancer can provide insight to better manage the chronic conditions as well as prostate cancer.

1.1.7 Chronic Conditions and Cancer Stage at Diagnosis, Initial Cancer Treatment and Outcomes

A large body of evidence suggests that men with a greater number of chronic conditions are associated with poor clinical outcomes-bowel, sexual and urinary dysfunction as compared to those with lower numbers of chronic conditions. With regards to cancer stage at diagnosis, the conflicting evidence exist on the presence of chronic conditions and diagnosis of advanced prostate cancer. In terms of the cancer treatment, guidelines recommend no aggressive prostate cancer treatment with RP or RT for individuals with multiple chronic conditions (4, 7). However, in the real-world practice settings, mixed evidence exists on receipt of cancer treatment among individuals with chronic conditions and prostate cancer (8-10).

Although elderly men with prostate cancer suffer from different types of chronic conditions, the association between the types of chronic conditions on the cancer stage at diagnosis, initial cancer treatment and clinical outcomes have not been studied. Most of the previous studies focused on the healthcare outcomes as a function of a co-morbidity index, such as Charlson Comorbidity Index (CCI), a numerator for describing weighted/un-weighted number of diseases with little consideration of how specific combinations of conditions affected outcomes among the individuals with prostate cancer. Different types of co-occurring chronic conditions may have a differential impact on cancer stage at the diagnosis, initial cancer treatment and clinical outcomes among men with prostate cancer. Understanding the differential impact is important to develop strategies, which can minimize the negative impact of the chronic conditions on prostate cancer care.

1.1.8 Case of Metformin: Risk of Advanced Stage of Cancer and Cancer Treatment in Prostate Cancer and Diabetes

As stated before, diabetes is highly prevalent among men with prostate cancer (5). Metformin is the first-line of treatment for diabetes with proven safety and efficacy in reducing the risk of cardiovascular disease and improving the blood sugar levels. Recently, due to anti-cancer properties

of metformin, a significant level of experimental evidence suggests the metformin could be associated with reduced risk of advanced stage of cancer at diagnosis (11) (12-14) (22) (12). In addition, it is also found to be beneficial alone with primary cancer therapy such as RT in reducing the all-cause mortality and cancer-related mortality. Therefore, the use of metformin could influence the initial cancer treatment decision. However, at present, none of the studies have examined the role of metformin on the risk of advanced prostate cancer and influence the initial cancer treatment among elderly men with prostate cancer.

1.1.9 Impact of Prostate Cancer Diagnosis on Non-cancer Hospitalizations

As stated above, nearly one third of elderly men with prostate cancer have pre-existing chronic conditions. A diagnosis of incident of prostate cancer may generate the psychological stress and if serious enough could lead to cardiovascular events. The diagnosis of cancer can take the attention away from the management of chronic conditions and all attention may be directed towards cancer care. This may lead to worsening of the pre-existing chronic conditions and can increase the risk of non-cancer hospitalizations. However, none of the studies assessed the impact of diagnosis of prostate cancer on non-cancer hospitalizations among elderly men with incident prostate cancer. An analysis of the extent to which cancer diagnosis affects non-cancer hospitalizations and whether the impact of cancer on non-cancer hospitalizations varies by chronic conditions will inform the payors, program planners and policy-makers and encourage investments in better management of chronic conditions.

1.2 RATIONALE FOR CLASSIFYING TYPES OF CHRONIC CONDITIONS

As stated above, men with prostate cancer suffer from multiple conditions. However, operationalizing the measurement of the types of chronic conditions is challenging. For example, if one tries to study chronic conditions and their combinations using only the sixteen chronic conditions captured by the CCI, one can expect 120 two-disease combinations, 560 three-disease combinations, 1,820 four-disease combinations with more than 20 trillion combinations of chronic conditions overall. If one selects chronic conditions based on 30 chronic conditions of Elixhauser index (15), or 53 chronic conditions in elderly men based on Piette *et al.* framework of chronic conditions

management (16), one will have even more combinations. While it is possible to use the number of chronic conditions such analyses may not provide any actionable intelligence.

Therefore, in this dissertation, an attempt is made to define clinically meaningful combinations of chronic conditions based on a conceptual framework from the Department of Health and Human Services (DHSS) on research, policy, program, and practice (17). Based on this framework, the following chronic conditions were selected: diabetes, coronary artery disease, cardiac arrhythmia, COPD, asthma, depression, schizophrenia, generalized anxiety disorders, bipolar disorders, and psychosis.

These conditions were grouped based on specific organ domains (22) and synergism in treatment patterns and self-management approaches. For example, management of cardio-metabolic conditions such as diabetes and heart disease have similar treatment patterns and self-management approaches. Thus, the chronic conditions were grouped into three major domains: cardio-metabolic diseases (diabetes, and heart disease), respiratory disease (COPD and asthma), and mental health conditions (depression, bipolar disorders, schizophrenia, psychoses, and anxiety). We classified these domains into eight mutually exclusive categories of chronic conditions: (1) cardio-metabolic conditions only; (2) mental health conditions only; (3) respiratory conditions only; (4) cardio-metabolic and mental health conditions, (5) cardio-metabolic and respiratory conditions, (6) respiratory and mental health conditions, (7) all the three conditions, and 8) none of the three types of chronic conditions. However, one should note that such grouping of chronic conditions reflect the presence or absences of multi-organ system conditions, therefore, the types of chronic conditions no longer represent the number of chronic conditions. For example, elderly men grouped in the only cardio-metabolic conditions group may have three chronic conditions-diabetes, coronary artery disease and congestive heart failure, whereas, elderly men with all three types of conditions may also have three chronic conditions such as diabetes, COPD and depression.

1.3 SPECIFIC AIMS

The specific aims of the dissertation are as below:

Specific Aim 1: To examine the associations between the types of pre-existing chronic conditions and cancer stage at diagnosis, initial cancer treatment and clinical outcomes after initial cancer treatment among fee-for-service Medicare beneficiaries with incident prostate cancer.

Objective 1.1: To examine the association between the types of chronic conditions and cancer stage at diagnosis among fee-for-service Medicare beneficiaries with incident prostate cancer.

Hypothesis: Elderly Medicare beneficiaries with only cardio-metabolic, only mental health and only respiratory conditions will be more likely to be diagnosed with advanced prostate cancer as compared to those with all three-cardio-metabolic, mental health, and respiratory conditions.

Objective 1.2: To analyze the association between the types of chronic conditions and cancer treatment (RP, RT, Hormone therapy and No treatment) among fee-for-service Medicare beneficiaries with incident prostate cancer.

Hypothesis: Elderly Medicare beneficiaries with only cardio-metabolic, only mental health and only respiratory conditions will be more likely to receive aggressive treatment (RP/RT) as compared to those with all the three types of chronic conditions.

Objective 1.3: To determine the association between the types of chronic conditions and clinical outcomes (bowel, sexual, urinary dysfunctions) after initial cancer treatment among fee-for-service Medicare beneficiaries with incident prostate cancer.

Hypothesis: Elderly Medicare beneficiaries with only cardio-metabolic, only mental health and only respiratory conditions will be less likely to have bowel, sexual and urinary dysfunctions as compared to elderly men with all the three cardio-metabolic, mental health and respiratory conditions.

Note: In all the analyses that compared across the types of chronic conditions, the reference group was those with all the three types of chronic conditions because the presence of multi-organ system chronic conditions were considered as more serious clinical conditions and expected to be associated with localized stage at diagnosis, no cancer treatment and poor clinical outcomes as compared to other chronic conditions groups.

Specific Aim 2: To examine the relationship between metformin use and cancer stage at diagnosis, and the initial cancer-treatment among elderly (age ≥ 66 years) fee-for-service Medicare beneficiaries with pre-existing diabetes and incident prostate cancer.

Objective 2.1: To investigate the association between metformin use and cancer stage at diagnosis among elderly fee-for-service Medicare beneficiaries with diabetes and incident prostate cancer.

Hypothesis: Among elderly men with diabetes and incident prostate cancer, metformin users will be less likely to be diagnosed with advanced prostate cancer as compared to non-users.

Objective 2.2: To analyze the association between metformin use and initial cancer treatment among elderly fee-for-service Medicare beneficiaries with diabetes and incident prostate cancer.

Hypothesis: Among elderly men with diabetes and prostate cancer, metformin users will be more likely to receive radiation therapy as compared to non-users; metformin users will be more likely to receive hormone therapy as compared to non-users.

Specific Aim 3: To analyze the impact of cancer diagnosis on the risk of non-cancer hospitalizations and evaluate whether the impact of cancer diagnosis on the risk of non-cancer hospitalizations vary by the types of pre-existing chronic conditions among fee-for-service Medicare beneficiaries with incident prostate cancer.

Objective 3.1: To analyze the association between cancer diagnosis and the risk of non-cancer hospitalizations by comparing the rates of hospitalizations between the pre- and post-cancer periods among elderly men with incident prostate cancer.

Hypothesis: The unadjusted rates and the adjusted risk of non-cancer hospitalizations will be higher during the post-cancer period as compared to the pre-cancer period.

Objective 3.2: To determine the varying associations between the cancer diagnosis and the risk of non-cancer hospitalizations by the types of chronic conditions among elderly fee-for-service Medicare beneficiaries with incident prostate cancer.

Hypothesis: Elderly Medicare beneficiaries with pre-existing cardio-metabolic conditions will have the greatest increase in the risk of non-cancer hospitalizations (from pre-cancer to post-cancer period) as compared to those with other types of chronic conditions.

1.4 DATA SOURCES

The cancer registry data from the Surveillance, Epidemiology and End Results (SEER) program linked with the Medicare administrative claims data were utilized for all the specific aims. These data were augmented with the county-level information contained in the Area Health Resource Files (AHRF).

1.4.1 Surveillance Epidemiology and End-Results Registry

The SEER registries are one of the few resources of population-based cancer data in the US. Since 1973, SEER registries have been collecting precise and accurate information on cancer stage, treatment, diagnostic procedures, and clinical variables on all newly diagnosed cancer by specific regions under the auspices of the National cancer Institute. The SEER data is released with a lag period of three years. At present, the released SEER data contain a total of 7,397,159 malignant cases of cancers and majorities of these cancer cases are diagnosed among the elderly population aged 65 years and over. The SEER data represent 28% of the US population from 18 registries or regions of SEER (18).

The Patient Entitlement and Diagnosis Summary File (PEDSF) file is a customized file from the SEER program. It has information on the cancer diagnosis for up to ten cancers, types of cancers, their stages, demographic attributes, marital status, and tumor characteristics at the time of each cancer diagnosis.

1.4.2 Medicare

The Medicare is the US Government mandated insurance program covering 97% of the US population aged 65 years and older (19). The NCI links the cases of SEER with Medicare cases using an algorithm based on the social security number, last name, first name and birth date of an individual. A total of 93% percent of men aged 65 years and older in SEER has been linked to Medicare enrollment records (20). More than 95% of the Medicare beneficiaries receive Part A and B coverage benefits. Medicare Part A benefits cover the use of inpatient care in hospitals or skilled nursing facilities, home health care, and hospice care, whereas Part B benefits cover the use of physician services and outpatient care. However, the Medicare part of data does not capture all the claims for the beneficiaries enrolled under the Health Maintenance Organizations (HMOs) as these organizations do not have a mandatory requirement to submit all their services claims to Center for Medicare and Medicaid (CMS). Therefore, managed care enrollees during the study period were excluded from the study.

SEER-Medicare Linked Data

A common encrypted identification number is provided for each enrollee so that the PEDSF file can be lined with the Medicare files. Medicare data consisted of Medicare Provider Analysis and Review (MEDPAR) files, the Carrier Claims (old name Physician/Supplier (NCH)), Outpatient (OUTPT), Home Health Agencies (HHA), Hospice, Durable Medical Equipment (DME) and Part D Event (PDE). The MEDPAR file includes Medicare Part A claims records from any short term or long term hospital or skilled nursing facility stay from each calendar year, while the outpatient file has Part B claims for outpatient visits. Each record represents an episode of hospital stay, and has up to 10 diagnoses according to the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*, and 10 *ICD-9-CM* procedures during each stay, date of admission, the date of discharge. The carrier file represents billing records from physicians and non-institutional providers and has procedure codes according to the *Healthcare Common Procedure Coding System (HCPCS)* and the *Common Procedural Terminology, 4th Edition (CPT-4)*, and *ICD-9-CM procedure*

codes with service dates (19). In the current study, we utilized data from the PEDSF file linked with MEDPAR, OUTPT, and NCH files for the years 2000 to 2010.

1.4.3 Medicare Part-D Data

Medicare introduced optional/volunteer Part D plans in 2006 that cover prescription drugs benefit through enrollment in a Medicare Advantage Prescription drug Plan (MA-PD) or a stand-alone drug plan (PDP). The plan typically starts with an annual deductible, after which Medicare pays for the prescription drugs up to an initial coverage limit with certain coinsurance associated with those payments. Medicare Part D plans stop payments once individuals reach the annual coverage limit until the cost of prescription drugs reaches to catastrophic limit. The phase between the annual coverage limit and catastrophic coverage is called "donut hole" or "Medication coverage gap" where enrollees have to pay the entire prescription drug costs out-of-pocket (21). Almost half of the Medicare Part A and B enrollee were also enrolled in Part D plans (22). We utilized the data of the Medicare Part D file (PDE) file in addition to PEDSF, MEDPAR, OUTPT and NCH for the years 2007 to 2010. We examined prostate cancer cases diagnosed between 2008 and 2009 so that we could study their medication status in a year prior to diagnosis of cancer.

1.4.4 Area Health Resources Files

The Area Health Resources Files (AHRF) is a nationwide county-level health resource files in the US. The file provides information for about 6,000 county-level variables including healthcare facilities, health professionals, resource scarcity, health status, economic activity, health training programs and socioeconomic characteristics (23). County-level healthcare resources were derived from the Area Health Resource files (AHRF). These included the number of radiation -oncology units, and urology units. The SEER-Medicare files were linked with AHRF using a five-digit Federal Information Processing Standard (FIPS) code at the state and county level (23).

1.5 CONCEPTUAL FRAMEWORK

The framework of the expanded Behavioral Model of Health Services Use, widely known as the Andersen Healthcare Utilization and Behavioral Model (ABM) was used to select the independent

variables for all our specific aims (24). The ABM model and adapted versions of this model have been extensively used in the health services research to study the factors associated with the healthcare service use and healthcare outcomes.

The ABM model states that the use of healthcare services is determined by individual and contextual determinants. These determinants can be categorized into four groups: 1) *Predisposing factors*: These factors represent the unique feature of individuals that tend to represent more or less use the healthcare services. In the current study, we included age, sex, race/ethnicity, marital status of the individuals as predisposing factors. 2) *Enabling factors*: These factors serve as conditions that enable individuals to use healthcare services. Based on the model, we considered income, education as well as cancer treatment, and medications as potential enabling factors for the healthcare service. 3) *Need factors*: These are the factors requiring the need to use healthcare services at the individual level. Based on the definition, we included the presence of chronic conditions and stage of prostate cancer as need factors. 4) *External environment*: These are the set of factors facilitating the use of healthcare services related to the structure of services in the geographical areas near to the individuals. The presence of healthcare providers in nearby regions such as number of radiation oncologists and urologists in the county of residence of the individuals was included as external environment characteristics. Details on the each type of independent variables for each study aims are provided in ***Table 1.2.***

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**Table 1. 1 American Joint Committee on Cancer (AJCC)
Clinical TNM Classification of Prostatic Tumors**

Primary tumor (T) – clinical

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor neither palpable nor visible by imaging
T1a	Tumor incidental histological finding in $\leq 5\%$ of tissue resected
T1b	Tumor incidental histological finding in $> 5\%$ of tissue resected
T1c	Tumor identified by needle biopsy (e.g. because of elevated PSA)
T2	Tumor confined within prostate
T2a	Tumor involves \leq one-half of one lobe
T2b	Tumor involves $>$ one-half of one lobe but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through the prostate capsule
T3a	Extrascapular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Regional lymph nodes (N)

NX	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastases in regional lymph node(s)

Distant metastasis (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

Table 1. 2 Details of Variables for Each Study Objectives-classified based on ABM

Objective	Dependent Variable (s)	Predisposing	Enabling	Need	External Environment
1.1	Cancer Stage	Age, Race/ethnicity, Marital status	Income, Education, Cancer screening, Primary care visit	Number of other chronic conditions	Region, Urology Units, Oncology units
1.2	Initial Cancer Treatment	Age, Race/ethnicity, Marital status	Income, Education, Primary care visit	Number of other chronic conditions, Cancer Stage	Region, Urology Units, Oncology units
1.3	Clinical Outcomes – Bowl Dysfunction Sexual Dysfunction Urinary Dysfunction	Age, Race/ethnicity, Marital status	Income, Education, Cancer-treatment, Primary care visit	Number of other chronic conditions, Cancer Stage	Region, Urology Units, Oncology units
2.1	Non-cancer Hospitalizations	Age, Race/ethnicity, Marital status	Income, Education, Cancer treatment, Primary care visit	Number of other chronic conditions, Cancer Stage	Region, Urology Units, Oncology units
2.2	Non-cancer Hospitalization	Age, Race/ethnicity, Marital status	Income, Education, Cancer treatment, Primary care visit	Number of other chronic conditions, Cancer Stage	Region, Urology Units, Oncology units
3.1	Advanced Prostate Cancer	Age, Race/ethnicity, Marital status	Income, Education, Cancer Screening, Primary care visit	Number of other chronic conditions, Cancer Stage	Region, Urology Units, Oncology units
3.2	Initial Cancer Treatment	Age, Race/ethnicity, Marital status	Income, Education, Cancer-treatment, Primary care visit	Number of other chronic conditions, Cancer Stage	Region, Urology Units, Oncology units

Note: Income and Education were 2000 census-track level data provided in SEER-PEDSF file. Number of Urology and Radiation-Oncology units are county-level variables derived from Areas Healthcare Resource file (AHRF). The quartiles of these variables were created for data analysis purpose.

Chapter 2

Types of Chronic Conditions and Cancer Stage at Diagnosis, Initial Cancer Treatment and Clinical Outcomes among Elderly Medicare Beneficiaries with Prostate Cancer

2.1 ABSTRACT

OBJECTIVE: To examine the associations between types of chronic conditions and cancer stage at diagnosis, initial cancer treatment and clinical outcomes among elderly Medicare Beneficiaries with prostate cancer.

METHODS: A population-based observational cohort study was conducted using the Surveillance, Epidemiology and End-Results (SEER)-Medicare linked database. The study population consisted of elderly men (≥ 66 years) with prostate cancer diagnosed between 2002 and 2009 ($N = 103,820$). Cancer stage at diagnosis (localized versus advanced) was derived using the American Joint Committee on Cancer (AJCC)-Tumor Node Metastasis (TNM) system. The initial cancer treatment was identified during the six months after cancer diagnosis and was categorized in a hierarchical order and consisted of: 1) Radical Prostatectomy (RP); 2) Radiation Therapy (RT); 3) Hormone therapy; and 4) No treatment. Clinical outcomes (bowel dysfunction (yes/no), sexual dysfunction (yes/no) and urinary dysfunction (yes/no)) were measured during one year after the initial cancer treatment.

Chronic conditions were identified during one year before the date of cancer diagnosis and classified as the presence or absence of 1) cardio-metabolic conditions; 2) mental health conditions; and 3) respiratory conditions. These three types of conditions were further classified into the following eight mutually exclusive categories: (1) cardio-metabolic conditions only; (2) mental health conditions only; (3) respiratory conditions only; (4) cardio-metabolic and mental health conditions; (5) cardio-metabolic and respiratory conditions; (6) mental health and respiratory conditions; (7) all three- cardio-metabolic, mental health and respiratory conditions; and 8) none of the three types of conditions. The independent variables were selected based on the Anderson Healthcare Behavior Model (ABM) and consisted of predisposing (age, race/ethnicity, marital status), enabling (income, education, access to care, cancer screening), need (number of other chronic conditions), and external-environment (regions, number of radiation-oncology and urology units in a county of residence) factors.

Significant differences in cancer stage at diagnosis, initial cancer treatment, and clinical outcomes by types of chronic conditions were examined with chi-square tests. Multivariable logistic regressions were used to test the adjusted associations between types of chronic conditions and cancer stage at diagnosis, and clinical outcomes. Multinomial logistic regression was used to test the adjusted associations between types of chronic conditions and receipt of initial cancer treatment.

RESULTS: In our study cohort, 46.2% did not have any cardio-metabolic, mental health, and respiratory conditions; 35.4% had only cardio-metabolic conditions; 8% had both cardio-metabolic and respiratory conditions; 5.2% had only respiratory conditions; 2.1% had both cardio-metabolic and mental health conditions; 1.9% had only mental health conditions; and 0.4% had both mental health and respiratory conditions.

Cancer Stage at Diagnosis: 94.6% of the men were diagnosed with localized prostate cancer and 5.4% were diagnosed with advanced prostate cancer. There was a significant association between types of chronic conditions and cancer stage at diagnosis. The highest percentage (5.8%) of advanced prostate cancer diagnosis was observed among elderly men with none of the three types of chronic conditions. After controlling for predisposing, enabling, need and external environment factors, elderly men with none of the three types of chronic conditions were 44% more likely to be diagnosed with advanced prostate cancer as compared to men with all the three types of chronic conditions (Adjusted Odds Ratio (AOR) = 1.44; 95% Confidence Interval (CI): 1.03, 2.00).

Initial Cancer Treatment: In our study cohort, 19.7% did not receive any cancer treatment; 46.9% received RT; 22% received RP; and 11.4% received hormone therapy. The highest percentage of no prostate cancer treatment (24.4%) was observed among men with all the three types of chronic conditions and lowest percentage of no prostate cancer treatment was observed among men with only respiratory conditions (18.3%). In multinomial logistic regression analysis, elderly men with none of the three types of chronic conditions (AOR = 1.32; 95% CI: 1.07, 1.61) or only one type of chronic physical condition - only cardio-metabolic conditions (AOR = 1.25; 95% CI: 1.02, 1.53) or only respiratory conditions (AOR = 1.36; 95% CI: 1.09, 1.69) were more likely to receive RP as compared to those with all the three types of chronic conditions. These groups were also more likely to receive

RT. Additionally, elderly men with cardio-metabolic and mental health conditions or respiratory conditions were more likely to receive RT. Those with only mental health conditions were as likely as those with all the three types of chronic conditions to receive initial cancer treatment. There were no statistically significant relationships between types of chronic conditions and receipt of only hormone therapy among elderly men with prostate cancer.

Clinical Outcomes: Overall, 14.5% elderly men had bowel dysfunction; 16.1% had sexual dysfunction; and 35.0% had urinary dysfunction. In multivariable logistic regression, elderly men with none of the three types of conditions (AOR = 1.33; 95% CI: 1.09, 1.63) or only respiratory (AOR = 1.26; 95% CI: 1.02, 1.56) or only mental health conditions (AOR = 1.32; 95% CI: 1.05, 1.67) were more likely to have sexual dysfunction as compared to those with all the three types of chronic conditions. There were no consistent patterns with regard to types of chronic conditions and clinical outcomes.

CONCLUSIONS: Elderly men with none of the three types of chronic conditions were more likely to be diagnosed with advanced prostate cancer. All chronic condition categories (except for only mental health conditions and both mental health and respiratory conditions) were associated with an increased likelihood of the initial cancer treatment with either RP or RT as compared to all the three types of chronic conditions. Varying associations between types of chronic conditions and clinical outcomes were found.

IMPLICATIONS: Among elderly men *without* cardio-metabolic, respiratory and mental health conditions, strategies to reduce the risk of advanced prostate cancer are needed. Although there is no evidence that RP or RT can be beneficial in long-term for elderly men with prostate cancer and pre-existing chronic conditions, an overwhelming majority of men with chronic conditions received prostate cancer treatment. Men with prostate cancer and some types of chronic conditions may need heightened surveillance, monitoring and therapies to reduce the risk of sexual dysfunction after the initial cancer treatment.

2.2 INTRODUCTION

Chronic conditions are highly prevalent among elderly men diagnosed with prostate cancer in the United States (US). Nearly one-third (31%) of elderly men with incident prostate cancer have at least one pre-existing chronic condition out of sixteen chronic conditions included in the Charlson Comorbidity Index (CCI) (1). The presence of pre-existing chronic conditions can affect the cancer stage at diagnosis (2-7), receipt of the initial cancer treatment (8-12) and clinical outcomes such as bowel, sexual, and urinary dysfunctions (13-15) among elderly men with prostate cancer. With regards to types of chronic conditions, cardio-metabolic conditions (diabetes and cardiovascular diseases) are the most common pre-existing chronic conditions (18.1%), followed by respiratory conditions (example - chronic obstructive pulmonary disease (COPD) (9.8%), (1) and mental health conditions (example - depression) (9%) among elderly men with prostate cancer (16). Therefore, the presence of such different types of chronic conditions can differently influence the development of cancer, cancer treatment and outcomes among elderly men with prostate cancer.

2.2.1 Pre-existing Chronic Conditions and Cancer Stage at Diagnosis

More than two-third cases of prostate cancer are diagnosed at localized stages (\leq T2 stage), in which tumors are confined to the prostate gland, whereas less than one third of cases of prostate cancer are diagnosed at advanced stages where tumors have spread to nearby tissue, bone or organs. The diagnosis of prostate cancer at localized stage is desirable as compared to diagnosis of advanced stage due to an excellent survival profile with localized stage even without active cancer treatment. The presence of chronic conditions can affect the cancer stage at diagnosis for many reasons. There are conflicting theories on the relationship between the presence of chronic conditions and risk of advanced prostate cancer at diagnosis. One of these theories hypothesizes that individuals with chronic conditions may be less likely to be diagnosed at an advanced prostate cancer because of increased contact with the healthcare system for care of their chronic conditions (17). Conversely, the theory on competing demand postulates that the care of chronic conditions may take the attention away from early symptoms of cancer and that individuals with chronic conditions may be more likely to be diagnosed with an advanced prostate cancer. The role of competing demands for care of

chronic conditions on advanced prostate cancer at diagnosis has been documented. For example, men with prostate cancer and pre-existing congestive heart failure were more likely to be diagnosed with advanced prostate cancer as compared to those without congestive heart failure (2).

Further, the association between pre-existing chronic conditions and cancer stage at diagnosis may differ by types of chronic conditions, due to the differential patho-physiological pathways of underlying diseases and prostate cancer. For example, the presence of cardiovascular disease may increase the risk of prostate cancer as it shares common risk factors for the development of aggressive prostate cancer, such as the presence of high cholesterol level and obesity (18, 19). Few studies have investigated the relationship between specific types of chronic conditions and the cancer stage at diagnosis. Findings from these studies suggest that the association between pre-existing chronic conditions and cancer stage at diagnosis depends on the types of chronic conditions. For example, three studies in the US using the population-level data found that the presence of diabetes was associated with an increase in the risk of advanced stage or grade of prostate cancer at diagnosis (20-22). With respect to the mental health conditions, a retrospective study found that elderly men with depression were not more likely to be diagnosed with higher grade of prostate cancer as compared to those without depression (9). While these studies have highlighted the relationship between specific chronic conditions and cancer stage at diagnosis, many of these studies are outdated, single-institutional database studies and suffer from the risk of detection bias because screening for prostate cancer was not included as one of the independent variables (4-6). Furthermore, none of these studies examined the association between types of chronic conditions combinations and cancer stage at diagnosis among elderly men. Understanding the association between types of chronic conditions and cancer stage at diagnosis is critical for patient-centered care and individualized treatment (23).

2.2.2 Pre-existing Chronic Conditions and Prostate Cancer Treatment

As elderly men with prostate cancer are at greater risk for mortality due to non-cancer conditions as compared to risk for mortality due to cancer, the practitioners determine the course of cancer treatment after taking into account the presence of pre-existing chronic conditions in addition to the cancer stage at diagnosis and life-expectancy. The clinical practice guidelines of the American

Urology Association (AUA) (24) and the National Cancer Comprehensive Network (NCCN) (25) recommend against the use of aggressive treatment such as RP or RT among men who have serious chronic conditions.

2.2.3 Number or Weighted Score of Chronic Conditions

Some studies have investigated the association between chronic conditions and the use of aggressive cancer treatment such as RP or RT among elderly men with prostate cancer. Using the Charlson Comorbidity Index (CCI) score to summarize the impact of chronic conditions, prior studies have found varying associations between the presence of chronic conditions and receipt of a particular prostate cancer treatment. Two retrospective studies reported that men with prostate cancer and greater CCI scores were less likely to receive RP/RT as compared to those with lower CCI scores (10, 26). Conversely, two studies reported that men with prostate cancer having greater CCI scores were more likely to receive RP/RT as compared to those with lower CCI scores (11) (12). Finding from these studies suggests that weighted summary scores such as CCI may not be useful in determining the course of prostate cancer treatment. Therefore, it is important to analyze the relationship between specific types of chronic conditions and receipt of a particular cancer treatment among men with prostate cancer.

2.2.4 Presence of a Specific Chronic Condition

Two previous studies have examined the association between specific chronic conditions and prostate cancer treatment. Hall *et al.* found that men with congestive heart failure were less likely to receive surgical therapy as compared to those without congestive heart failure (27). Using the SEER-Medicare linked data, Prasad *et al.* reported that men with depression were less likely to receive aggressive therapy such as RP or RT as compared to those without depression (6). While these studies suggest the presence of single chronic condition such as congestive heart failure or depression would have negative impact on the receipt of RP/RT among men with prostate cancer, these studies did not account for the presence of other co-existing chronic conditions. However, in the real-world practice settings, elderly men have multiple chronic conditions which may determine the course of cancer treatment. To the best of our knowledge, studies analyzing the associations between types of

chronic conditions and their combinations and receipt of initial treatment for prostate cancer are non-existent.

2.2.5 Preexisting Chronic Conditions and Clinical outcomes

2.2.5.1 Number or Weighted Score of Chronic Conditions:

Among elderly men with prostate cancer, pre-existing chronic conditions can affect clinical outcomes such as bowel, urinary and sexual dysfunctions. A handful of real-world observational studies have examined the relationship between CCI and the risk of urinary, bowel and sexual dysfunctions following the initial cancer treatment among elderly men with prostate cancer. These studies reported that elderly men with higher CCI scores were more likely to have bowel, and urinary dysfunctions (13-15, 28) as compared to those with lower CCI scores. Using the SEER-Medicare linked data, one study found that CCI scores were not associated with sexual dysfunction (29). Again, the weighted summary scores such as CCI may not be useful in determining strategies for reducing the risk of these dysfunctions after the initial cancer treatment. Therefore, it is important to analyze the relationship between specific types of chronic conditions and clinical outcomes.

2.2.5.2 Presence of a Specific Chronic Condition

A single-institutional study by Hamstra *et al.* analyzed relationship between the presence of myocardial infarction and the risk of bowel dysfunction among men with prostate cancer. The authors found that men with myocardial infarction were more likely to have bowel dysfunction during the three years after the initial cancer treatment as compared to those without myocardial infarction (13). To the best of our knowledge, none of the population-based studies examined the association between types of chronic conditions and the clinical outcomes such as bowel, urinary and sexual dysfunction among elderly men with prostate cancer.

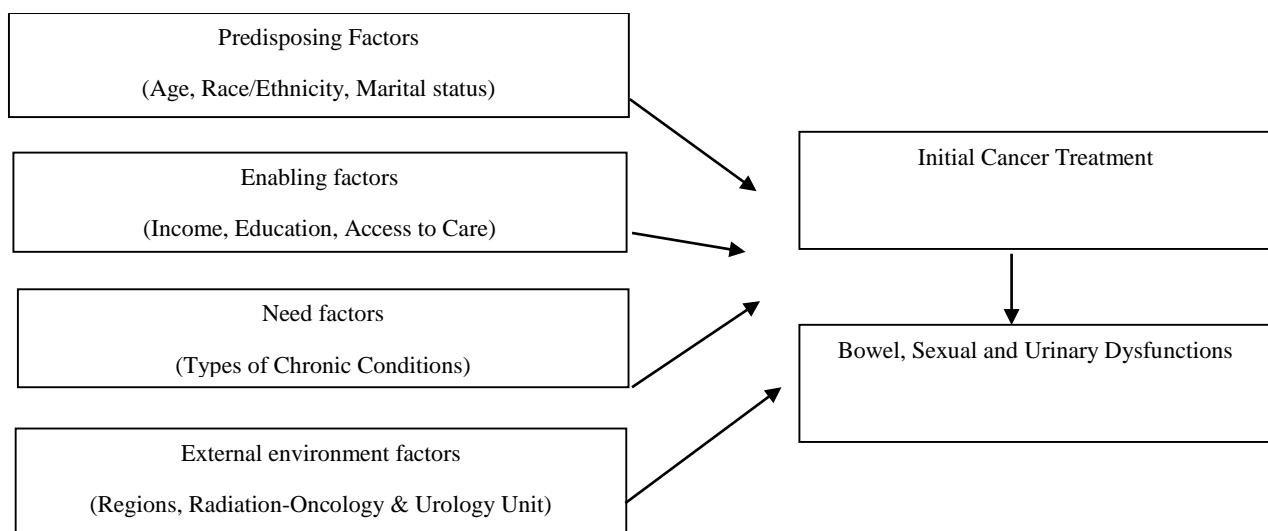
Based on the literature review till date, it can be concluded that knowledge gaps exist in how specific combinations of conditions affect the cancer stage at diagnosis, the initial cancer treatment and the clinical outcomes among elderly men with incident prostate cancer. Examining the associations between combinations of chronic conditions and cancer stage at diagnosis, initial cancer

treatment and clinical outcomes are important because such analyses can inform the practitioners on the management of cancer care in the presence of chronic conditions. Therefore, the primary objectives of the current study are to examine the associations between the types of pre-existing chronic conditions and cancer stage at diagnosis, initial cancer treatment, and clinical outcomes after the initial cancer treatment among fee-for-service Medicare beneficiaries with incident prostate cancer.

2.3 CONCEPTUAL FRAMEWORK

To accomplish the objectives, the current study adapted the Andersen Behavioral Model, which is described in chapter 1. The selected predisposing, enabling, need and external environment-related factors for the current study are depicted in *Figure 2.1*.

Figure 2.1 Study Theoretical Framework: Adaptation of Andersen Behavioral Model for Aim 1



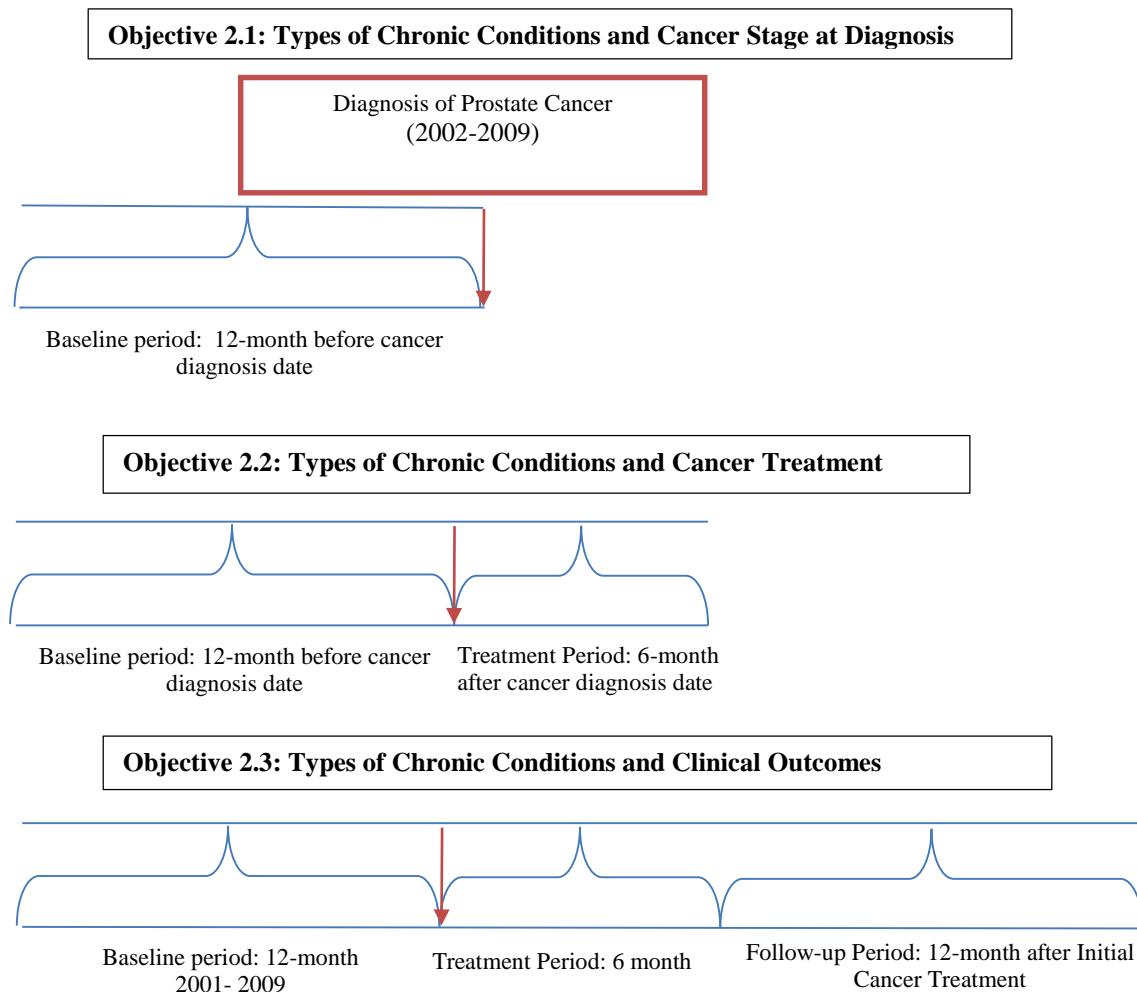
2.4 METHOD

2.4.1 Study Design

This study adopted a retrospective cohort design with a baseline and follow-up period. The date of diagnosis of prostate cancer was considered as the index date. The baseline period was defined as one year before the index date. All independent variables were identified during the baseline period. For objective 1.2, the follow-up period consisted of 6 months after prostate cancer diagnosis. Initial prostate cancer treatment was measured during this period. For objective 1.3, the clinical

outcomes were identified during a 12 months after the end of initial prostate cancer treatment (i.e. end of 6-months) as depicted in the **Figure 2.2**.

Figure 2.2 Schematic diagram of study design for Aim 1



2.4.2 Data Sources

The current study utilized the SEER-Medicare linked database. The SEER part of the data comprised of cancer cases diagnosed with prostate cancer between January 1st 2002 and December 31st 2009 and linked with Medicare claims of those individuals for the years January 1st 2000 and December 31st 2010. The detailed description of the data sources are provided in Chapter 1.

2.4.3 Study Cohort

The study cohort was based on 358,439 men with an incident diagnosis of prostate cancer. Elderly men with multiple cancers (N = 65,794), diagnosed with prostate cancer at the time of autopsy or on the death certificate (N = 2,944), younger than 66 years of age (N=97, 159), died during the observation period (N =41, 205), did not have continuous fee-for-service enrollment in Medicare Part A and B during the observation period (N = 70,559), and missing information on cancer stage at diagnosis, race, income, education or county of residence (N = 5,390) were excluded. Thus, the final cohort consisted of 103,820 elderly men with incident prostate cancer. **Appendix 2.1** depicts the analytical population selection process.

2.4.4 Key Dependent Variables

2.4.4.1 Prostate Cancer Stage at Diagnosis (Localized and Advanced Stage)

We utilized the American Joint Committee on Cancer (AJCC) Tumor-Node-Metastases (TNM) classifications for staging of prostate cancer. Based on the TNM systems, we classified cases with into two categories: localized and advanced prostate cancer at diagnosis. Localized prostate cancer was classified as the cancer with T1 to T2 clinical stage with no regional lymph node (NX-N0) or distant metastasis (M0) (24). Advanced prostate cancer was classified as the cancer with T3 or T4 clinical stage with or without regional lymph node (N1) or distant metastasis (M1).

2.4.4.2 Initial Cancer Treatment

The receipt of initial prostate cancer treatment as either receipt of radiation or surgical therapy or hormonal therapy was identified using inpatient, outpatient and carrier files with appropriate ICD-9 CM diagnostic and procedure codes, CPT or HCPCS codes or Revenue Center code during the six months after the index date (30, 31),(32). **Appendix 2.2** comprises the details of the codes used to identify the initial cancer treatment in the current study.

We classified elderly men with the initial cancer treatment receipt into four hierarchical groups: 1) those who received RP alone or along with any RT or hormone therapy; 2) those who received RT alone or along with hormone therapy; 3) those who only received hormone therapy; and

3) no-treatment group as those who did not receive RP or RT or hormone therapy during six-month after the diagnosis of prostate cancer. Such grouping of the initial cancer treatment hierarchical preference for particular cancer treatments among men with prostate cancer.

2.4.4.3 Clinical Outcomes-Urinary, bowel, and sexual dysfunction

Clinical outcomes consisted of bowel, sexual, and urinary dysfunction during one-year after the initial cancer treatment. The bowel, sexual and urinary dysfunction were identified using ICD-9 CM codes and HCPCS codes from the inpatient, outpatient and carrier claims files during one year after the initial cancer treatment. Codes used to define urinary, bowel, and sexual dysfunction are listed in **Appendix 2.3**. Bowel dysfunction included the presence of rectal hemorrhage, ulcers, fistulas, hyperbaric oxygen therapy and rectal repairs; and sexual dysfunction included the presence of impotence, penile prostheses, and intra-cavernosal injections; (33), whereas, urinary dysfunction included the presence of any of the following conditions: incontinence, obstruction, irradiation cystitis, bladder hemorrhage, and urinary fistulas (34).

2.4.5 Key Independent Variable

2.4.5.1 Types of pre-existing chronic conditions

Chronic conditions were identified using one inpatient or two outpatient claims with ICD-9 CM diagnostic codes and procedure codes during the year before diagnosis of prostate cancer (**Appendix 2.4**). To define clinically meaningful combinations of chronic conditions, we used several criteria. These included: high prevalence, specific organ domains, common pathophysiology and synergistic management of different chronic conditions (35). Based on prior literature, as well as the conceptual model of chronic condition measurement, we selected 12 chronic conditions. These 12 chronic conditions were among the 20 conditions selected by the US Department of Health and Human Services (DHS) for research, policy, program and practice (36). These 12 conditions were grouped into 3 broad categories using specific organ domains, common pathophysiology and synergistic management. They were: cardio-metabolic conditions (diabetes, coronary artery disease, congestive heart failure, and cardiac arrhythmia), mental health conditions (anxiety, bipolar disorders,

depression, schizophrenia, post-traumatic stress disorders, and psychosis) and respiratory conditions (COPD and asthma). Such type of classifications have been used in many studies (37-39).

Furthermore, we classified these three types of chronic conditions into eight mutual categories: (1) cardio-metabolic conditions only (2) mental health conditions only; (3) respiratory conditions only (4) cardio-metabolic and mental health conditions; (5) cardio-metabolic and respiratory conditions; (6) mental health and respiratory conditions (7) all three -cardio-metabolic, mental health and respiratory conditions; and 8) none of the three types of conditions.

2.4.6 Other Independent Variables

2.4.6.1 Predisposing Characteristics

In the current study, the demographic factors such as age, race/ethnicity, and marital status were included as the predisposing characteristics. Age at the time of diagnosis was identified from the PEDSF file and was categorized into two groups (66 to 74 years, 75 and above years). Race/Ethnicity and marital status were also derived from the PEDSF file. Race/Ethnicity was categorized into four groups: White, African American, Hispanic, and other. Marital status was categorized into four groups: Married, Divorced/Separated, Unmarried, and others.

2.4.6.2 Enabling Characteristics

Enabling factors were income, education, access to care and prostate-cancer screening. The PEDSF file contains census-tract level information on income and education variables. Access to care was defined using a proxy measure in the absence of any direct measures for the same. The proxy for access to care was measured using visits to a primary care provider during the baseline period (40). The HCPCS codes of 84152, 84154, 84153, G0103 represented prostate-specific-antigen (PSA) test, and these codes were used to identify prostate-cancer screening during the baseline period.

2.4.6.3 Need Characteristics

During the baseline period, a very small percentage of men (<5%) had at least one of the other forty-two conditions, which were not captured by the cardio-metabolic, mental health, and respiratory conditions. These forty-two other conditions were derived using the list of chronic

conditions from published literature (41). The total number of other chronic conditions were calculated and categorized into two groups as the presence of either “0-1 condition” or “two or more conditions”.

2.4.6.4 External environment characteristics

External environment characteristics comprised of individual’s-resident level county, region, county-level radiation oncology units and urology units. The 18 regions of SEER were categorized into four groups: 1) Northeast-which included two registries of Connecticut, and New Jersey; 2) South– which included five registries from Atlanta, Greater Georgia, Kentucky, Louisiana, and Rural Georgia,; 3) North-Central which included two registries from Detroit and Iowa; and 4) West which included registries from Arizona, Alaska, Greater California, Cherokee Nation, Hawaii, Los Angeles, New Mexico, San Francisco-Oakland, San Jose-Monterey, Seattle-Puget Sound, and Utah (42).

County-level healthcare resources were derived from the AHRF. The AHRF is a nationwide county-level health resource files in the US. The file provides information for about 6,000 county-level variables including healthcare facilities, health professionals, resource scarcity, health status, economic activity, health training programs and socioeconomic characteristics (42). The number of radiation -oncology units, and urology units in counties were used to present county-level healthcare resources. SEER-Medicare files were matched with the AHRF using FIPS state and county codes (42). For the purposes of our analyses, the quartiles of radiation-oncology units and urology units at the county level were calculated. In addition, the year of diagnosis was also considered as an external factor.

2.5 STATISTICAL ANALYSES

The significant differences in predisposing, enabling, need, and external environment characteristics by types of pre-existing chronic conditions among the men with incident prostate cancer were tested using chi-square tests. Multivariable binary logistic regressions were used to test the association between types of chronic conditions and advanced prostate cancer diagnosis after controlling for the predisposing, enabling, need, and external environment characteristics.

Multinomial logistic regressions were performed to test the association between types of chronic conditions and cancer treatment receipt (RP, RT, hormone therapy only) after controlling predisposing, enabling, need and external environment characteristics. In this regression, cancer stage was additionally included as a need factor. Separate multivariable binary logistic regressions were used to test the associations between types of chronic conditions and clinical outcomes (urinary, bowel or sexual dysfunction) after adjusting for predisposing, enabling including the initial cancer treatment, need, and external environment characteristics. In these regressions, cancer stage at diagnosis was included as a need factor and cancer treatment was included as an enabling factor. All statistical analyses were carried out using *Statistical Analysis System* (SAS) version 9.4 (SAS Institute Inc., Cary, NC).

2.6 RESULTS

2.6.1 Study Population

Table 2.1 summarizes the characteristics of the study cohort (N = 103,820). A majority of men were diagnosed with prostate cancer between age 66 and 74 years (59.7%). The study cohort was primarily white (81.7%) and married (67.1%). Nearly three-quarters of men had at least one primary care visit (73.8%) and had a screening of PSA (81.6%) during the baseline period.

2.6.2 Study Population by Types of Chronic Conditions

Table 2.2 reports the characteristics of the study population by types of chronic conditions. Overall, 53.8% of the study population had either cardio-metabolic, mental health, or respiratory conditions during the year before the prostate cancer diagnosis and 46.2% had none of these conditions. The majority of men had only cardio-metabolic conditions (35.4%), followed by men with both cardio-metabolic and respiratory conditions (8%), only respiratory conditions (5.2%), cardio-metabolic and mental health conditions (2.1%), only mental health conditions (1.9%), and mental health conditions and respiratory conditions (0.4%). Significant differences in the predisposing, enabling, need and external environment factors by types of chronic conditions were observed among elderly men with incident prostate cancer.

2.6.3 Types of Chronic Conditions and Cancer Stage at Diagnosis

Table 2.3 describes the relationship between the types of chronic conditions and cancer stage at diagnosis. Overall, 94.6% of the study cohort were diagnosed with localized prostate cancer and 5.4% were diagnosed with advanced prostate cancer. Significant relationships between types of chronic conditions and cancer stage at diagnosis were observed. As compared to men with all the three types of chronic conditions (4.5%), a lower percentage of men with cardio-metabolic and respiratory conditions were diagnosed (3.8%) with advanced prostate cancer.

Table 2.3 also reports the adjusted odds ratios (AOR) and 95% Confidence Intervals (CI) from the logistic regression on cancer stage at diagnosis. After adjusting for predisposing, enabling, need and external environment factors among elderly men with prostate cancer, elderly men with none of the three conditions were 44% more likely to be diagnosed with advanced prostate cancer as compared to those with all the three types of chronic conditions (aOR = 1.44, 95% CI = 1.03, 2.00).

2.6.4 Types of Chronic Conditions and Initial Cancer Treatment Type

Tables 2.4 displays the rates of initial cancer treatment by types of chronic conditions. Overall, 80.3% of the study population received either RP/RT or hormone therapy during the six months after the cancer diagnosis: 22 received RP; 46.9% received RT; 11.4% received hormone therapy, and 19.7% received no treatment for cancer. The highest rate of RP was observed among those with only mental health conditions (24.4%), whereas, the highest rate of RT was observed among elderly men with cardio-metabolic conditions (49%). The highest rates of only hormone therapy (16.2%) or no treatment (24.4%) were observed among elderly men with prostate cancer with all the three types of chronic conditions (59.4%).

The bottom panel of **Table 2.4** displays the AORs and 95% CIs from the multinomial logistic regression on initial cancer treatment categories. After adjusting for predisposing, enabling, need factors including cancer stage, and external-environment factors, elderly men with none of the three types of chronic conditions (AOR = 1.32, 95% CI: 1.07, 1.61) or only cardio-metabolic conditions (AOR = 1.25; 95% CI: 1.02, 1.53) or only respiratory conditions (AOR = 1.36; 95% CI: 1.09, 1.69)

were more likely to receive RP as compared to those with all the three types of chronic conditions. These groups were also more likely to receive RT. Additionally, elderly men with cardio-metabolic and mental health conditions (AOR: 1.27 95% CI: 1.04, 1.57) or respiratory conditions (AOR: 1.49, 95% CI: 1.24, 1.79) were more likely to receive RT. Those with only mental health conditions were as likely as those with all the three types of chronic conditions to receive initial cancer treatment. There were no statistically significant relationships between types of chronic conditions and receipt of only hormone therapy among elderly men with prostate cancer.

2.6.5 Types of Chronic Conditions and Clinical Outcomes

Table 2.5 reports rates of clinical outcomes by the types of chronic conditions. Overall, 14.5% elderly men had any bowel dysfunction; 16.1% had any sexual dysfunction and 35.0% had any urinary dysfunction. Elderly men with prostate cancer and all the three types of chronic conditions had the highest rate of bowel dysfunction (20.5%) whereas, men with mental health conditions had the highest rate of sexual dysfunction (17.4%) and men with cardio-metabolic and mental health conditions had the highest rates of urinary dysfunction (44.3%).

In adjusted analysis, as compared to men with all the three types of chronic conditions, elderly men with none of the three types of conditions (AOR = 1.33; 95% CI: 1.09, 1.63) or only respiratory (AOR = 1.26; 95% CI: 1.02, 1.56) or only mental health conditions (AOR = 1.32; 95% CI: 1.05, 1.67) were more likely to have sexual dysfunction. There were no consistent patterns with regard to the types of chronic conditions and bowel dysfunction or urinary dysfunction.

2.7 DISCUSSION

One in two elderly men (54%) with incident prostate cancer had pre-existing cardio-metabolic, mental health, and respiratory conditions. The commonly prevalent types of chronic conditions were: cardio-metabolic and respiratory chronic conditions (15%). These findings suggest that elderly men with prostate cancer have significant disease burden prior to the diagnosis of prostate cancer.

2.7.1 Types of Chronic Conditions and Cancer Stage at Diagnosis

In our study cohort, 1 in 10 elderly men with prostate cancer were diagnosed with advanced prostate cancer. Our study estimates are consistent with published literature on rates of advanced prostate cancer (6, 9, 43). A statistically significant association was observed between the absence of any three types of chronic conditions and diagnosis with advanced prostate cancer. Closer examination of our results suggested that a significantly lower proportion of elderly men with none of three types of chronic conditions had a PSA screening and visit to a primary care physician in the year before the diagnosis of cancer as compared to those with any other types of chronic conditions. Taken together these findings confirm that contact with healthcare system may improve screening for prostate cancer (44). Elderly men with cardio-metabolic, respiratory and mental health conditions are more likely to use healthcare before diagnosis of cancer as compared to those without these chronic conditions leading to higher likelihood of prostate cancer screening. Therefore, our study findings suggest a strong need for the screening those with none of the three common types of chronic conditions.

2.7.2 Types of Chronic Conditions and Initial Cancer Treatment

Nearly 4 in 5 elderly men with incident prostate cancer received initial cancer treatment. Our findings are consistent with published studies (8, 27). Elderly men with none of the three types of chronic conditions were more likely to receive initial cancer treatment compared to those with all the three types of chronic conditions. Clinical guidelines encourage aggressive treatment with RP or RT for men without pre-existing chronic conditions because these men are considered relatively healthy and therefore may have long-term survival benefit and a better prognosis from initial cancer treatment.

Despite the availability of accurate estimates of survival based on age, CCI score and cancer stage (8, 9, 11), in the current study, elderly men with prostate cancer and some types of chronic conditions were more likely to be treated for cancer as compared to those with all the three types of chronic conditions. These findings suggest that many elderly men with chronic conditions may have been treated aggressively even though such treatment may not provide long-term survival benefit

(45) and may lead to adverse health consequences (46). The current guidelines for prostate cancer treatment recommend “no aggressive treatment should be an option for those with serious chronic conditions”. However, these guidelines did not explicitly define the term “serious chronic conditions”. Therefore, the providers may not consider the presence of some types of chronic conditions serious enough and may have treated the cancer aggressively with RP/RT. Our study reinforces the need for clinical guidelines that explicitly incorporate the types of chronic conditions along with age and life-expectance to recommend cancer treatment options for elderly men with prostate cancer.

Even after controlling for cancer stage and other factors, men with prostate cancer and only cardio-metabolic conditions were more likely to receive RP/RT as the initial cancer treatment as compared to those with all the three types of chronic conditions. Prior research has shown that elderly men with cardio-metabolic conditions may not benefit from cancer treatment as these men are at high risk for non-cancer related mortality (8, 45). There is also evidence of the increased risk for adverse clinical outcomes such as poor wound healing, risk of perioperative complications due to cancer treatment (47, 48) and treatment regret (46) among elderly men with prostate cancer and pre-existing cardio-metabolic conditions. Our study findings highlight the need to increase the physician and patient awareness of adverse risks associated with active treatment among elderly men with prostate cancer and cardio-metabolic conditions.

Another noteworthy finding from this study is that the elderly men with prostate cancer and only mental health conditions and both mental health conditions and respiratory conditions did not have significant differences between the receipt of RP/RT treatment. These findings are not consistent with a published study in which elderly men with prostate cancer and mental health conditions were less likely to receive aggressive treatment compared to elderly men without mental health conditions. The difference in findings could be explained by lack of adjustments for types of chronic conditions in the current study (6).

2.7.3 Types of Chronic Conditions and Clinical Outcomes

Consistent with previous studies (13-15), poor clinical outcomes were common among elderly men with prostate cancer during the year after the initial cancer treatment. The current study is the first of its kind to examine the relationships between types of chronic conditions and clinical outcomes. Elderly men with only mental health conditions and only respiratory conditions were more likely to have sexual dysfunction as compared to men with all the three types of chronic conditions. Similar to our study finding, Punnen *et al.* found that the presence of depression was associated with sexual dysfunction even after controlling for the primary treatment choice among men with prostate cancer in a prospective cohort study (49). Therefore, our study findings reinforce the need to actively monitor men with prostate cancer and only mental conditions or only respiratory conditions for reducing the risk of sexual dysfunction.

Elderly men with prostate cancer and some types of chronic conditions were less likely to experience bowel and urinary dysfunction, after controlling for the initial cancer treatment and other factors. For example, as compared to those with all the three types of chronic conditions, elderly men with prostate cancer and only cardio-metabolic or only respiratory conditions were less likely to have bowel and urinary dysfunction. The reasons for why these particular combinations are associated with lower risk of bowel and urinary dysfunction are unknown. Future research needs to explore the possible patho-physiological link between types of chronic conditions and bowel and urinary dysfunction.

Finally, our study findings have to be interpreted in the context of strengths and limitations. Our study is timely and is aligned with the goals of the Office of Cancer Survivorship (OCS) and Institute of Medicine (IOM) regarding the management of prostate cancer in the presence of pre-existing chronic conditions. To the best of our knowledge, our study is the largest population-based registry study to assess the association between the types of chronic conditions and the cancer stage at diagnosis, initial cancer treatment and clinical outcomes among elderly men with prostate cancer.

As the current study used observational data, the causal associations between the presence of types of chronic condition and cancer stage at diagnosis, and outcomes could not be determined. Our

study population was restricted to men older than 66 years and older. Therefore, the findings cannot be generalizable to younger men with prostate cancer. In addition, as the presence of chronic conditions were identified using validated codes from the literature, the clinical severity and seriousness of chronic conditions could not be measured which would also be important factors for the initial cancer treatment receipt and outcomes among men with prostate cancer. Furthermore, the current study utilized the registry-linked administrative claims data which have either no information or limited validity of codes to identify body-mass index, exercise and smoking status, which may be associated severity, cancer stage at diagnosis, treatment receipt and clinical outcomes.

2.8 CONCLUSION

Elderly men with none of the three types of chronic conditions were more likely to be diagnosed with advanced prostate cancer. Therefore, strategies to reduce the risk of diagnosing prostate cancer at an advanced stage are needed and tailored to such subgroup of population.

All chronic condition categories (except for only mental health conditions and both mental health and respiratory conditions) were associated with an increased likelihood of initial cancer treatment with either RP or RT as compared to all the three types of chronic conditions. Although there is no evidence that RP or RT can be beneficial in long-term for elderly men with prostate cancer and pre-existing chronic conditions, an overwhelming majority of men with chronic conditions received cancer treatment. Future research is needed to identify the long-term benefit and risk of treatment in subgroup of population with different types of chronic conditions.

Although men with some types of chronic conditions were associated with increased risk of sexual dysfunction, no consistent patterns were found for other clinical outcomes by types of chronic conditions. Therefore, men with prostate cancer and some types of chronic conditions i.e. mental health conditions may need heightened surveillance, monitoring and therapies to reduce the risk of sexual dysfunction after the initial cancer treatment.

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Table 2. 1
Characteristics of Elderly Medicare Beneficiaries with Prostate Cancer
Surveillance, Epidemiology and End Results (SEER)-Medicare Linked
Database-2002-2010

Characteristics	Total	%
All	103,820	
Types of Chronic Conditions		
CM only	36,719	35.4
MH only	1,940	1.9
RESP only	5,421	5.2
CM + MH	2,169	2.1
CM + RESP	8,216	7.9
MH + RESP	416	0.4
None	48,009	46.2
All Three	930	0.9
Predisposing Characteristics		
Age at diagnosis, years		
66-74	62,020	59.7
75+	41,800	40.3
Race/ethnicity		
Whites	84,787	81.7
African-American	11,679	11.2
Hispanic/Latino	2,148	2.1
Others	5,206	5.0
Marital status		
Unmarried	6,954	6.7
Married	69,628	67.1
Divorced/Separated	13,599	13.1
Others	13,639	13.1
Enabling Characteristics		
Quartile of median census 2000 income		
\$ 7- \$ 34,522	25,920	25.0
\$ 34,523-46,224	25,959	25.0
\$ 46,229-62,764	25,947	25.0
\$ 62,767-200,008	25,994	25.0
Quartile of median census 2000 education		
0 - 8.52	25,946	25.0
8.53-15.16	26,057	25.1
15.17-26.09	25,821	24.9
26.1-100	25,996	25.0
PSA Screening		
Yes	84,681	81.6
No	19,139	18.4
Visit to a PCP		
Yes	76,632	73.8
No	27,188	26.2
Need Characteristics		
Number of Chronic Conditions		
≤ One	63,217	60.9
> One	40,603	39.1

(Continued...)

Table 2. 1
Characteristics of Elderly Medicare Beneficiaries with Prostate Cancer
Surveillance, Epidemiology and End Results (SEER)-Medicare Linked
Database-2002-2010

Characteristics	Total	%
External-Environment Characteristics		
SEER-Regions		
Northeast	20,726	20.0
South	25,185	24.3
North-Central	12,907	12.4
West	45,002	43.3
Quartile of Radiation Oncology		
0 to 1	27,475	26.5
2 to 6	23,281	22.4
7 to 22	27,014	26.0
23 to 147	26,050	25.1
Quartile of Urology Centers		
0 to 3	25,677	24.7
4 to 16	25,467	24.5
17 to 44	27,053	26.1
45 to 343	25,623	24.7
Year of diagnosis		
2002-2005	53,412	51.4
2006-2009	50,408	48.6
Cancer Stage at Diagnosis		
Stage		
Localized	98,264	94.6
Advanced	5,556	5.4
Initial Cancer Treatment		
Treatment		
RP	22,864	22.0
RT	48,684	46.9
Hormone Therapy	11,803	11.4
None	20,469	19.7
Clinical Outcomes		
Bowel Dysfunction		
Yes	15,043	14.5
No	88,777	85.5
Sexual Dysfunction		
Yes	16,707	16.1
No	87,113	83.9
Urinary Dysfunction		
Yes	36,368	35.0
No	67,452	65.0

Notes: Based on the data of 103,820 elderly men aged 66 years and older diagnosed with prostate cancer between 2002 and 2009 using a Surveillance, Epidemiology, and End-Results (SEER)-linked Medicare data.

Abbreviations: CM: Cardio-metabolic conditions; MH: Mental health conditions; PCP: Primary Care Physician; PSA: Prostate-Specific Antigen Test; RESP: Respiratory conditions; RP: Radical Prostatectomy; RT: Radiation Therapy

Table 2. 2 Characteristics of Elderly Medicare Beneficiaries with Prostate Cancer by Types of Chronic Conditions Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database-2002-2010																	
	None		CM Only		MH only		RESP Only		CM+ MH		CM + RESP		MH + RESP		All Three		Sig.
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Overall	48,009	46.2	36,719	35.4	1,940	1.9	5,421	5.2	2,169	2.1	8,216	7.9	416	0.4	930	0.9	
Predisposing Characteristics																	
Age at diagnosis, years																	***
66-74	31,152	64.9	20,270	55.2	1,228	63.3	3,258	60.1	1,173	54.1	4,170	50.8	252	60.6	517	55.6	
75+	16,857	35.1	16,449	44.8	712	36.7	2,163	39.9	996	45.9	4,046	49.2	164	39.4	413	44.4	
Race/ethnicity																	***
Whites	39,460	82.2	29,827	81.2	1,686	86.9	4,415	81.4	1,813	83.6	6,469	78.7	354	85.1	763	82.0	
African-American	5,379	11.2	4,143	11.3	159	8.2	581	10.7	198	9.1	1,079	13.1	36	8.7	104	11.2	
Hispanic/Latino	876	1.8	794	2.2	34	1.8	119	2.2	75	3.5	209	2.5	6	1.4	35	3.8	
Others	2,294	4.8	1,955	5.3	61	3.1	306	5.6	83	3.8	459	5.6	20	4.8	28	3.0	
Marital status																	***
Unmarried	3,283	6.8	2,167	5.9	218	11.2	414	7.6	193	8.9	554	6.7	47	11.3	78	8.4	
Married	33,078	68.9	24,782	67.5	1,178	60.7	3,461	63.8	1,282	59.1	5,121	62.3	226	54.3	500	53.8	
Divorced/Separated	5,934	12.4	4,565	12.4	317	16.3	788	14.5	369	17.0	1,324	16.1	90	21.6	212	22.8	
Others	5,714	11.9	5,205	14.2	227	11.7	758	14.0	325	15.0	1,217	14.8	53	12.7	140	15.1	
Enabling Characteristics																	
Quartile of median census 2000 income																	***
\$ 7- \$ 34,522	11,533	24.0	8,625	23.5	502	25.9	1,624	30.0	627	28.9	2,540	30.9	138	33.2	331	35.6	
\$ 34,523-46,224	11,864	24.7	9,086	24.7	528	27.2	1,436	26.5	522	24.1	2,178	26.5	109	26.2	236	25.4	
\$ 46,229-62,764	12,052	25.1	9,456	25.8	453	23.4	1,262	23.3	509	23.5	1,900	23.1	100	24.0	215	23.1	
\$ 62,767-200,008	12,560	26.2	9,552	26.0	457	23.6	1,099	20.3	511	23.6	1,598	19.4	69	16.6	148	15.9	
Quartile of median census 2000 education																	***
0 - 8.52	13,111	27.3	9,001	24.5	508	26.2	1,135	20.9	529	24.4	1,426	17.4	85	20.4	151	16.2	
8.53-15.16	12,186	25.4	9,337	25.4	490	25.3	1,319	24.3	523	24.1	1,919	23.4	90	21.6	193	20.8	
15.17-26.09	11,512	24.0	9,331	25.4	473	24.4	1,374	25.3	506	23.3	2,263	27.5	113	27.2	249	26.8	
26.1-100	11,200	23.3	9,050	24.6	469	24.2	1,593	29.4	611	28.2	2,608	31.7	128	30.8	337	36.2	
PSA Screening																	***
Yes	36,251	75.5	32,144	87.5	1,632	84.1	4,642	85.6	1,852	85.4	7,044	85.7	357	85.8	759	81.6	
No	11,758	24.5	4,575	12.5	308	15.9	779	14.4	317	14.6	1,172	14.3	59	14.2	171	18.4	
Visit to PCP																	
Yes	32,188	67.0	28,848	78.6	1,568	80.8	4,221	77.9	1,847	85.2	6,798	82.7	356	85.6	806	86.7	
No	15,821	33.0	7,871	21.4	372	19.2	1,200	22.1	322	14.8	1,418	17.3	60	14.4	124	13.3	
(Continued...)																	

Table 2. 2 Characteristics of Elderly Medicare Beneficiaries with Prostate Cancer by Types of Chronic Conditions Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database-2002-2010																	
	None		CM Only		MH only		RESP Only		CM+ MH		CM + RESP		MH + RESP		All Three		Sig.
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Overall	48,009	46.2	36,719	35.4	1,940	1.9	5,421	5.2	2,169	2.1	8,216	7.9	416	0.4	930	0.9	
Need Characteristics																	
Number of Other Chronic Conditions																	***
≤ One	36,724	76.5	21,031	57.3	1,035	53.4	1,945	35.9	708	32.6	1,618	19.7	80	19.2	76	8.2	
> One	11,285	23.5	15,688	42.7	905	46.6	3,476	64.1	1,461	67.4	6,598	80.3	336	80.8	854	91.8	
External-Environment Characteristics																	
SEER-Regions																	***
Northeast	8,712	18.1	8,347	22.7	342	17.6	953	17.6	439	20.2	1,679	20.4	61	14.7	193	20.8	
South	11,735	24.4	8,450	23.0	535	27.6	1,538	28.4	507	23.4	2,020	24.6	129	31.0	271	29.1	
North-Central	5,404	11.3	4,810	13.1	208	10.7	641	11.8	280	12.9	1,361	16.6	61	14.7	142	15.3	
West	22,158	46.2	15,112	41.2	855	44.1	2,289	42.2	943	43.5	3,156	38.4	165	39.7	324	34.8	
Quartile of Urology Centers																	***
0 to 3	12,241	25.5	8,290	22.6	531	27.4	1,593	29.4	511	23.6	2,089	25.4	130	31.3	292	31.4	
4 to 16	11,985	25.0	9,035	24.6	477	24.6	1,314	24.2	521	24.0	1,839	22.4	112	26.9	184	19.8	
17 to 44	12,295	25.6	10,000	27.2	491	25.3	1,274	23.5	548	25.3	2,141	26.1	86	20.7	218	23.4	
45 to 343	11,488	23.9	9,394	25.6	441	22.7	1,240	22.9	589	27.2	2,147	26.1	88	21.2	236	25.4	
Quartile of Radiation Oncology																	***
0 to 1	12,994	27.1	8,991	24.5	554	28.6	1,686	31.1	558	25.7	2,254	27.4	140	33.7	298	32.0	
2 to 6	10,852	22.6	8,305	22.6	452	23.3	1,205	22.2	437	20.1	1,739	21.2	105	25.2	186	20.0	
7 to 22	12,555	26.2	9,931	27.0	486	25.1	1,287	23.7	569	26.2	1,909	23.2	82	19.7	195	21.0	
23 to 147	11,608	24.2	9,492	25.9	448	23.1	1,243	22.9	605	27.9	2,314	28.2	89	21.4	251	27.0	
Year of diagnosis																	***
2002-2005	25,127	52.3	18,344	50.0	951	49.0	2,926	54.0	1,039	47.9	4,343	52.9	210	50.5	472	50.8	
2006-2009	22,882	47.7	18,375	50.0	989	51.0	2,495	46.0	1,130	52.1	3,873	47.1	206	49.5	458	49.2	

Notes: Based on 103,820 elderly men aged 66 years and older diagnosed with incident prostate cancer between 2002 and 2009. Significant group differences by types of chronic conditions combinations were based on Chi-square tests.

Abbreviations: CM: Cardio-metabolic conditions; MH: Mental health conditions; PCP: Primary Care Physician; PSA: Prostate-Specific Antigen Test; RESP: Respiratory conditions;

Sig: Level of Significance; *** p < .001; ** .001 ≤ p < .01; * .01 ≤ p < .05

Table 2. 3
Number and Percent with Advanced Prostate Cancer and Adjusted Odds Ratios (AOR) and 95% Confidence Intervals from Logistic Regressions for Advanced Stage Diagnosis among Elderly Medicare Beneficiaries with Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database 2002-2010

	Cancer Stage				Logistic Regressions on Advanced Prostate Cancer Diagnosis				
	Localized		Advanced		Sig.	AOR	95% CI	Sig.	
	N	%	N	%					
Types of Chronic Conditions									
None	45,209	94.2	2,800	5.8	***	1.44	[1.03 , 2.00]	*	
CM only	34,916	95.1	1,803	4.9		1.29	[0.93 , 1.80]		
MH only	1,838	94.7	102	5.3		1.33	[0.90 , 1.95]		
RSP only	5,151	95.0	270	5.0		1.32	[0.93 , 1.88]		
CM + MH	2,086	96.2	83	3.8		0.89	[0.60 , 1.33]		
CM + RSP	7,783	94.7	433	5.3		1.37	[0.97 , 1.92]		
MH + RSP	393	94.5	23	5.5		1.24	[0.71 , 2.17]		
All Three	888	95.5	42	4.5		Ref			

Notes: Based on 103,820 elderly men aged 66 years and older diagnosed with prostate cancer between 2002 and 2009. Significant differences by types of chronic conditions were based on the log-likelihood test using a logistic regression for adjusted models and chi-square tests for difference in the rates of stages by types of chronic conditions. Adjusted model controlled for predisposing (age, race/ethnicity, marital status), enabling (income, education, access to care, cancer screening), need (number of other chronic conditions), and external-environment factors (county level-radiation unit, urology units, regions, year of diagnosis)

Abbreviations: CM: Cardio-metabolic conditions; MH: Mental health conditions; RESP: Respiratory conditions; Ref: Reference Group; Sig: Level of Significance; *** $p < .001$; ** $.001 \leq p < .01$; * $.01 \leq p < .05$

Table 2. 4									
Number and Percentage with Initial Cancer Treatment by Types of Chronic Conditions Unadjusted and Adjusted Odds Ratios and 95% Confidence Intervals from Multinomial Logistic Regressions among Elderly Medicare Beneficiaries with Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database 2002-2010									
	RP		RT		Hormone Therapy		None		Sig.
	N	%	N	%	N	%	N	%	
All	22,864	22.0	48,684	46.9	11,803	11.4	20,469	19.7	
Types of Chronic Conditions									***
None	11,648	24.3	22,130	46.1	4,553	9.5	9,678	20.2	
CM Only	7,300	19.9	18,008	49.0	4,487	12.2	6,924	18.9	
MH Only	473	24.4	819	42.2	221	11.4	427	22.0	
RESP Only	1,212	22.4	2,537	46.8	678	12.5	994	18.3	
CM + MH	484	22.3	895	41.3	322	14.8	468	21.6	
CM + RESP	1,459	17.8	3,758	45.7	1,334	16.2	1,665	20.3	
MH + RESP	91	21.9	182	43.8	57	13.7	86	20.7	
All Three	197	21.2	355	38.2	151	16.2	227	24.4	
Adjusted Model-Initial Cancer Treatment (Ref = No Treatment)									
	RP			RT			Hormone Therapy		
	AOR	95% CI	Sig.	AOR	95% CI	Sig.	AOR	95% CI	Sig.
Types of Chronic Conditions									
None	1.32	[1.07,1.61]	**	1.44	[1.20,1.71]	***	0.91	[0.73,1.14]	
CM Only	1.25	[1.02,1.53]	*	1.69	[1.41,2.01]	***	1.12	[0.90,1.40]	
MH Only	1.12	[0.88,1.43]		1.17	[0.95,1.44]		0.92	[0.70,1.21]	
RESP Only	1.36	[1.09,1.69]	**	1.63	[1.35,1.97]	***	1.11	[0.88,1.40]	
CM + MH	1.20	[0.95,1.53]		1.27	[1.04,1.57]	*	1.14	[0.88,1.48]	
CM + RESP	1.07	[0.87,1.33]		1.49	[1.24,1.79]	***	1.18	[0.94,1.47]	
MH + RESP	1.09	[0.75,1.57]		1.31	[0.96,1.80]		1.02	[0.68,1.53]	
All Three	Ref			Ref					

Notes: Based on 103,820 elderly men aged 66 years and older diagnosed with prostate cancer between 2002 and 2009. Significant differences in initial cancer treatment by types of chronic conditions were based on chi-square test.

Significant differences by types of chronic conditions were based on the log-likelihood test using a logistic regression for adjusted model. Adjusted model controlled for predisposing (age, race/ethnicity, marital status), enabling (income, education, access to care, cancer screening), need (number of other chronic conditions, cancer stage), and external-environment factors (county level-radiation unit, urology units, regions, year of diagnosis)

Abbreviations: CM: Cardio-metabolic conditions; MH: Mental health conditions; Ref: Reference Group; RESP: Respiratory conditions; Sig: Level of Significance; *** $p < .001$; ** $.001 \leq p < .01$; * $.01 \leq p < .05$

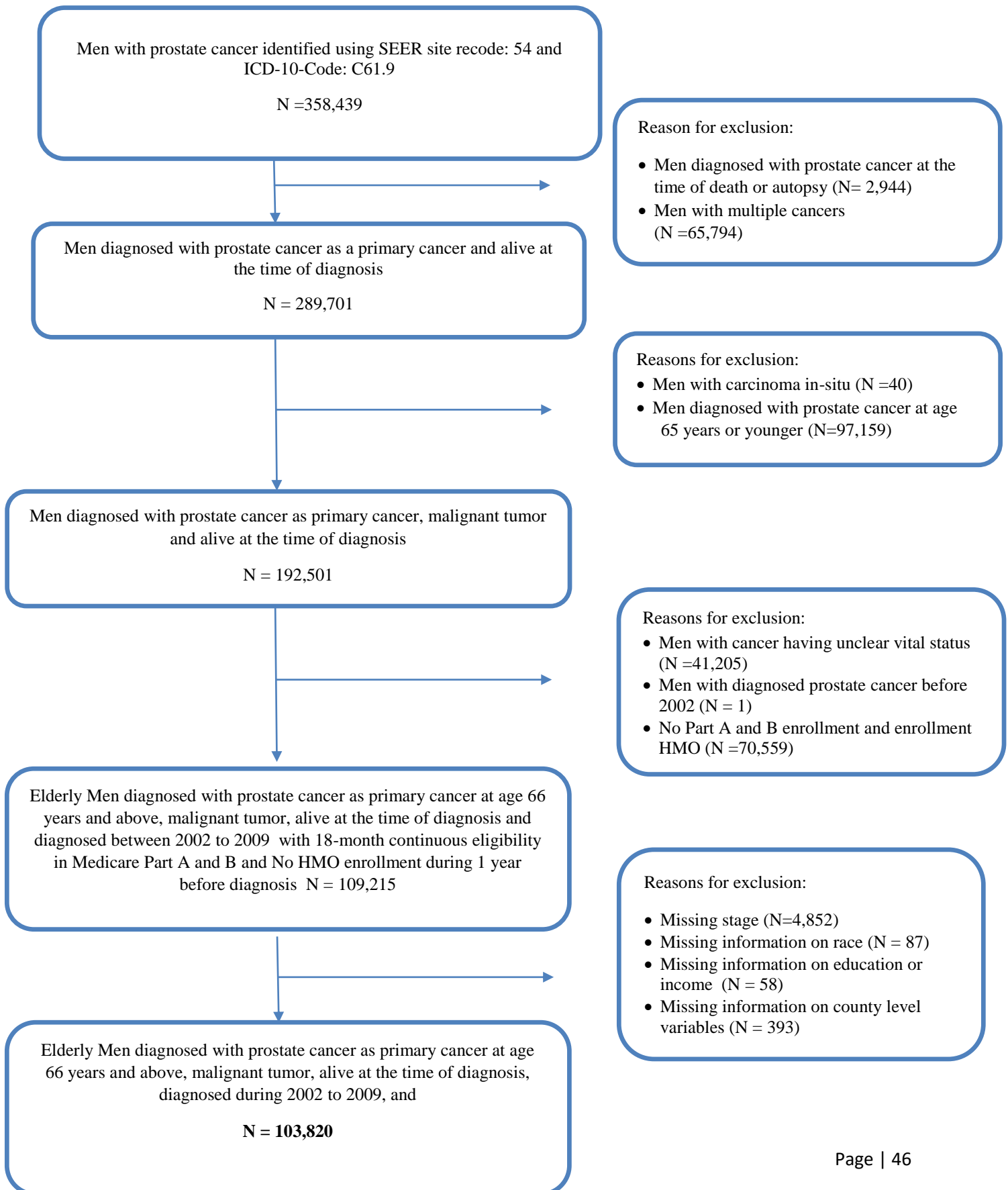
Table 2. 5
Number and Percentage with Poor Clinical Outcomes Unadjusted and Adjusted Odds Ratios and 95% Confidence Intervals from Logistic Regressions of Clinical Outcomes among Elderly Men with Prostate Cancer by Types of Chronic Conditions Surveillance, Epidemiology and End Results-Medicare Linked Database 2002-2010

	Bowel			Sexual			Urinary		
	N	%	Sig.	N	%	Sig.	N	%	Sig.
Overall	15,043	14.5		16,707	16.1		36,368	35.0	
Types of Chronic Conditions			***			***			***
None	5,918	12.3		8,401	17.5		15,247	31.8	
CM only	5,852	15.9		5,535	15.1		13,680	37.3	
MH only	335	17.3		338	17.4		731	37.7	
RESP only	802	14.8		880	16.2		1,866	34.4	
CM + MH	367	16.9		314	14.5		961	44.3	
CM + RESP	1,496	18.2		1,063	12.9		3,316	40.4	
MH + RESP	82	19.7		60	14.4		159	38.2	
All Three	191	20.5		116	12.5		408	43.9	
Adjusted Odds Ratios and 95% Confidence Intervals									
	AOR	95% CI	Sig.	AOR	95% CI	Sig.	AOR	95% CI	Sig.
Types of Chronic Conditions									
None	0.65	[0.55,0.77]	***	1.33	[1.09,1.63]	**	0.75	[0.65,0.86]	***
CM only	0.81	[0.69,0.95]	*	1.18	[0.96,1.44]		0.86	[0.75,0.98]	*
MH only	0.90	[0.73,1.09]		1.32	[1.05,1.67]	*	0.89	[0.76,1.04]	
RESP only	0.70	[0.59,0.84]	***	1.26	[1.02,1.56]	*	0.74	[0.64,0.85]	***
CM + MH	0.82	[0.67,0.99]	*	1.14	[0.90,1.44]		1.08	[0.92,1.26]	
CM + RESP	0.87	[0.73,1.03]		1.08	[0.87,1.33]		0.89	[0.78,1.02]	
MH + RESP	0.96	[0.72,1.29]		1.11	[0.79,1.57]		0.83	[0.65,1.05]	
All Three	Ref			Ref			Ref		

Notes: Based on 103,820 elderly men aged 66 years and older diagnosed with prostate cancer between 2002 and 2009. Significant differences by types of chronic conditions were based on the log-likelihood test using a logistic regression for adjusted models and chi-square tests for difference in the rates of stages by types of chronic conditions. Adjusted model controlled for predisposing (age, race/ethnicity, marital status), enabling (income, education, access to care, cancer screening, cancer treatment), need (number of other chronic conditions, cancer stage), and external-environment factors (county level-radiation unit, urology units, regions, year of diagnosis)

Abbreviations: CM: Cardio-metabolic conditions; MH: Mental health-conditions; RESP: Respiratory conditions; Sig: Level of Significance; *** $p < .001$; ** $.001 \leq p < .01$; * $.01 \leq p < .05$

Appendix 2. 1 Study Cohort Development Flow diagram for Study Population of Elderly Medicare Beneficiaries diagnosed with Prostate Cancer



Appendix 2. 2						
Codes to Identify Radiation Therapy, Surgery, Hormonal and Chemotherapy Utilization Among Elderly Medicare Beneficiaries with Prostate Cancer Using Surveillance, Epidemiology and End Results-Medicare Linked Data 2002-2010						
Types of Therapy	Medicare Claims			SEER		
	ICD-9 Procedure codes in MedPAR/SAF	ICD-9 diagnostic codes in MedPAR/SAF	CPT-4 codes in NCH/Carrier file/SAF	Surgery codes	Radiation codes	Revenue center codes
Active Treatment						
Radical Prostatectomy	60.2-60.6		55810, 55812, 55840, 55842, 55845, 55815, 55866	30,50,80		
Radiation Therapy	9221-9229, 9227,4604,4610	V58.0, V66.1, V67.1	55859, 55860, 55862, 55865, 55875, 76873 76968, 77261-77299, 77300, 77301 77305, 77326, 77327, 77328, 77338, 77401-77499, 77520, 77522, 77523, 77525, 77750-77799, C1164, C1174, C1325, C1350 C1700-C1712, C1715-C1720, C1728 C1790-C1806, C2638 C2639, C2640 C2641, G0256, G0261, Q3001, 0073T		1-5, 7	0330 or 0333
Hormonal therapy	62.4		J1950, J9217-J9219, J9202, J9165, 54520, 54521, 54522, 54530, 54535	01,		

Note: 3D-CRT, three-dimensional conformal radiation therapy; MIRC- Minimum Invasive Robotic Radical Prostatectomy; CPT-4, Current Procedural Terminology, fourth edition; ICD-9, International Classification of Diseases, ninth revision; IMRT, intensity-modulated radiation therapy; LRP, Laparoscopic Radical Prostatectomy; Open RP, open radical prostatectomy.

Appendix 2. 3		
Diagnostic and Procedure codes used to Identify Clinical Outcomes-Bowel, Sexual and Urinary Dysfunctions Among Elderly Men with Prostate cancer using SEER-Medicare data from the year 2002 to 2010		
	ICD-9 diagnostic codes	Procedure codes (ICD-9 procedure codes and HCPCS codes)
Bowel Dysfunction		
Ulcer, stricture or fistula of rectum or anus	565.1, 569.2, 569.41, 569.81	ICD9: 56.31,59.8,55.02,55.03,55.12,55.93,55.94,59.93,97.61,97.62, 56.1, 56.41,56.74, 56.75,56.81,56.84,56.86,56.89,56.91 HCPCS: 50390,50392,50393,50394,50572,50951,50953,50970,50972, 52005,52335, 50040,50120,50125,50395,50398,50605,52290,52332, 52334,50600,50700, 50715, 50760,50770,50780,50782,50783,50785, 50800,50810,50815, 50820, 50825,50840
Intestinal or vesical fistula	596.1,596.2,599.1,998.6	ICD-9: 54.91,54.0,54.19,59.19 HCPCS: 51715,11950,11951,11952,11954,L8603,51840,51841,53440, 53442,53445,53447,53449,53443
Lymphocele, pelvic abcess, or urinoma	457.8,567.2,567.8,595.89,682.2,998.59	ICD-9: 89.22,89.21,89.23,89.25 HCPCS: 51715,11950,11952,11954,L8603,51840,51841,53440,53442, 53445, 53447, 53449, 53443
Proctitis, Hemorrhage Hyperbaric oxygen	558.1, 569.3, 569.49, 578.9	ICD-9: 93.95 HCPCS: 99183, G0167
Sexual dysfunction		
Impotence	607.84	ICD-9: 64.94, 64.95, 64.96, 64.97 HCPCS: 54400, 54401, 54402, 54405, 54407, 54408, 54409, 54410, 54411, 54415, 54416, 54417, C1007, C1813, C2622, C3500, C8514, C8516, C8534, L7900
Intracavetary injection		HCPCS: 54231, 54235, J0270, J0275, J2440, J2760
Urinary Dysfunction		
Retention	788.20, 788.21, 788.29, 788.62	
Stricture	593.3, 598.0, 598.00, 598.01, 598.1, 598.2, 598.8, 598.9, 599.2, 599.4	
Cystitis, hematuria	595.1, 595.3, 595.82, 595.89, 595.9, 596.7, 597.8, 597.80, 597.81, 597.89, 599.7	ICD-9: 57.93 HCPCS: 52000, 52001, 52214, 52224

Obstruction	593.4, 596.0, 596.3, 596.4, 596.5, 596.51, 596.52, 596.53, 596.54, 596.55, 596.59, 596.6, 596.8, 596.9, 599.6	ICD-9 : 55.02, 55.03, 55.12, 55.93, 55.94, 56.1, 56.31, 56.41, 56.74, 56.75, 56.81, 56.86, 56.89, 56.91, 57.0, 57.11, 57.12, 57.17, 57.18, 57.19, 57.21, 57.22, 57.4, 57.41, 57.49, 57.82, 57.85, 57.89, 57.91, 57.92, 57.93, 57.94, 57.95, 58.0, 58.1, 58.31, 58.39, 58.44, 58.46, 58.47, 58.5, 58.6, 58.99, 59.8, 59.93, 59.94, 60.21, 60.29, 60.95, 97.61, 97.62, 97.63, 97.64, 97.65, 97.69, 98.19 HCPCS: 50040, 50120, 50125, 50390, 50392-50395, 50398, 50572, 50600, 50605, 50700, 50715, 50760, 50770, 50780, 50782, 50783, 50785, 50800, 50810, 50815, 50820, 50825, 50840, 50951, 50953, 50970, 50972, 51040, 51520, 51600, 51705, 51800, 51820, 51880, 52005, 52275, 52276, 52281-52283, 52290, 52310, 52332, 52334, 52335, 52500, 52601, 52612, 52614, 52620, 52620, 52630, 52640, 53000, 53010, 53020, 53400, 53405, 53410, 53415, 53420, 53425, 53600, 53601, 53605, 53620, 53621, 53850, 53852
Incontinence or sphincter deficiency	599.82, 788.3, 788.30, 788.31, 788.32, 788.33, 788.34, 788.35, 788.36, 788.37, 788.38, 788.39	ICD-9: 58.93, 58.99, 59.3, 59.4, 59.5, 59.6, 59.7, 59.71, 59.72, 59.79 HCPCS: 11950, 11951, 11952, 11954, 51701, 51715, 51840, 51841, 51990, 51992, 53431, 53440, 53442, 53443, 53444, 53445, 53446, 53447, 53448, 53449
Fistula	596.1, 596.2, 599.1, 998.6	ICD-9: 56.84, 57.83, 57.84, 58.43 HCPCS: 45800, 45805, 45820, 45825, 50920, 50930, 53520
Miscellaneous supplies		HCPCS: E0740,A4335,A5149

Appendix 2. 4

Codes Used to Identify the Types of Chronic Conditions and List of Other Chronic Conditions Among Elderly Medicare Beneficiaries with Incident Prostate Cancer Surveillance, Epidemiology, End-Results-Medicare Linked Data of 2002 to 2009

Types of Chronic Conditions	ICD-9 Diagnostic Codes
Cardio-metabolic Conditions	
Coronary Artery Disease	410,411,412,413, 414,
Congestive Heart Failure	402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 428
Conductive Disorders	423, 427.31
Diabetes	250
Mental Health Conditions	
Depression	296.2, 296.3, 311,300.4,311, 300.4
Bipolar Disorders	296.0, 296.1, 296.4, 296.5, 296.6,296.7, 296.8, 296.9
Schizophrenia	297, 298, 299
Psychoses	309.81
Anxiety	300.0, 300.2,300.3
Respiratory Conditions	
COPD and other pulmonary conditions	490, 491, 492, 495, 496, 500, 501, 502, 503, 504, 505, 506.4
Asthma	493

List of other Chronic Conditions

Abuse of drugs, Acute Renal Failure, AIDS, Alcohol abuse, Amputations, Blindness, Cerebrovascular Disease, Chronic Renal Failure, Cognitive impairment, Dementia, Diverticulitis, End-stage kidney disease, End-stage liver disease, Epilepsy, Gallstones, Gangrene, Gastritis, Gastroparesis, GERD, Gout, Hemiplegia, Hip Arthroplasty, Low Back Pain, Multiple sclerosis, Muscular Dystrophy, Nephropathy, Nephrotic syndrome, Osteoarthritis, Parkinson's Disease, Peptic Ulcers, Peripheral Vascular Disease, Retinopathy, Rheumatoid Arthritis, Spinal Cord Injury Systemic Lupus Erythematosus, Ulcer, Viral Hepatitis

Chapter 3

Association between Metformin Use and Cancer Stage at Diagnosis and Initial Cancer Treatment among Elderly Medicare Beneficiaries with Diabetes and Prostate Cancer

3.1 ABSTRACT

OBJECTIVE: To examine the associations between metformin use and cancer stage at diagnosis and the initial cancer treatment among elderly men with pre-existing diabetes and incident prostate cancer.

METHODS: A population-based observational cohort study was conducted using the Surveillance, Epidemiology and End-Results (SEER) –Medicare linked database. The study population consisted of elderly men (> 66 years) with pre-existing type 2 Diabetes Mellitus (T2DM) and incident prostate cancer between January 2008 and December 2009 (N = 2,652). Cancer stage at diagnosis was categorized into two groups (localized and advanced) based on the American Joint Cancer Committee Tumor-Node-Metastasis (TNM) System classification. The initial cancer treatment during the six months after cancer diagnosis was categorized into four groups using a hierarchy: 1) receipt of radical prostatectomy (RP); 2) receipt of radiation therapy (RT); 3) receipt of only hormone therapy; and 4) no cancer treatment.

The key independent variable, metformin use, and other independent variables were measured during the one year period before cancer diagnosis. The independent variables were selected using the Anderson Behavior and Healthcare Utilization Model and consisted of predisposing (age, race/ethnicity, and marital status), enabling (income, education, access to care,), need (severity of diabetes, cancer stage, insulin and other medication use), and external environment factors (region, number of urology and radiation-oncology units measured at the county-level).

Significant unadjusted associations between metformin use and cancer stage at diagnosis and the initial cancer treatment were examined using chi-square tests. The adjusted association between metformin use and cancer stage diagnosis was analyzed using logistic regression after controlling for predisposing, enabling, need, and external environment-related factors. The adjusted association between metformin use and the initial cancer treatment was analyzed using multinomial logistic regression. The reference group for the dependent variable was “no cancer treatment.” To control for the observed selection bias in metformin use, inverse probability treatment weights (IPTW) were constructed using logistic regression on

metformin use. The IPTWs were used in analyses related to the stage of cancer diagnosis and the initial cancer treatment.

RESULTS: In the study cohort, 35.7% used metformin during the year before diagnosis of prostate cancer. Significant associations were observed between predisposing, enabling, need, and external environment factors and metformin use, suggesting the presence of observed selection bias between metformin users and non-users. Overall, 93.7% of the study population had a diagnosis of localized prostate cancer and 6.3% had a diagnosis of advanced prostate cancer. A significantly lower percentage of metformin users were diagnosed with advanced prostate cancer as compared to non-users of metformin (4.7% vs. 6.7%, $p < 0.03$). After controlling for the observed selection bias and other independent variables, metformin use was significantly associated with a reduction in the risk of advanced prostate cancer (Adjusted Odds Ratio, AOR: 0.68, 95% Confidence Interval, CI: 0.48, 0.97).

Overall, 72.4% of the study population received either RP (17.4%), RT (46.5%) or hormone therapy (8.6%) during the six months after the diagnosis of prostate cancer. A higher percentage of metformin users as compared to non-users received RP (21.3% vs 16.3%, $p < 0.001$). After adjusting for the observed selection bias and other independent variables, metformin users were 45% more likely to receive RP as compared to non-users (AOR = 1.45, 95% CI = 1.14, 1.86).

CONCLUSIONS: Among elderly men with T2DM and incident prostate cancer, metformin use was associated with a reduction in the risk of advanced prostate cancer. Metformin users were more likely to receive RP as compared to non-users. No statistically significant relationships were observed between metformin use and RT or hormone therapy.

IMPLICATIONS: The findings from the current study add to the nascent literature on the association between metformin use and the risk for advanced cancer stage and treatment based on observational data. Well-designed, randomized clinical trials are needed to confirm the causal link between metformin use and stage of prostate cancer diagnosis.

3.2 INTRODUCTION

Individuals with diabetes, specifically those with type 2 diabetes mellitus (T2DM) have a higher risk for many cancers such as breast, colon and rectum, endometrium, liver and pancreatic cancers as compared to those without diabetes (1) due to biological mechanisms and shared risk factors (2-4). In pre-clinical studies, T2DM has been found to be associated with increased levels of plasma insulin, insulin resistance and hyperglycemia, which may have a direct effect on the growth of tumors (5, 6) leading to the development of many types of cancers (1).

3.2.1 Diabetes and Prostate Cancer Risk and Stage at Diagnosis

In the case of prostate cancer, an inverse relationship between diabetes and cancer risk has been observed (3). However, among men who developed prostate cancer, diabetes was associated with an advanced stage of cancer diagnosis (7, 8). Three population-based studies in the United States (US) reported that the presence of diabetes was associated with an increased risk for advanced prostate cancer measured either by stage or tumor grade. In case-control studies and cohort studies, men with diabetes were less likely to be diagnosed with localized stage of prostate cancer. The risk ratio (RR) was 0.70, 95% CI = 0.56-0.86 for case-control studies and the RR was 0.72, 95% CI 0.67, 0.77 for cohort studies (7). Although the exact biological mechanisms for the link between diabetes and prostate cancer are not known, it is speculated that men with diabetes have low levels of androgen, which may be associated with advanced stage of cancer at diagnosis (7, 8).

3.2.2 Anti-diabetes Drugs (Metformin) and Cancer Stage at Diagnosis

The main modality of treatment for diabetes is pharmacotherapy with anti-diabetes drugs such as metformin, thiazolidinediones, sulfonylureas, and insulin. All classes of anti-diabetes drugs may indirectly affect the risk of prostate cancer by controlling hyperglycemia. Of special interest is the use of metformin for diabetes management because of its unique actions on insulin resistance and hyperinsulinemia (9) as well as its anti-cancer properties (10-12). A systemic review found that metformin use reduced the risk of prostate cancer among men with diabetes (13) perhaps by regulating adenosine monophosphate-activated protein kinase (AMPK) pathways (10) and mammalian target of rapamycin (mTOR) (12). Based on pre-

clinical evidence, one can speculate that metformin may also reduce the risk of advanced prostate cancer among men with diabetes and incident prostate cancer (14). This relationship between metformin and advanced prostate cancer diagnosis was explored by one population-based study from Canada (15). The study investigators used a cohort of 119,315 men with diabetes and measured cancer stage using tumor grade. After adjusting for other risk factors, the investigators concluded that metformin use was not associated with the advanced form of cancer diagnosis (23). The investigators of the study did not control for severity of diabetes, which may have affected the findings. Controlling for diabetes severity is important because individuals with severe diabetes have micro and macro-vascular complications and may have adverse pathological profiles (16). Therefore, diabetes severity may alter the relationship between metformin use and cancer stage at diagnosis. Furthermore, the study did not control for the observed selection bias between metformin users and non-users; such bias may lead to misleading findings on the association between metformin use and cancer stage at diagnosis. Thus, there is a need for population-based studies to examine the relationship between metformin use and cancer stage at diagnosis that control for a comprehensive set of risk factors and the observed selection bias between metformin users and non-users.

3.2.3 Metformin Use and the Initial cancer treatment

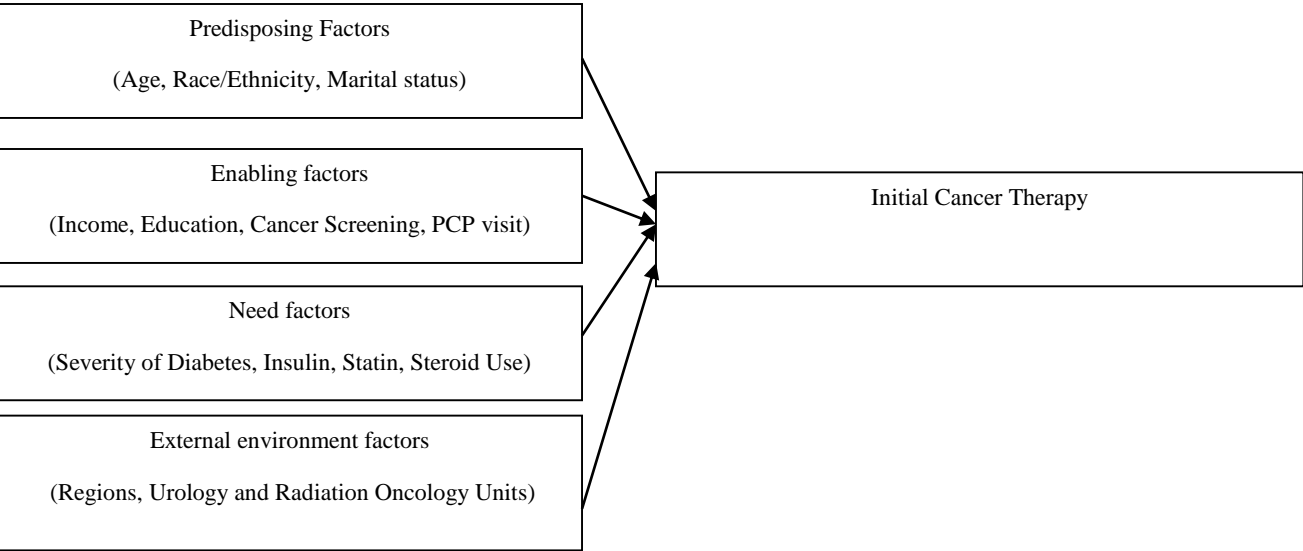
Metformin use may also affect the types of initial cancer treatment. The initial cancer treatment is often determined by the stage of diagnosis, life expectancy of an individual and pre-existing chronic conditions (17). However, in the light of recent findings about the anti-cancer properties of metformin, physicians may take into account the use of metformin when deciding the types of initial cancer treatment among men with diabetes and prostate cancer. For example, metformin down regulates the androgen-receptors levels, which in turn maximizes the anti-cancer properties of hormone therapy (18). Radiation therapy along with metformin has been found to inhibit the progression of cancer and reduce mortality among men with prostate cancer (19). Therefore, among men with prostate cancer and diabetes, metformin users may be more likely to receive radiation therapy or hormone therapy as compared to non-users. However, there are no population-based studies examining the association between metformin use and the types of initial cancer treatment among men with diabetes and incident prostate cancer.

Therefore, the primary objective of the study is to investigate the association between metformin use and cancer stage at diagnosis and the initial cancer treatment among elderly fee-for-service Medicare beneficiaries with T2DM and incident prostate cancer.

3.3 CONCEPTUAL FRAMEWORK

We utilized the ABM model (20) described in chapter 1, for selection of independent variables. The depiction of the current study-specific independent characteristics are provided in *Figure 3.1*.

Figure 3.1: Study Theoretical Framework: Adaptation of Andersen Behavioral Model for Aim 2

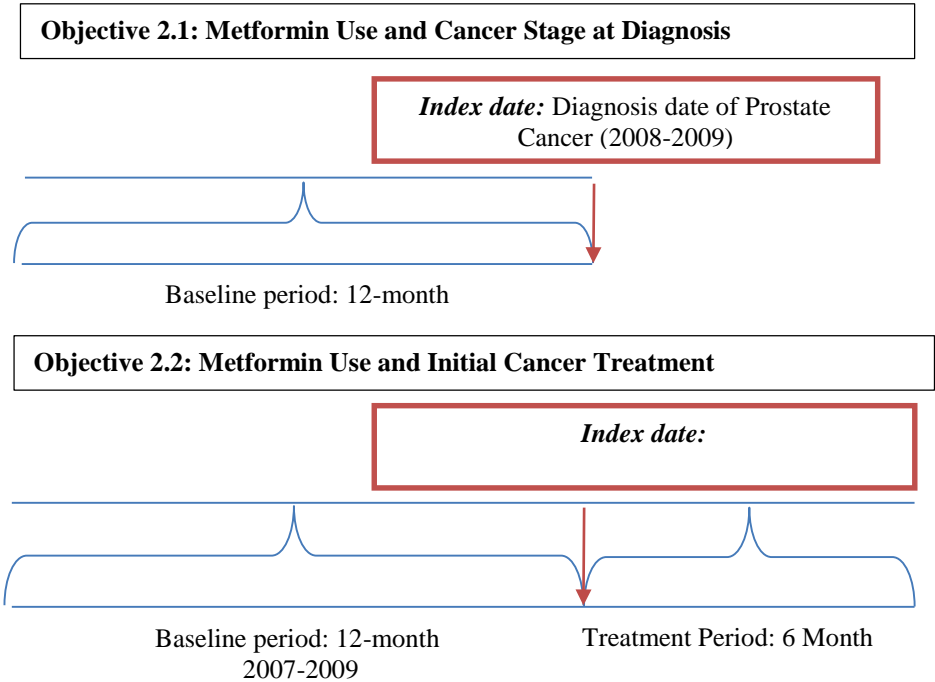


3.4 METHODS

3.4.1 Study Design

A cohort study design was adopted with a baseline and a follow-up period as depicted in *Figure 3.2*. The index date was defined as the date of diagnosis of prostate cancer. The baseline period consisted of 12 months before the index date and the follow-up period consisted of 6 months after the index date. Diabetes, metformin use and other independent variables were identified during the baseline period. The types of initial cancer treatment were identified during the follow-up period.

Figure 3. 2 Schematic Presentation of Study Design for Aim 2



3.4.2 Data Source

Data were derived from the SEER-Medicare linked database, details of which are provided in the Chapter 1.

3.4.3 Study Cohort

The study cohort comprised of 74,791 men with incident prostate cancer diagnosed between 2008 and 2009. We excluded 7,763 cases for the following reasons: diagnosis of prostate cancer during the autopsy; the presence of multiple cancers; carcinoma in-situ; aged 65 years and younger; died during the study period; enrolled in Medicare Health Maintenance Organizations; not continuously enrolled in Medicare PART A, B, and D during the study period, and missing cancer stage at diagnosis. The details on the study cohort selection process are provided in *Appendix 3.I*.

After all the exclusions, the final study cohort consisted of 2,652 elderly men with Type 2 diabetes Mellitus (T2DM) and incident prostate cancer. The presence of T2DM was identified using at least one inpatient visit or two or more physician visits with a primary or a secondary diagnosis codes for T2DM (ICD-9-CM codes: 250. x0 or 250. x2) during the baseline period.

3.4.3 Key Dependent Variable

3.4.3.1 Cancer Stage at Diagnosis

The American Joint Committee on Cancer (AJCC) Tumor-Node-Metastases (TNM) classification was used to identify the stage of prostate cancer from the PEDSF file. Based on the AJCC-TNM systems, men were classified as having localized cancer stage if they had T1 or T2 clinical stage with no regional lymph node (NX-N0) involvement and absence of any distant metastasis (M0) (21). Men were classified as having advanced cancer if they were diagnosed with T3 or T4 clinical stage with or without regional lymph node (N1) or distant metastasis (M1).

3.4.3.2 The initial cancer treatment

The initial cancer treatment categories were identified using both SEER-PEDSF file and inpatient, outpatient and carrier files using validated algorithms (22, 23, 24) during the follow-up period. The details on diagnosis and procedure codes used to identify types of cancer treatment are provided in **Appendix 2.2**. The initial cancer treatment receipt was classified using a hierarchy. Men who received radical prostatectomy (RP) were classified into one group; among men who did not receive RP, receipt of radiation therapy (RT) was considered; among men who did not receive RT, hormone therapy was considered. The final classification consisted of men who: 1) received RP; 2) received RT alone or RT with hormone therapy; 3) those who received only hormone therapy, and 4) those who did not receive any RP, RT or hormone therapy. This hierarchical classification was adopted to reflect clinical practices in the real-world settings (25, 26) .

3.4.4 Key Independent Variable

3.4.4.1 Metformin Use

Metformin use was identified using the Medicare Part-D files. Metformin prescriptions were identified using the national drug codes (NDCs). Men with at least one prescription for metformin during the baseline period were considered as metformin users and men without any prescriptions for metformin were considered as non-users.

3.4.5 Other Independent Variables

3.4.5.1 Predisposing characteristics

Predisposing characteristics consisted of age at diagnosis, race, and marital status. These were identified from the PEDSF file. Age at the time of diagnosis was categorized into two groups (66 to 74 years, ≥ 75 years). Race/ethnicity was categorized into four groups: White, African American, Latino, and other. Marital status was categorized into four groups: Married, Divorced/Separated, Unmarried, and Others.

3.4.5.2 Enabling characteristics

Enabling characteristics were: education, income, PSA test, visits to primary care physicians, and medication coverage gap. Median income and median education at the census tract of residence were derived from the PEDSF file. Income and education were measured by quartiles. The receipt of PSA test was identified using the following HCPCS codes: 84152, 84153, 84154, and G0103 using the Medicare carrier files during the baseline period. The presence or absence of primary care visits during the baseline was identified using the provider specialty codes (27).

Medication coverage gap (i.e. donut hole) was identified at the time of prostate cancer diagnosis. Coverage gap was defined as follows: 1) donut hole not reached at the time of cancer diagnosis; 2) in donut hole at the time of cancer diagnosis; and 3) out of donut hole at the time of cancer diagnosis.

3.4.5.3 Need characteristics

The severity of diabetes, insulin use, statins use and corticosteroid use were considered as need factors. The Diabetes Complications Severity Index (DCSI) was calculated using the modified algorithm by Chang *et al.* (28). The DSCI is based on seven categories: retinopathy, nephropathy, neuropathy, cerebrovascular, cardio-vascular, peripheral vascular disease, and metabolic conditions. Based on the severity of particular types of complications, a score of 1 or 2 were assigned to each of the seven categories, with a total DCSI score ranging from 0 to 13. The DCSI scores were grouped into quartiles. Details of the ICD-9-CM codes and the scoring algorithm are provided in **Appendix 3.2**. The use of

insulin, statins, and corticosteroids were identified using the NDCs recorded in the Medicare Part D files during the baseline period.

3.4.5.4 External environment characteristics

The SEER data has 18 registries/regions which were categorized into four regions: 1) Northeast with two registries of Connecticut, and New Jersey; 2) South, with five registries of Kentucky, Louisiana, Atlanta, Rural Georgia, Greater Georgia; 3) North-Central with two registries of Detroit and Iowa; and 4) West with Hawaii, New Mexico, Seattle-Puget Sound, Utah, San Francisco-Oakland, San Jose-Monterey, Los Angeles, Greater California, Arizona, Alaska, and Cherokee Nation (29). The number of radiation oncology units, and urology units at the county-level (converted into quartiles) were also included (29).

3.5 STATISTICAL ANALYSES

Significant group differences in the study population characteristics by metformin use was examined with chi-square tests. A binary logistic regression was used to determine the associations between predisposing, enabling, need, and external environment characteristics and metformin use. C-statistics and area under the curve were used to assess the model fit. Logistic regression was used to derive inverse probability treatment weights (IPTW) and these IPTWs were used to control for the observed selection bias in regressions on the cancer stage and the initial cancer treatment.

Significant unadjusted associations between metformin use and cancer stage at diagnosis and the initial cancer treatment were examined with chi-square tests. The IPTW-adjusted multivariable logistic regression and multinomial logistic regression were used to analyze the relationship between metformin use and cancer stage at diagnosis and the initial cancer treatment respectively. As the odds ratios and relative risk are approximately similar for the events with low prevalence such as advanced prostate cancer ($\leq 10\%$) (30), these terms risk ratio or odds ratio of advanced prostate cancer were used interchangeably. All statistical analyses were carried out using *Statistical Analysis System* (SAS) version 9.4 (SAS Institute Inc., Cary, NC).

3.6 RESULTS

3.6.1 Description of the Study Cohort

The study cohort consisted of 2,757 elderly men with pre-existing diabetes and incident prostate cancer between 2008 and 2009. **Table 3.1** represents the characteristics of the study cohort. An overwhelming majority of men were whites (92.3); 59.7% were diagnosed with prostate cancer between the ages of 66 and 74 years; 58.6% were married and 46.2% resided in the Western region of the US. Nearly three-quarters (70.0%) of study cohort had a primary care visit. An overwhelming majority (91.1%) had PSA tests during the baseline period.

3.6.2 Description of the Study Cohort by Metformin Use

Table 3.1 also summarizes the characteristics of the study cohort by metformin use. Overall, 35.6% of the study cohort had at least one prescription of metformin during the baseline period. Significant differences in predisposing, enabling, need and external environment factors by metformin use were observed.

Table 3.2 describes the adjusted odds ratios (AOR) and 95% CI for the metformin use among elderly men with diabetes and prostate cancer. Elderly men aged 66 to 74 years as compared to those with 75 years and older (AOR: 1.31, 95% CI: 1.10, 1.56), Latinos as compared to Whites (AOR: 1.62, 95% CI: 1.12, 2.34), those who received insulin as compared to no insulin (AOR: 2.95, 95% CI: 1.94, 4.49), those who received statins as compared to no statins (AOR: 1.94, 95% CI: 1.63, 2.31) were more likely to receive metformin. Whereas, elderly men with a severe DCSCI score (4 to 13) were less likely to receive metformin as compared to those with zero or one DCSCI score (AOR: 0.65, 95% CI: 0.51, 0.84).

3.6.3 Metformin and Cancer Stage at Diagnosis

Table 3.3 describes the relationship between metformin use and cancer stage at diagnosis among elderly men with prostate cancer and diabetes. Overall, 93.7% of the study population were diagnosed with localized prostate cancer; 6.3% were diagnosed with advanced prostate cancer. We did not observe a statistically significant difference in the rates of localized or advanced prostate cancer at diagnosis by metformin use.

Table 3.3 also reports unadjusted odds ratios (OR) and adjusted ORs (AOR) from IPTW logistic regressions for the advanced prostate cancer among elderly men with diabetes and prostate cancer. In unadjusted logistic regression, we observed a significant association between metformin and risk of advanced prostate cancer at diagnosis (OR: 0.69, 95% CI: 0.49, 0.95). After adjusting for predisposing, enabling, need and external-environment factors among elderly men with prostate cancer and diabetes, metformin use was significantly associated with a reduction in the risk of advanced prostate cancer (AOR: 0.68, 95% CI: 0.48, 0.97).

3.6.4 Metformin and the Initial Cancer Treatment

Overall, 72.4% of the study population received either RP/RT or hormone therapy during the six months after the cancer diagnosis. RT was the most received initial cancer treatment in the study population (46.5%), followed by RP (17.4%) and only hormone therapy (8.6%). Nearly one quarter of the study population did not receive any cancer treatment. A greater proportion of the elderly men using metformin received RP (21.3%) as compared to those who did not use metformin (16.6%), whereas, a lower proportion of elderly men using metformin (23.8%) did not receive any cancer treatment as compared to those who did not use metformin (28.5%).

Table 3.4 displays the ORs and AORs from multinomial logistic regressions on the receipt of active treatment of either RP, RT or only hormone therapy among elderly men with prostate cancer and diabetes. In unadjusted analysis, metformin users were 54% more likely to receive the RP as the initial cancer therapy (OR: 1.54, 95% CI: 1.24, 1.92), and RT (OR: 1.20, 95% CI: 1.04, 1.44) as compared to non-metformin users among elderly men with prostate cancer. Even after controlling for predisposing, enabling, need and external environment-related factors, metformin users were 45% more likely to receive RP as compared non-metformin users among elderly men with diabetes and prostate cancer (AOR: 1.45, 95% CI: 1.14, 1.86). The use of metformin was not associated with RT or only hormone therapy among elderly men with diabetes and prostate cancer.

3.5 DISCUSSION

The current study is the first largest population-based study to examine whether the risk of advanced prostate cancer diagnosis is reduced with metformin use among elderly men with pre-existing T2DM and incident prostate cancer in the US. After controlling for the observed selection bias between metformin users and non-users and other independent variables, the risk for advanced stage cancer diagnosis is reduced with metformin use among elderly men with T2DM and incident prostate cancer. The current study addressed the limitations of the single population-based examination of metformin use and the cancer stage by incorporating a validated diabetes severity complications index and controlling for the observed selection bias. The current study findings are consistent with the pre-clinical evidence on the role of metformin in prevention of advanced prostate cancer (22) (10). If the findings of the current study are confirmed by other population-based studies, randomized clinical trials can be conducted to establish the causal link between metformin use and risk of advanced prostate cancer diagnosis.

With regards to the initial cancer treatment, the current study findings revealed that the initial cancer treatment with RP or RT or hormone therapy was very common (72.4%) among elderly men with T2DM and incident prostate cancer. In the absence of clear guidelines for management of prostate cancer among men with diabetes, the choice of initial cancer treatment has been a subject of debate. Active treatment is often not preferred because elderly men with T2DM and incident prostate cancer may be at higher risk for mortality due to cardiovascular conditions than mortality due to prostate cancer (31). Additionally, RP can lead to increased surgical complications as well as greater risk of bowel, and urinary dysfunction (32, 33). Therefore, the benefits of RP should be considered after taking into account the harms associated with the active treatment for prostate cancer.

Although the clinical evidence suggests that RT (19) or hormone therapy (34) augmented with metformin are associated with better clinical outcomes as compared to those without metformin, the current study did not find a statistically significant associations between metformin use and the receipt of RT or hormone therapy. It is plausible that the choice of initial cancer treatment may be solely determined based on age, stage of cancer, and pre-existing chronic conditions and metformin use may not have been considered. The reasons for the positive association between metformin use and RP could not be examined

due to the inherent limitations of the claims data analysis. In the future, studies need to be conducted to identify the reasons for the higher rates of RP among metformin users as compared to non-users, among elderly men with T2DM and incident prostate cancer.

It should be noted that the current study controlled for the observed selection bias because metformin users and non-users were significantly different with respect to their predisposing, enabling, need, and external environment characteristics. Without adjustments for the observed selection bias, there was not a statistically significant difference in the cancer stage between metformin users and non-users. Therefore, accounting for the observed selection bias is important in establishing an association between metformin use and the reduction in the risk of advanced prostate cancer diagnosis.

The current study has a number of strengths. First, the large cohort size and high quality data on the clinical and pathological features of cancer at the time of diagnosis enabled us to examine not only the association between metformin use and the cancer stage diagnosis but also the initial choice of cancer treatment (35). Furthermore, the inclusion of variable on severity of diabetes using a validated method enabled to control and relate the effect of severity of disease on the risk of advanced prostate cancer at diagnosis and receipt of initial cancer treatment.

The current study has some limitations as well. The prescription claims for metformin and other drugs were used. Filling the prescriptions cannot be equated to the actual use of these drugs. The study population consisted of elderly men residing in SEER-Regions and enrolled as fee-for-services Medicare Beneficiaries, therefore, one cannot generalize the study finding to younger men or all Medicare beneficiaries with incident prostate cancer in the US. Information on many important prognostic factors such as body-mass index and smoking could not be adjusted; these factors may be associated with an increased risk of advanced prostate cancer diagnosis. Duration of metformin use could not be adjusted due to data limitations. Future studies need to examine whether a greater duration of metformin use is associated with a decrease in the risk of advanced prostate cancer at diagnosis. As the study population was restricted to elderly men with T2DM, the current study findings cannot be generalized to men without T2DM and incident prostate cancer.

3.7 CONCLUSIONS

Metformin use was associated with a statistically significant reduction in the risk advanced prostate cancer diagnosis among elderly men with T2DM and incident prostate cancer. Among elderly men with T2DM and incident prostate cancer, RP was more likely among metformin users as compared to non-users. No statistically significant associations were observed with regard to metformin use and RT or hormone therapy.

The current study findings highlight the need for additional studies in this area. Other population-based studies need to be conducted to confirm the study findings. If confirmed, randomized controlled trials can be carried out to examine the causal link between metformin use and the risk of advanced prostate cancer diagnosis. If the findings of the current study are replicated, metformin may be used as a preventive therapy to reduce the risk of aggressive prostate cancer among elderly men with T2DM and incident prostate cancer. Future studies should be conducted to evaluate clinical outcomes of metformin use among elderly men with prostate cancer and diabetes.

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Table 3. 1							
Characteristics of the Study Cohort Elderly Medicare Beneficiaries with Diabetes and Incident Prostate Cancer by Metformin Use SEER-Medicare-linked Database 2007- 2010							
	Overall		Metformin Users		Non-Metformin User		Sig.
	N	%	N	%	N	%	
All	2,652	100	948	35.7	1,704	64.3	
Predisposing Characteristics							
Age at diagnosis, in years							***
66-74	1,579	59.5	609	64.2	970	56.9	
75+	1,073	40.5	339	35.8	734	43.1	
Race/ethnicity							*
Whites	1,914	72.2	680	71.7	1,234	72.4	
African-American	323	12.2	108	11.4	215	12.6	
Hispanic/Latino	150	5.7	70	7.4	80	4.7	
Others	265	10.0	90	9.5	175	10.3	
Marital status							
Unmarried	222	8.4	73	7.7	149	8.7	
Married	1,550	58.4	581	61.3	969	56.9	
Divorced/Separated	393	14.8	136	14.3	257	15.1	
Others	487	18.4	158	16.7	329	19.3	
Enabling Characteristics							
Quartile of median census 2000 income							*
\$ 7- \$ 34,522	664	25.0	265	28.0	399	23.4	
\$ 34,523-46,224	664	25.0	243	25.6	421	24.7	
\$ 46,229-62,764	664	25.0	229	24.2	435	25.5	
\$ 62,767-200,008	660	24.9	211	22.3	449	26.3	
Quartile of median census 2000 education							
0 - 8.52	666	25.1	222	23.4	444	26.1	
8.53-15.16	655	24.7	229	24.2	426	25.0	
15.17-26.09	664	25.0	248	26.2	416	24.4	
26.1-100	667	25.2	249	26.3	418	24.5	
PSA Screening							
Yes	2,415	91.1	872	92.0	1,543	90.6	
No	237	8.9	76	8.0	161	9.4	
Visit to a PCP							
Yes	1,858	70.1	672	70.9	1,186	69.6	
No	794	29.9	276	29.1	518	30.4	
Statin Use							***
Yes	1,576	59.4	656	69.2	920	54.0	
No	1,076	40.6	292	30.8	784	46.0	
Insulin							***
Yes	102	3.8	62	6.5	40	2.3	
No	2,550	96.2	886	93.5	1,664	97.7	
External-Environment Characteristics							
SEER-Regions							**
Northeast	487	18.4	146	15.4	341	20.0	
South	570	21.5	223	23.5	347	20.4	
North-Central	351	13.2	112	11.8	239	14.0	
West	1,244	46.9	467	49.3	777	45.6	
(Continued...)							

Table 3. 1
Characteristics of the Study Cohort Elderly Medicare Beneficiaries with Diabetes and Incident Prostate Cancer by Metformin Use SEER-Medicare-linked Database 2007- 2010

	Overall		Metformin Users		Non-Metformin User		Sig.
	N	%	N	%	N	%	
Need Characteristics							
DCSI Quartile							**
0 to 0	846	31.9	305	32.2	541	31.7	
1 to 1	476	17.9	195	20.6	281	16.5	
2 to 3	811	30.6	297	31.3	514	30.2	
4 to 13	519	19.6	151	15.9	368	21.6	

Notes: Based on the data of 2,652 elderly men aged 66 years and older diagnosed with prostate cancer between 2008 and 2009 using a Surveillance, Epidemiology, and End-Results (SEER)-linked Medicare Part D data. Significant group differences by metformin use are based on Chi-square tests. % represented in the column are row percentages.

Abbreviations: DCSI: Diabetes Complication Severity Index; PCP: Primary Care Physician; PSA: Prostate Specific Antigen; Sig: Level of Significance;

*** $p < .001$; ** $.001 \leq p < .01$; * $.01 \leq p < .05$

Table 3. 2			
Adjusted Odds Ratios and 95% Confidence Intervals from Logistic Regressions On Metformin Use among Elderly Medicare Beneficiaries with diabetes Incident Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Data-2007-2010			
	AOR	95% CI	Sig.
Predisposing Characteristics			
Age at Diagnosis			
66-74 years	1.31	[1.10,1.56]	**
75 years or above	Ref		
Race/ethnicity			
Whites	Ref		
African-American	0.91	[0.69,1.21]	
Latino	1.62	[1.12,2.34]	**
Others	0.80	[0.59,1.10]	
Marital status			
Married	Ref		
Unmarried	0.81	[0.59,1.11]	
Divorced/Separated	0.94	[0.74,1.20]	
Others	0.83	[0.66,1.04]	
Enabling Characteristics			
Quartile of median census 2000 income			
\$ 7- \$ 34,522	1.72	[1.20,2.46]	**
\$ 34,523-46,224	1.34	[0.97,1.84]	
\$ 46,229-62,764	1.18	[0.89,1.56]	
\$ 62,767-200,008	Ref		
Quartile of median census 2000 education			
0 - 8.52	1.24	[0.87,1.77]	
8.53-15.16	1.21	[0.90,1.62]	
15.17-26.09	1.18	[0.92,1.51]	
26.1-100	Ref		
Visit to a PCP			
Yes	1.12	[0.92,1.35]	
No	Ref		
Statin Use			
Yes	1.94	[1.63,2.31]	***
No	Ref		
Insulin			
Yes	2.95	[1.94,4.49]	***
No	Ref		
Need-Factors			
DCSI Quartile			
0 to 1	Ref		
2 to 2	1.13	[0.89,1.44]	
3 to 3	0.98	[0.79,1.21]	
4 to 13	0.65	[0.51,0.84]	***
External-Environment Characteristics			
SEER-Regions			
Northeast	Ref		
South	1.40	[1.06,1.85]	*
North-Central	1.07	[0.78,1.47]	
West	1.37	[1.08,1.75]	*

Notes: Based on the data of 2,652 elderly men aged 66 years and older diagnosed with prostate cancer between 2008 and 2009 using a Surveillance, Epidemiology, and End-Results (SEER)-linked Medicare Part D data. Significant group differences are based on log-likelihood test for metformin use.

Abbreviations: DCSI: Diabetes Complication Severity Index; PCP: Primary Care Physician; Ref: Reference group; Sig: Level of Significance;

*** p < .001; ** .001 ≤ p < .01; * .01 ≤ p < .05

Table 3. 3					
Number and IPTW-Adjusted Percentage of Men with Localized Versus and Advanced Stage of Prostate Cancer by Metformin Use Elderly Medicare Beneficiaries with Diabetes and Incident Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database-2007-2010					
	Localized		Advance		Sig.
	N	Weighted %	N	Weighted %	
Overall	2,493	93.7	159	6.3	
Metformin Use					*
Yes	902	95.3	46	4.7	
No	1,591	93.3	113	6.7	
Unadjusted and Adjusted Odds Ratios and 95% Confidence Intervals from I (IPTW) Logistic Regressions for Advanced Stage at diagnosis of Cancer					
Advanced Stage At Diagnosis					
IPTW					
Unadjusted Odds Ratios and 95% Confidence Intervals					
	OR	95% CI	Sig.		
Metformin					
Yes	0.69	[0.49,0.95]	*		
No	Ref				
Adjusted Odds Ratios and 95% Confidence Intervals					
	AOR	95% CI			
Metformin					
Yes	0.68	[0.48,0.97]	*		
No	Ref				

Notes: Based on the data of 2,652 elderly men aged 66 years and older diagnosed with prostate cancer between 2008 and 2009 using a Surveillance, Epidemiology, and End-Results (SEER)-linked Medicare data. % are weighted percentage for IPTW. Significant difference are based on the log-likelihood test using a logistic regression with IPTW weights. Adjusted model controlled for predisposing, enabling, need and external-environment related factors.

Abbreviations: IPTW: Inverse Probabilities Treatment Weights; PSA: Prostate Specific Antigen Level; PCP; Primary Care Physician Visit Sig: Level of Significance; *** $p < .001$; ** $.001 \leq p < .01$; * $.01 \leq p < .05$

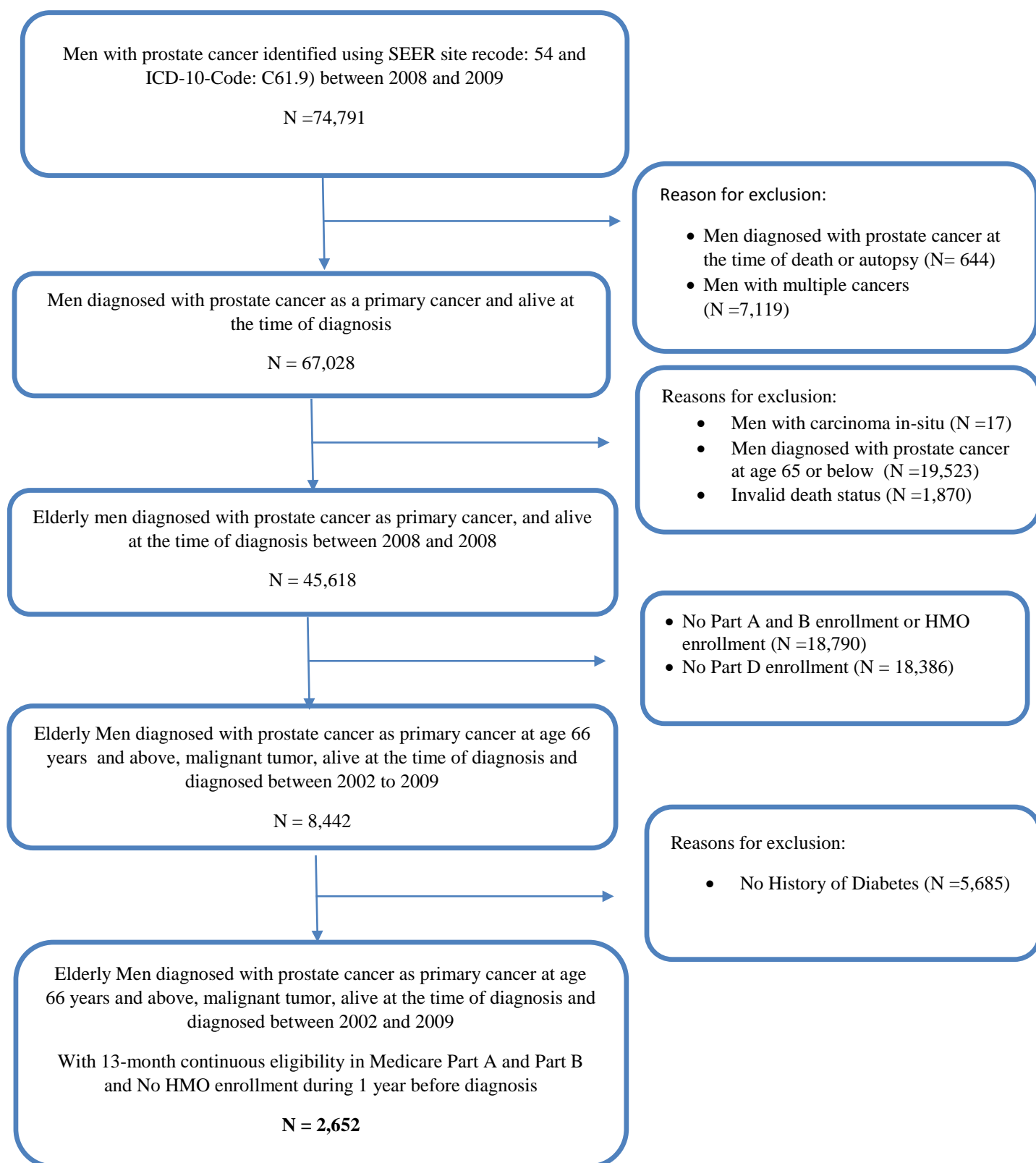
Table 3. 4									
Numbers and IPTW-Adjusted Percentages of the Initial Cancer Treatment Categories By Metformin Use Elderly Medicare Beneficiaries with Diabetes and Incident Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database-2007-2010									
Initial Cancer Treatment									
	RP		RT		Hormone only		None		Sig.
	N	Wt %	N	Wt %	N	Wt %	N	Wt. %	
All	503	17.4	1,273	46.5	214	8.6	662	27.6	**
Metformin Use									
Yes	211	21.3	457	46.6	71	8.6	209	23.8	
No	292	16.3	816	46.4	143	8.7	453	28.5	
Unadjusted and Adjusted Odds Ratios and 95% Confidence Intervals (CI) from IPTW-adjusted Multinomial Logistic Regressions on Initial Cancer Treatment (Reference Group = No Cancer Treatment)									
Unadjusted Odds Ratios and 95% Confidence Intervals									
	RP		Sig.	RT		Sig.	Hormone Therapy		Sig.
	OR	95% CI		OR	95% CI		OR	95% CI	
Metformin Use									
Yes	1.54	[1.24,1.92]	***	1.20	[1.04,1.44]		1.18	[0.89,1.56]	
No	Ref			Ref			Ref		
Adjusted Odds Ratios and 95% Confidence Intervals (CI)									
	RP		Sig.	RT		Sig.	Hormone Therapy		Sig.
	AOR	95% CI		AOR	95% CI		AOR	95% CI	
Metformin									
Yes	1.45	[1.14,1.86]	**	1.08	[0.89,1.32]		1.15	[0.85,1.56]	
No	Ref			Ref			Ref		

Notes: Based on the data of 2,652 elderly men aged 66 years and older diagnosed with prostate cancer between 2008 and 2009 using a Surveillance, Epidemiology, and End-Results (SEER)-linked Medicare Part D data. Significant group differences by metformin use are based on Chi-square tests. % represented in the column are weighted percentages. Adjusted model controlled for predisposing, enabling, need and external-environment related factors.

Abbreviations: IPTW: Inverse-Probability Treatment Weights; RP: Radical Prostatectomy; RT: Radiation Therapy; Sig: Level of Significance, Wt: Weighted percentage.

*** $p < .001$; ** $.001 \leq p < .01$; * $.01 \leq p < .05$

Appendix 3. 1 Study Cohort Development Flow diagram for Study Population of Elderly Medicare Beneficiaries diagnosed with Prostate Cancer and Diabetes



Appendix 3. 2

Codes and Algorithms to Identify Diabetes Severity Diabetes Complication Severity Index (DCSI) developed by Young *et al.* and modified by Chang *et al.*

Complications	ICD-9 CM Code	DCSI Score
Retinopathy		
Diabetic ophthalmologic disease	250.5x	1
Background retinopathy	362.01	1
Other retinopathy	362.1	1
Retinal edema	362.83	1
CSME	362.53	1
Other rerinal disorders	362.81, 362.82	1
Proliferative retinopathy	362.02	2
Retinal detachment	361.xx	2
Blindness	369.xx.00-.99	2
Vitreous hemorrhage	379.23	2
Nephropathy		
Diabetic nephropathy	250.4	1
Acute glomerulonephritis	580	1
Nephrotic syndrome	581	1
Hypertension, nephrosis	581.81	1
Chronic glomerulonephritis	582	1
Nephritis/nephropathy	583	1
Chronic renal failure	585	
Renal failure NOS	586	
Renal insufficiency	593.9	
Neuropathy		
Diabetic nephropathy	356.9, 250.6	1
Amyotrophy	358.1	1
Cranial nerve palsy	951.0, 951.1, 951.3	1
Mononeuropathy	354.0-355.9	1
Charcot's arthropathy	713.5	1
Polyneuropathy	357.2	1
Cerebrovascular		
TIA	435	1
Stroke	431, 433, 434, 436	2
Cardiovascular		
Atherosclerosis	440.xx	1
Other IHD	411	1
Angina pectoris	413	1
Other chronic IHD	414	1
Myocardial infarction	410	2
<i>(Continued..)</i>		
Ventricular fibrillation, arrest	427.1, 427.3	2
Atrial fibrillation, arrest	427.4, 427.5	2
Other ASCVD	429.2	1
Old myocardial infarction	412	2

Appendix 3. 2

Codes and Algorithms to Identify Diabetes Severity Diabetes Complication Severity Index (DCSI) developed by Young *et al.* and modified by Chang *et al.*

Complications	ICD-9 CM Code	DCSI Score
Heart failure	428	2
Atherosclerosis, severe	440.23, 440.24	2
Aortic aneurysm/dissection	441	2
Peripheral vascular disease		
Diabetic PVD	250.7	1
Other aneurysm, LE	442.3	1
PVD	443.81, 443.9	1
Foot wound + complication	892.1	1
Claudication, intermittent	443.9	1
Embolism/thrombosis (LE)	444.22	2
Gangrene	785.4	2
Gas gangrene	0.4	2
Ulcer of lower limbs	707.1	2
Metabolic		
Ketoacidosis	250.1	2
Hyperosmolar	250.2	2
Other coma	250.3	1

Note: The table is adapted from the previous algorithm defined by Young et al. and modified by Chang et al. to identify the severity of diabetes using claims database. Severity index was based on a scale ranging from 0 to 2 for each complication as follows: 0 = no abnormality, 1 = some abnormality, 2 = severe abnormality.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CSME, cystoid macular edema/degeneration; DCSI, Diabetes Complications Severity Index; IHD, ischemic heart disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; LE, lower extremity; NOS, not otherwise specified; PVD, peripheral vascular disease; TIA, transient ischemic attack.

Chapter 4

Impact of Prostate Cancer Diagnosis on Non-Cancer Hospitalizations by Types of Chronic Conditions among Elderly Medicare Beneficiaries with Incident Prostate Cancer

4.1 ABSTRACT

OBJECTIVES: To analyze the impact of cancer diagnosis on non-cancer hospitalizations by comparing them between the pre- and post-cancer period in a cohort of fee-for-service Medicare beneficiaries with incident prostate cancer. The study additionally examined the impact of cancer diagnosis on non-cancer hospitalizations by the types of pre-existing chronic conditions, after controlling for the predisposing, enabling, need, and external environment factors.

METHODS: A population-based retrospective cohort study was conducted using the Surveillance, Epidemiology and End-Results (SEER) -Medicare linked database for the years 2000 to 2010. The study cohort consisted of 57,489 elderly men (≥ 67 years) with incident prostate cancer. Non-cancer hospitalizations were identified in six time periods (t_1 - t_6) before and after the incidence of prostate cancer. Each time period consisted of 120 days. Time periods 1, 2, and 3 represented the pre-cancer period, and time periods 4, 5, and 6 represented the post-cancer period. For each time period, non-cancer hospitalizations were defined as inpatient admissions with primary diagnosis codes not related to prostate cancer.

The types of chronic conditions were grouped into the following seven mutually exclusive categories: (1) only cardio-metabolic conditions; (2) only mental health conditions; (3) only respiratory conditions; (4) cardio-metabolic and mental health conditions; (5) cardio-metabolic and respiratory conditions; (6) all three-cardio-metabolic, mental health, and respiratory conditions, and 7) none of the three types of chronic conditions. Individuals who were diagnosed with new chronic conditions during the pre- and post-cancer periods were excluded. Selection of other independent variables was based on the ABM model and consisted of the predisposing (age, race/ethnicity, and marital status), enabling (income, education, cancer-treatment, and primary care visit), need (number of other chronic conditions), and external environment (region, number of oncology and urology unit in a county) factors.

Bivariate and multivariate comparisons of the rates of non-cancer hospitalizations between the pre- and post-cancer period accounted for repeated measures design. Multivariable regressions were performed using the generalized estimating equation (GEE) technique with logit link function. The extent to which the pre- and post-cancer period non-cancer hospitalizations differed by the types of chronic conditions, after controlling for other independent variables, are reported in terms of the estimated probabilities from the GEE models.

RESULTS: The rate of non-cancer hospitalizations during the post-cancer period was higher as compared to the pre-cancer period. For example, the rates were 9.2% during the post-cancer period, t_4 (i.e. 120 days immediately after the diagnosis of incident cancer) and 3.8% during the pre-cancer period, an increase of 5.4 percentage points. After accounting for correlations due to repeated measures and unadjusted model, elderly men were 77% more likely to have any non-cancer hospitalizations during the post-cancer period as compared to the pre-cancer period (Odds Ratio, OR: 1.77, 95% Confidence Interval, CI: 1.71, 1.82). After adjusting for predisposing, enabling, need and external-environment-related factors, elderly men were 80% more likely to have non-cancer hospitalizations during the post-cancer period as compared to pre-cancer period (Adjusted OR, AOR: 1.80, 95% CI: 1.75, 1.86).

For all categories of chronic conditions, the rates of non-cancer related hospitalizations were higher during the post-cancer period as compared to the pre-cancer period. For example, among elderly men with all the three types of chronic conditions, the rates were 26.5% during the post-cancer period (t_4) and 15.1% during the pre-cancer period (t_1), an increase of 11.4 percentage points. Among elderly men with none of the chronic conditions, the rates were 5.8% during the post-cancer period (t_4) and 1.4% during the pre-cancer period (t_1), an increase of 4.4 percentage points. . After adjusting for correlations due to repeated measures, elderly men with all the three types of chronic conditions had the greatest increase in the rates of non-cancer hospitalizations during the post-cancer period as compared to the pre-cancer period. Elderly men with none of the three types of chronic conditions had the lowest increase in the rates of non-cancer hospitalizations in the post-cancer period as compared to the pre-cancer period.

CONCLUSIONS: Elderly men with prostate cancer had a significant increase in the risk of non-cancer hospitalizations after the diagnosis of prostate cancer. For all chronic condition categories, there was an

increase in non-cancer hospitalizations during the post-cancer period as compared to the pre-cancer period. Elderly men with all the three types of chronic conditions had the greatest increase in non-cancer hospitalizations compared to all other chronic condition categories.

IMPLICATIONS: The study findings highlight the negative impact of cancer diagnosis on the risk for non-cancer hospitalizations among men with prostate cancer pre-existing chronic conditions. The risk for non-cancer hospitalizations was the highest among those with pre-existing chronic conditions that span multiple organ systems. Future studies need to evaluate whether appropriate management of the pre-existing conditions can reduce the risk of non-cancer hospitalization during the post-cancer period.

4.2 INTRODUCTION

The period immediately following a cancer diagnosis can be considered as a period of turbulence for the management of pre-existing chronic conditions. As pointed out by Piette *et al.*, cancer is often considered as a dominant condition that eclipses the management of all other chronic conditions (1). It has been reported that among individuals with cancer, the management of conditions that are not related to cancer may be neglected (2). Undermining the management of chronic conditions among individuals with any cancer may result in adverse outcomes and poor quality of care for non-cancer related conditions. One study among elderly men with prostate cancer found that men with prostate cancer received poor-quality of non-cancer management (3). However, this study did not examine the relationship between non-cancer related hospitalizations and pre-existing chronic conditions.

It is important to examine hospitalizations among elderly men with prostate cancer as they indicate a worsening of existing conditions to the point of requiring immediate attention for monitoring and management in an inpatient environment. In addition, hospitalizations have been associated with significant mortality and healthcare costs (4). In 2012, \$892.4 billion was spent on hospitalizations in the US and hospitalization expenditures were expected to increase by 5% every year (5). Therefore, the rate of non-cancer hospitalizations among the elderly with prostate cancer not only reflect the hospitalizations for non-cancer related conditions, but also reflect enormous financial burden to the US healthcare system.

Among men of all ages with prostate cancer, many hospitalizations are attributable to chronic conditions other than prostate cancer. For example, using the encounter-level data for the years 1997 through 2004, Milenkovic *et al.* found that among adults with prostate cancer, 84% of the inpatient encounters were for chronic conditions other than prostate cancer (6). An overwhelming majority of these inpatient encounters (90%) was observed among elderly men aged 65 years or older. However, the study investigators did not provide any information on the impact of cancer diagnosis on non-cancer hospitalizations. Furthermore, the study used encounter-level data rather than patient-level data ignoring multiple hospitalizations by the same individual. Thus, the impact of prostate cancer diagnosis on the hospitalizations due to conditions other than cancer remains unknown.

The initial treatment of prostate cancer may also increase the risk of hospitalizations among elderly men with prostate cancer. Many observational studies have shown a positive association between use of androgen deprivation therapy (ADT) or radiation therapy (RT) and hospitalizations for cardio-metabolic conditions among men with prostate cancer (7-9), (10). However, these studies included a population with established prostate cancer and examined the risk of hospitalizations only for specific non-cancer hospitalizations. Furthermore, these studies did not investigate the association between cancer diagnosis and non-cancer hospitalizations.

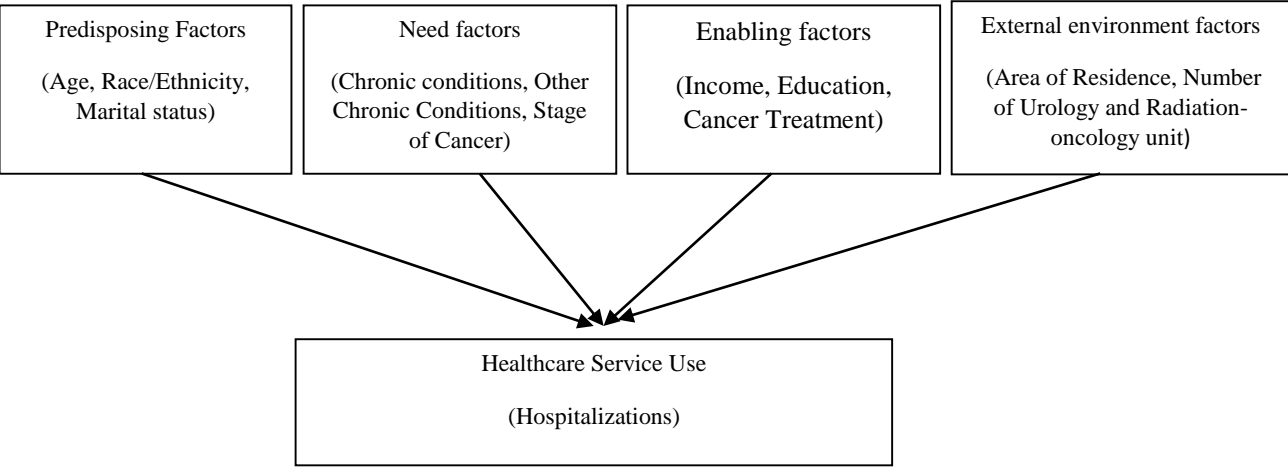
It is important to analyze the association between cancer diagnosis and the risk for non-cancer hospitalizations by types of chronic conditions. Elderly men with prostate cancer have differential rates of chronic conditions. For example, cardio-metabolic conditions (example: heart disease and diabetes) are observed in 18.1% of men with prostate cancer, followed by respiratory conditions (example: chronic obstructive pulmonary disease-9.8%) (11) and mental health conditions (example: depression-8%) (12). Thus, the risk for hospitalizations may differ by the types of chronic conditions. One study, not specific to prostate cancer, reported that individuals with cardio-metabolic conditions had higher rates of annual hospitalizations (40%) as compared to those with respiratory conditions (20%) among adults aged 50 years and older in the US (13). The incidence of prostate cancer can have varying impact on the risk for non-cancer hospitalizations among men different types of pre-existing chronic conditions. Therefore, it is important to analyze the impact of cancer diagnosis on the risk of non-cancer hospitalizations by the types of pre-existing chronic conditions among elderly men diagnosed with prostate cancer.

An understanding of the risk of non-cancer hospitalization risk after the diagnosis of cancer for those with incident prostate cancer can inform surveillance efforts and the management of chronic conditions among elderly men with prostate cancer. Therefore, the primary objectives of the current study are to analyze the impact of cancer diagnosis on non-cancer hospitalizations among elderly men with incident prostate cancer and examine whether the impact of cancer diagnosis on non-cancer hospitalizations differs by the types of chronic conditions.

4.3 CONCEPTUAL FRAMEWORK

The conceptual framework was based the ABM model, described in Chapter 1. The independent variables for the current study are depicted in the *Figure 4.1*.

Figure 4. 1 Study Theoretical Framework: Adaptation of Andersen Behavioral Model for Aim 3

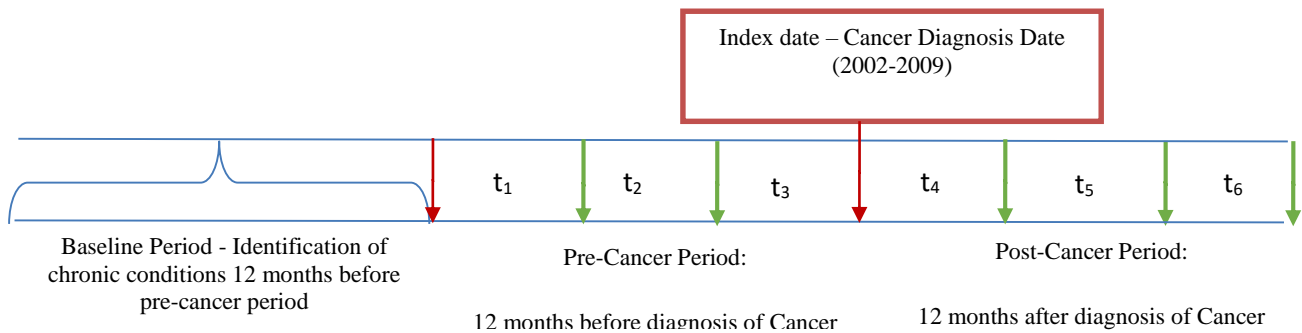


4.4 METHODS

4.4.1 Study Design

A retrospective longitudinal cohort design with baseline, pre and post-cancer periods was used. Using the date of cancer diagnosis as the index date, a 24-month window before the index date was constructed. This 24-month period was split into two 12-month periods (i.e. the baseline and pre-cancer period). This was necessary because identification of pre-existing chronic conditions and non-cancer hospitalizations during the pre-cancer period involved the use of inpatient claims. To avoid circular reasoning, the first 12-month period was used as the baseline period, during which the types of chronic conditions and other independent variables were measured. The 12-month period before the diagnosis of cancer was considered as the pre-cancer period and this period was used to derive non-cancer hospitalizations. The post-cancer period consisted of 12 months after the diagnosis of cancer. However, to ensure a robust study design, the non-cancer hospitalizations were measured repeatedly every 120 days during the pre- and post-cancer period, yielding a total 6 repeated measures per individual. Thus, t_1 , t_2 , t_3 represented the pre-cancer period and t_4 , t_5 , and t_6 represented the post-cancer period. The graphical representation of the study design is shown in *Figure 4.2*.

Figure 4. 2 Study Design for Aim 3



4.4.2 Data Sources

The current study utilized the SEER-Medicare linked database with prostate cancer cases diagnosed between 2002 and 2009 and their linked claims between 2000 and 2010. Please see Chapter 1 for details.

4.4.3 Study Cohort

The study population was based on 289,701 men diagnosed with incident prostate cancer between January 1st 2002 and December 31st 2009. Men with multiple cancers (N =25, 785); diagnosed with prostate cancer during the autopsy (N = 2,944); men younger than 67 years of age and died during the study period (N = 111,643) were excluded. The cohort was further restricted to those with continuous fee-for-service Medicare Part A and Part B enrollment during the entire study period (N = 101,302). To reduce misclassification bias, individuals with newly diagnosed conditions during the pre-cancer and post-cancer periods (N = 40,544) were excluded. After excluding individuals with missing information on race/ethnicity, county, and in-situ, unknown, and advanced cancer stage, the final study cohort comprised of 57,589 elderly men with incident prostate cancer. **Appendix 4.1** provides details of the study cohort development.

4.4.4 Key Dependent Variable: Non-cancer hospitalizations

Inpatient admissions during the pre- and post-cancer periods were derived from the MEDPAR file. Non-cancer hospitalization was defined as any admission to an inpatient facility with a principal diagnosis for conditions other than prostate cancer. Hospitalizations with the primary diagnosis of prostate cancer

(ICD-9 CM codes - 185, 233.4, or V1046) were considered as prostate-cancer-related hospitalizations and were excluded from the analysis (6). This approach is commonly used in published studies to identify disease-specific hospitalizations (4, 14).

However, the challenges in measuring non-cancer hospitalizations should also be noted. Elderly men with prostate cancer may have hospitalizations due to cancer-related complications such as bowel, sexual or urinary dysfunction or cancer-related procedures such as surgery. Therefore, a sensitivity analysis was carried out by excluding hospitalizations for cancer-related complications or primary or secondary procedure codes for cancer-related procedures. As the findings remained consistent between the two definitions, only the results from the primary analyses are reported.

4.4.5 Key Independent Variable: Types of co-occurring chronic condition (One of the need factors)

We classified the common types of chronic conditions using the organ domains (15). We selected this approach because of the synergism in treatment and self-management approaches. For example, the management of cardio-metabolic conditions such as diabetes and heart disease have similar treatment and self-management strategies. Among men with prostate cancer, cardio-metabolic diseases (diabetes and heart disease), respiratory diseases (COPD and asthma), and mental health conditions (depression and other mental conditions) are common. These common chronic conditions were classified into seven mutually exclusive categories: (1) cardio-metabolic conditions only; (2) mental health conditions only; (3) respiratory conditions only; (4) cardio-metabolic and mental health conditions; (5) cardio-metabolic and respiratory conditions; (6) having all the three types of chronic conditions; and 7) having none of the three types of chronic conditions. *Due to insufficient numbers for the category “respiratory and mental health conditions”, this category was excluded from analysis.* All the chronic conditions were identified during the baseline period using one inpatient claim or two outpatient claims for each of the chronic conditions.

4.4.6 Other Independent Variables

4.4.6.1 Predisposing Characteristics

Age, race/ethnicity, and marital status were the predisposing characteristics. Age at the time of diagnosis (67 to 74 years, 75 and above years), race/ethnicity (White, African American, Hispanic, and

other), and marital status (married, divorced/separated, unmarried, and others) were identified from the PEDSF file.

4.4.6.2 Enabling Characteristics

Income, education, access to care and the initial cancer treatment were the enabling factors. The PEDSF file provides 2000 census-tract level information as education level and median income. For our population, we created quartiles of census tract education levels and median income. Access to care was defined using proxy measures in the absence of any direct measures for the same. The proxy measure for access to care was measure with at least one visit to a primary care provider during the baseline period (16).

Receipt of active treatment was identified using inpatient, outpatient and carrier files with appropriate ICD-9 CM diagnostic and procedure codes, CPT or HCPCS codes or Revenue Center code during the six months after the index date (*Appendix 2.2*). Based on previously validated codes, active treatment was either the receipt of radiation, surgery, or hormonal therapy (17, 18). Use of the combination of Luteinizing Hormone Releasing hormone (LHRH) agonist and an anti-androgen during the fourth time period after diagnosis of prostate cancer from inpatient or outpatient or carrier file was labeled as hormone therapy (19). Men who did not have any of the above-mentioned treatment categories were classified as having no cancer treatment. We classified the cancer treatment into four groups based on a hierarchy: 1) Radical Prostatectomy (RP); 2) Radiation Therapy (RT); 3) Hormone Therapy; and 4) None of the RP, RT or hormone therapy.

4.4.6.3 External environment characteristics

External environment characteristics comprised of the individual's region (Northeast, South, North-Central, and West) and county-level healthcare resources such number of radiation-oncology units and urology units. (20). County-level healthcare resources were captured by the number of radiation oncology units and urology units were derived from the AHRF. The description of the AHRF file can be found in chapter 1 in method section.

Need Characteristics:

A very small percentage of men (<5%) had chronic conditions other than the cardio-metabolic, mental-health, and respiratory conditions. Forty-two other conditions were derived using the list of chronic conditions from published literature (1). We calculated the total number of other chronic conditions during the baseline period and categorized as “zero or one condition” and “two or more conditions”.

The American Joint Committee on Cancer (AJCC) Tumor-Node-Metastases (TNM) stage classifications was utilized for staging of prostate cancer. The cohort was restricted to elderly men with no-node positive or non-metastatic prostate cancer. Three groups of cancer stage at diagnosis were created as: 1) T1 or less; 2) T2 and 3) T3 or T4.

4.5 STATISTICAL ANALYSES

As the non-cancer hospitalizations were measured repeatedly during each of the six-time periods, the observations are no longer independent and are correlated. The use of standard methods may lead to erroneous variance estimates because these methods assume “independence of observations”. Therefore, both the bivariate and multivariate comparisons of the rates of non-cancer hospitalizations between the pre- and post-cancer period accounted for correlations due to the repeated measures design.

There are many multivariable methods to account for correlations due to repeated measures. One such model is suggested by Liang et al (21). This method involves the use of the generalized estimating equations (GEE) with specific the correlation-matrix. The general form of the model is given in the equation below.

$$\ln\left(\frac{p_{ij}}{1 - p_{ij}}\right) = \beta_0 + \beta_1 (time_{ij}) + \beta_2 (CC)_i + \dots + \beta_n (N_{th} Variable)_i$$

where p_{ij} denotes the probability of non-cancer hospitalizations for individual i , in time period j . $Time_{ij}$ denotes a specific time period j (pre- or post-cancer period) for an individual, i . CC_i denotes presence of particular types of chronic conditions at baseline period for an individual, i . The model also included other independent variables such as predisposing, enabling, need and external-environment characteristics measured for an individual, i . β s are the regression coefficients to be estimated. As can be

seen from the equation, except for the pre- and post-cancer time periods, none of the other independent variables varied over time and were considered fixed effects.

The GEE approach developed by Liang and Zeger specifies three types of correlation structures - exchangeable, autoregressive, and unstructured –to control for correlations between repeated observations. Exchangeable correlation structure, the most commonly used, assumes that every pair of residuals for a subject have the same correlation. i.e. the same correlation between pairs (t_1, t_3) and (t_4, t_6) for every individual. The autoregressive correlation structure depends on the time separating two repeated events for the same individual. In other words, the correlation for the non-cancer hospitalizations pair (t_1, t_2) may be greater than that of the pair (t_1, t_4) . In the unstructured correlation structure, the correlations between the particular pairs of time periods can be different than any other pairs of time periods. As the parameter estimates of the association between non-cancer hospitalization and types of chronic conditions remained the same under different correlation structures (i.e. autoregressive and unstructured), only the results from GEE models with exchangeable correlation structure are reported. The overall model fit was examined by the quasi-likelihood information criterion (qIC) (22).

For ease of interpretation, the predicted probabilities of non-cancer hospitalizations between the pre-and post-cancer period were compared. These probabilities were calculated using the parameter estimates from the GEE models, assuming an additive effect (23). Statistical analyses using GEE models were carried out in STATA version 13. (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.) The predicted probabilities were derived using the “*margins*” command in STATA-13.

It should be noted that in the current study, the term “risk” is often used to describe the results associated with odds ratios (OR). Although the risk ratio and OR will yield different estimates, for events with low prevalence ($\leq 10\%$) (24) such as non-cancer hospitalizations, these two measures will produce similar results.

4.6 RESULTS

4.6.1 Study Population

The study cohort (N = 57,489) were primarily whites (82.4%), in the age group 67-74 years (58.3%, mean age = 74.6 years, standard deviation = 5.1), and married (68.5%). Most men in the study cohort received treatment for cancer (80.5%). (see **Table 4.1**).

4.6.2 Non-cancer-Hospitalizations during the pre- and post-cancer period

Table 4.2 reports the rates of non-cancer-hospitalizations during each of the time periods. The rates of non-cancer-hospitalizations were the highest during the post-cancer period (t_4 , i.e., 120 days immediately after the cancer diagnosis) and lowest during the pre-cancer period (t_2) (9.2% vs 3.4%), an increase of 5.8 percentage points.

Table 4.2 also shows the rates of non-cancer hospitalizations by the types of chronic conditions. Of all the categories of chronic conditions, the rates of non-cancer hospitalizations during the post-cancer were significantly higher compared to the pre-cancer period. Among elderly men with all three types of chronic conditions, the rates were 26.5% during the post-cancer period (t_4) and 15.1% during the pre-cancer period (t_4), an increase of 11.4 percentage points. Among elderly men with none of the chronic conditions, the rates were 5.8% during the post-cancer period (t_4) and 1.4% during the pre-cancer period (t_1), an increase of 4.4 percentage points. Similar increases were seen for other chronic condition categories.

Table 4.3 displays the ORs and AORs and 95% confidence intervals (CI) using the unadjusted (Model I) and adjusted GEE models (Models II and III) for non-cancer hospitalizations with exchangeable correlation structures. After accounting for the correlations due to repeated measures, model I revealed that elderly men were 77% more likely to have non-cancer hospitalizations during the post-cancer period as compared to pre-cancer period (OR: 1.77, 95% CI: 1.71, 1.82). In model II, with adjustments for only the types of chronic conditions, elderly men were 79% more likely to have non-cancer hospitalizations during post-cancer period (AOR: 1.79, 95% CI: 1.73, 1.84) as compared to the pre-cancer period., In model III,

which controlled for all the independent variables, elderly men were 80% more likely to have non-cancer hospitalizations during the post-cancer period as compared to the pre-cancer period.

4.6.3 Probabilities of Non-cancer hospitalizations by Pre and Post-Cancer Period

Table 4.4 displays the probabilities of non-cancer hospitalizations by the pre-and post-cancer period for the types of chronic conditions. Based on the fully adjusted model (Model III), an increase in the probability of non-cancer hospitalizations was observed for the post cancer period ($p = 0.028$) as compared to pre-cancer period (probabilities, $p: 0.028$ vs. 0.050 , change in $p = .022$).

Elderly men with all the three types of chronic conditions had the greatest increase in the probabilities of non-cancer hospitalizations during post cancer period ($p: 0.121$) as compared to pre-cancer period ($p: 0.159$), whereas, elderly men with none of the types of chronic conditions had the lowest change in the probabilities of non-cancer hospitalizations ($p: 0.021$) during post-cancer period as compared to pre-cancer period ($p: 0.028$). With regard to other chronic condition categories, those with cardio-metabolic conditions alone, those with cardio-metabolic and respiratory conditions, those with cardio-metabolic and mental-health conditions had higher risk of non-cancer hospitalizations during the post-cancer period and pre-cancer period (0.046 vs 0.061 , 0.073 vs 0.097 , 0.067 vs 0.090), respectively.

4.7 DISCUSSION

The current study analyzed the impact of prostate cancer diagnosis on the risk of non-cancer hospitalizations among elderly fee-for-service Medicare beneficiaries with localized incident prostate cancer between 2002 and 2009 using the SEER-Medicare linked database. Till date, the current study is the largest population-based cohort that has examined the risk of non-cancer hospitalizations before and after a diagnosis of prostate cancer among elderly men with incident prostate cancer. We observed many noteworthy findings, which have implications for a better management of pre-existing chronic conditions among men with incident prostate cancer.

Elderly men with an incident prostate cancer had a higher risk of non-cancer hospitalization during the post-cancer period as compared to the pre-cancer period, after controlling for a comprehensive list of risk factors. A closer examination of the rates of hospitalizations over six time periods suggested that the

highest rates of non-cancer hospitalizations occurred during first four months after the cancer diagnosis. There are several plausible explanations for this increased risk. It has been documented that the diagnosis of prostate cancer, by itself, can trigger psychological distress, anxiety and suicidal ideations (39). The increase in the psychological stress may increase the blood levels of epinephrine and norepinephrine resulting in increased heart rate, blood pressure and levels of blood sugars. In fact, studies have shown that acute psychological stress may lead to stimulate inflammatory markers such as interleukins, sex hormones and cortisol levels, which may precipitate into serious conditions such as heart disease (25). Another plausible explanation is that a diagnosis of cancer may eclipse the management of all other chronic conditions and patient care may be centered on cancer treatment and recovery from cancer.

Upon closer examination of our study findings by types of chronic conditions, we found that those with cardio-metabolic conditions alone or combinations of cardio-metabolic conditions with respiratory or mental health conditions had a greater increase in the risk of non-cancer hospitalizations during the post-cancer period as compared to the pre-cancer period. Previous literature suggests that elderly men with pre-existing cardio-metabolic conditions may experience acute emotional or psychological stress, which may lead to greater incidence of cardiovascular events (26, 27), which in turn may lead to increased hospitalizations. It has to be noted that the current study did not include newly-diagnosed chronic conditions, therefore, increased hospitalizations during the post-cancer period for this group may suggest the worsening of pre-existing cardio-metabolic conditions due to prostate cancer diagnosis.

The study findings reinforce the need for more research on management of non-cancer conditions before and after diagnosis of cancer and its effect on the non-cancer hospitalizations among elderly men with pre-existing chronic conditions. Special attention needs to be paid to chronic disease care given during the period immediately following the cancer diagnosis. As elderly men with cardio-metabolic conditions are most vulnerable to increased hospitalizations, research, program, policy, and intervention efforts need to focus on reducing the excess non-cancer hospitalizations in this group.

The study findings have a key methodological implication for estimating cancer-related healthcare utilization. Typically, cancer-related annual utilization among men with prostate cancer is estimated by subtracting the total utilization during the year before cancer diagnosis from the total utilization after in a

year after cancer diagnosis with an assumption of no change of non-cancer related utilizations during pre- and post-cancer period (28-32). The current study findings revealed a greater risk of non-cancer hospitalizations during the year after as compared to the year before the diagnosis of prostate cancer. Therefore, the standard methods of calculating cancer-related utilization may overestimate the cancer-related utilizations.

Our study has many advantages. The current study is one of the very few studies to explore the trajectory of non-cancer outcomes (i.e. hospitalizations) during the pre-cancer and post-cancer period among fee-for-service Medicare beneficiaries with incident localized prostate cancer. To the best of our knowledge, this study is the largest population-based study, which used a comprehensive list of factors using the cancer registry-linked administrative claims data. This study used a robust repeated measures study design. The pre-existing chronic conditions were classified using a conceptual framework adopted by the Department of Health and Human Services (DHHS) for research, program, and policy perspectives.

However, the current study findings need to be interpreted in the context of its limitations. Although, due diligence was given in measuring non-cancer hospitalizations based on previously published studies, one cannot rule out the possibility that some non-cancer hospitalizations may be due to cancer treatment or cancer-related complications. For example, cancer surgery may have led to complications such as the sepsis or other infections, which were considered as non-cancer hospitalizations in the current study. Despite having a large cohort, cell sizes for some chronic conditions were too small to be included in the analyses.

Furthermore, an observational study design was used, which has its own limitations. The study population was restricted to elderly men enrolled in fee-for-service Medicare services only residing in the SEER-regions, therefore, we cannot generalize the study findings to all elderly Medicare beneficiaries with prostate cancer. Although we controlled for a comprehensive list of variables to examine multivariable associations between the risk of non-cancer hospitalizations and incidence of prostate cancer, we were not able to control for other risk factors such as the body-mass index, physical activity, and smoking, which may be associated with greater risk of non-cancer hospitalizations among elderly men with prostate cancer.

4.8 CONCLUSION

Diagnosis of incident prostate cancer was associated with an increase in the risk of non-cancer hospitalizations among elderly men with incident localized prostate cancer. Specifically, those with cardio-metabolic conditions only or those with cardio-metabolic conditions and mental health or respiratory conditions had a higher increase in the risk of non-cancer hospitalizations during the post-cancer period as compared to the pre-cancer period. Future research needs to examine whether better management strategies for cardio-metabolic and other chronic conditions can reduce the increased risk for non-cancer hospitalizations after a diagnosis of prostate cancer.

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Table 4. 1 Characteristics of Elderly Medicare Beneficiaries with Incident Prostate Cancer Surveillance, Epidemiology and End Results (SEER)- Medicare Linked Database 2000 – 2010		
	N	%
All	57,489	100
Types of Chronic Conditions		
CM only	21,712	37.8
MH Only	813	1.4
RSP only	2,277	4.0
CM + MH	1,148	2.0
CM + RSP	5,114	8.9
None	25,811	44.9
All Three	614	1.1
Predisposing Characteristics		
Age at diagnosis, in years		
66-74	33,495	58.3
75+	23,994	41.7
Race/ethnicity		
Whites	47,384	82.4
African-American	6,272	10.9
Hispanic/Latino	1,011	1.8
Others	2,822	4.9
Marital status		
Unmarried	3,654	6.4
Married	39,386	68.5
Divorced/Separated	6,993	12.2
Others	7,456	13.0
Enabling Characteristics		
Quartile of median census 2000 income		
\$ 7- \$ 34,522	14,362	25.0
\$ 34,523-46,224	14,368	25.0
\$ 46,229-62,764	14,369	25.0
\$ 62,767-200,008	14,390	25.0
Quartile of median census 2000 education		
0 - 8.52	14,371	25.0
8.53-15.16	14,376	25.0
15.17-26.09	14,373	25.0
26.1-100	14,369	25.0
Visit to a PCP		
Yes	37,405	65.1
No	20,084	34.9
Active Treatment		
RP	11,520	20.0
RT	29,234	50.9
Hormone Therapy	5,510	9.6
No Treatment	11,225	19.5
External-Environment Characteristics		
SEER-Regions		
Northeast	11,360	19.8
South	14,095	24.5
North-Central	7,288	12.7
West	24,746	43.0
<i>(Continued...)</i>		

Table 4. 1		
Characteristics of Elderly Medicare Beneficiaries with Incident Prostate Cancer		
Surveillance, Epidemiology and End Results (SEER)-		
Medicare Linked Database 2000 – 2010		
	N	%
Quartile of Radiation Oncology		
0 to 1	15,127	26.3
2 to 6	13,203	23.0
7 to 22	14,739	25.6
23 to 147	14,420	25.1
Quartile of Urology Centers		
0 to 3	14,107	24.5
4 to 16	14,390	25.0
17 to 44	14,130	24.6
45 to 343	14,862	25.9
Year of Diagnosis		
2002-2005	28,275	49.2
2006-2009	29,214	50.8
Need Characteristics		
Number of Other Chronic Conditions		
≤ One	38,435	66.9
> One	19,054	33.1
T-Stage		
≤T1	32,063	55.8
T2	23,905	41.6
≥ T3	1,521	2.6

Notes: Notes: Based on 57,489 elderly men, aged 67 years and older, diagnosed with incident prostate cancer between 2002 and 2009 and alive throughout the observation period.

Abbreviations: CM: Cardio-metabolic conditions; MH: Mental health conditions; PCP: Primary Care Physician; RESP: Respiratory conditions; RP: Radical Prostatectomy; RT: Radiation Therapy

	Pre-Cancer Period						Post-Cancer Period					
	t ₁		t ₂		t ₃		t ₄		t ₅		t ₆	
	N	%	N	%	N	%	N	%	N	%	N	%
Overall	2,202	3.8	1,967	3.4	2,244	3.9	5,297	9.2	2,835	4.9	2,875	5.0
Types of Chronic Conditions***												
None***	367	1.4	357	1.4	477	1.8	1,493	5.8	528	2.0	553	2.1
CM only**	1,015	4.7	929	4.3	992	4.6	2,308	10.6	1,331	6.1	1,322	6.1
MH only**	26	3.2	23	2.8	35	4.3	63	7.7	33	4.1	33	4.1
RESP only**	74	3.4	55	2.4	60	2.6	192	8.4	80	3.5	74	3.2
CM + MH**	101	4.6	76	6.6	90	7.8	204	17.8	112	9.8	113	9.8
CM + RESP**	499	9.8	435	8.5	497	9.7	874	17.1	622	12.2	659	12.9
All Three***	120	19.5	92	15.0	93	15.1	163	26.5	129	21.0	121	19.7

Notes: Based on 57,489 elderly men, aged 67 years and older, diagnosed with incident prostate cancer between 2002 and 2009 and alive throughout the observation period. Significant differences in non-cancer hospitalizations over time were tested with Wald chi-square, after accounting for correlations due to repeated measures. % represented in the column are column percentage.

Abbreviations: CM: Cardio-metabolic conditions; MH: Mental illness; Q1-Q6: Quarter1 -6; RESP: Respiratory conditions;

*** p < .001; ** .001 ≤ p < .01; * .01 ≤ p < .05

Table 4. 3
Adjusted Odds Ratios and 95% Confidence Intervals (CI) of
Cancer Diagnosis Period From GEE models on Non-Cancer
Related Hospitalizations Elderly Men with Incident Prostate
Cancer Surveillance, Epidemiology and End Results (SEER)-
Medicare Linked Database-2000-2010

<i>Model 1, adjusting for pre- and post-cancer period</i>			
	OR	95% CI	Sig.
Variable			
Pre-cancer	Ref		
Post-cancer	1.77	[1.71,1.82]	***
<i>Model 2, adjusting for pre- and post-cancer period + Types of Chronic Conditions</i>			
	AOR	95% CI	Sig.
Pre-cancer	Ref		
Post-cancer	1.79	[1.73,1.84]	***
<i>Model 3, adjusting for pre- and post-cancer period + Types of Chronic Conditions + predisposing, enabling, need, and external environment characteristics</i>			
	AOR	95% CI	Sig.
Pre-cancer	Ref		
Post-cancer	1.80	[1.75, 1.86]	***

Notes: Based on 57,489 elderly men, aged 67 years and older, diagnosed with incident prostate cancer between 2002 and 2009 and alive throughout the observation period. Significant differences are based on the log-likelihood test using a repeated measure generalized estimating equations.

AOR: Adjusted Odds Ratio; GEE: Generalized Estimating Equation; OR: Odds Ratio; Sig: Level of Sig: Significance.

*** $p < .001$; ** $.001 \leq p < .01$; * $.01 \leq p < .05$

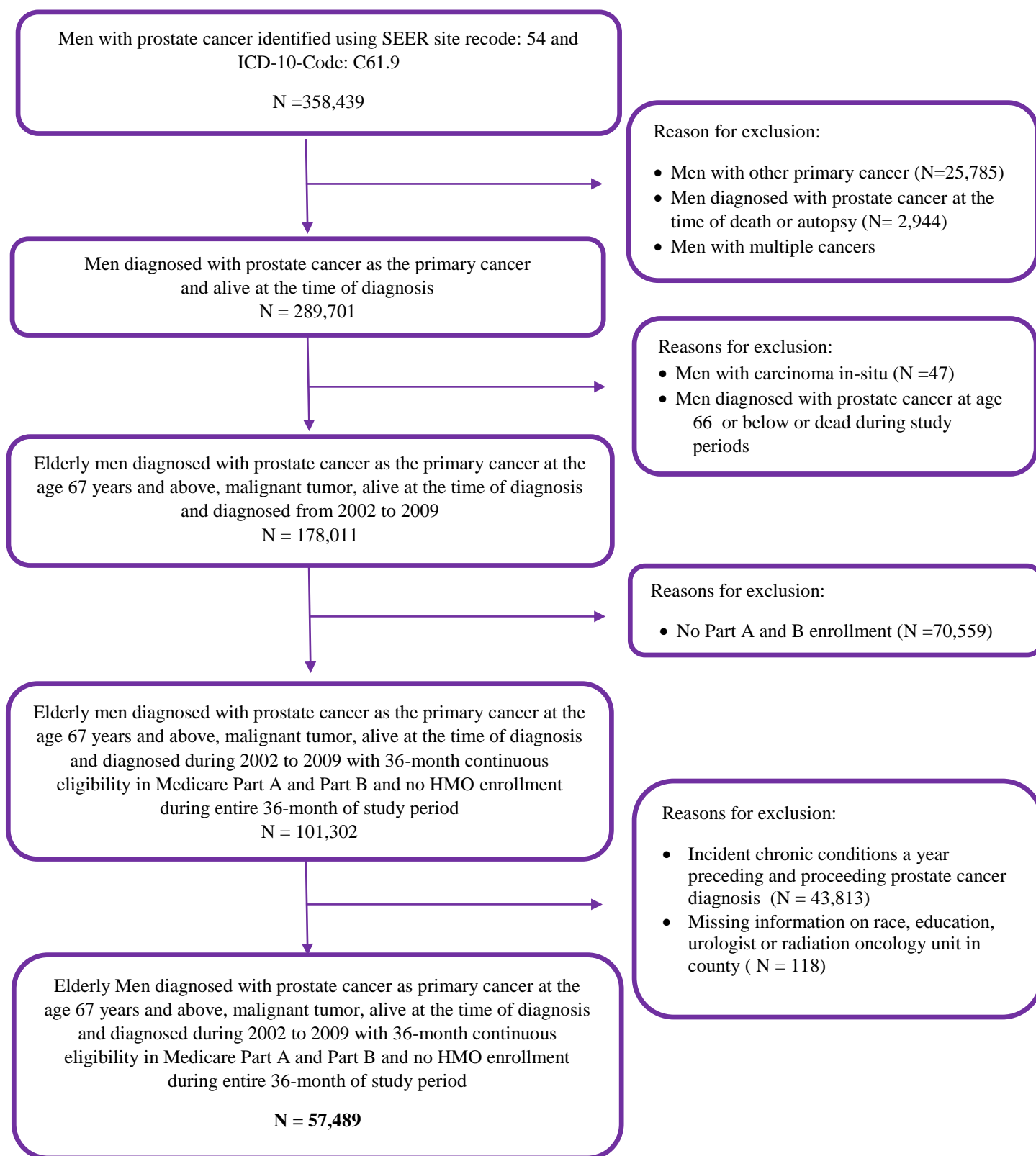
Table 4. 4 Predicted Probabilities with 95% Confidence Intervals for Types of Chronic Conditions From GEE analysis on Non-Cancer Related Hospitalizations Elderly Medicare Beneficiaries with Incident Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database-2000-2010						
	Pre-cancer		Post-cancer		Changes in	Additive
	P	95% CI	P	95% CI	Probabilities	Effect
<i>Model 1, adjusted for pre- and post-cancer period</i>						
Overall***	0.037	[0.036, 0.038]	0.064	[0.063, 0.065]	0.027	
<i>Model 2, adjusted for pre- and post-cancer period + Types of Chronic Conditions</i>						
Overall***	0.031	[0.030, 0.031]	0.055	[0.054, 0.056]	0.024	
Types of Chronic Conditions***						
None	0.018	[0.017, 0.018]	0.031	[0.030, 0.032]	0.013	Ref
CM only	0.044	[0.043, 0.046]	0.077	[0.075, 0.079]	0.033	0.020
MH only	0.032	[0.027, 0.037]	0.055	[0.047, 0.063]	0.023	0.010
RESP only	0.029	[0.026, 0.031]	0.05	[0.045, 0.054]	0.021	0.008
CM + MH	0.075	[0.069, 0.081]	0.127	[0.117, 0.137]	0.052	0.039
CM + RESP	0.087	[0.084, 0.091]	0.146	[0.141, 0.151]	0.059	0.046
All Three	0.150	[0.138, 0.162]	0.239	[0.222, 0.256]	0.089	0.076
<i>Model 3 adjusted for pre- and post-cancer period + Types of Chronic Conditions + predisposing, enabling, need, and external environment characteristics</i>						
Overall***	0.028	[0.027, 0.029]	0.050	[0.049, 0.051]	0.022	
Types of Chronic Conditions***						
None	0.017	[0.017, 0.018]	0.031	[0.030, 0.032]	0.014	Ref
CM only	0.039	[0.038, 0.041]	0.069	[0.067, 0.071]	0.030	0.016
MH only	0.027	[0.023, 0.031]	0.048	[0.041, 0.055]	0.021	0.007
RESP only	0.022	[0.020, 0.024]	0.039	[0.035, 0.043]	0.017	0.003
CM + MH	0.056	[0.051, 0.061]	0.097	[0.089, 0.105]	0.041	0.027
CM + RESP	0.063	[0.061, 0.065]	0.108	[0.103, 0.112]	0.045	0.031
All Three	0.103	[0.095, 0.115]	0.172	[0.159, 0.187]	0.069	0.055

Notes: Based on 57,489 elderly men, aged 67 years and older, diagnosed with incident prostate cancer between 2002 and 2009 and alive throughout the observation period. Significant differences are based on the log-likelihood test using a repeated measure generalized estimating equations.

Abbreviations: CM: Cardio-metabolic conditions; MH: Mental health conditions; RESP: Respiratory conditions; Sig: Level of Significance;

*** $p < .001$; ** $.001 \leq p < .01$; * $.01 \leq p < .05$

Appendix 4. 1 Study Cohort Development Chart for Study Population of Elderly Medicare Beneficiaries diagnosed with Prostate Cancer



Appendix 4. 2 Sensitivity Analysis: Non-cancer hospitalization definition 2-Number and Percentage with Non-Cancer Related Hospitalizations during the Pre- and Post-Cancer Period Elderly Medicare beneficiaries with Incident Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database-2002-2010

	Pre-Cancer Period						Post-Cancer Period					
	t ₁		t ₂		t ₃		t ₄		t ₅		t ₆	
	N	%	N	%	N	%	N	%	N	%	N	%
Overall	2,080	3.6	1,848	3.2	2,109	3.7	2,905	5.1	2,572	4.5	2,664	4.6
Types of Chronic Conditions***												
None***	332	1.3	326	1.3	433	1.7	660	2.6	437	1.7	488	1.9
CM only**	964	4.4	874	4.0	942	4.3	1,311	6.0	1,203	5.5	1,220	5.6
MH only**	24	3.0	21	2.6	34	4.2	29	3.6	30	3.7	30	3.7
RESP only**	71	3.1	49	2.2	58	2.5	96	4.2	72	3.2	68	3.0
CM + MH**	98	8.5	74	6.4	86	7.5	116	10.1	101	8.8	102	8.9
CM + RESP**	478	9.3	415	8.1	468	9.2	579	11.3	601	11.8	639	12.5
All Three***	113	18.4	89	14.5	88	14.3	114	18.6	128	20.8	117	19.1

Notes: Based on 57,489 elderly men, aged 67 years and older, diagnosed with incident prostate cancer between 2002 and 2009 and alive throughout the observation period. Significant differences in NCHs over time were tested with Wald chi-square, after accounting for correlations due to repeated measures. % represented in the column are column percentage.

Abbreviations: CM: Cardio-metabolic conditions; MH: Mental illness; RESP: Respiratory conditions;

*** $p < .001$; ** $.001 \leq p < .01$; * $.01 \leq p < .05$

Appendix 4. 3 Sensitivity Analysis: Non-cancer hospitalization definition 2-Adjusted Odds Ratios and 95% Confidence Intervals (CI) of Cancer Diagnosis Period From GEE models on Non-Cancer Related Hospitalizations Elderly Men with Incident Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database-2000-2010

<i>Model 1, adjusting for pre- and post-cancer period</i>			
	OR	95% CI	Sig.
Variable			
Pre-cancer	Ref		
Post-cancer	1.37	[1.32,1.41]	***
<i>Model 2, adjusting for pre- and post-cancer period + Types of Chronic Conditions</i>			
	AOR	95% CI	Sig.
Pre-cancer	Ref		
Post-cancer	1.38	[1.33,1.42]	***
<i>Model 3, adjusting for pre- and post-cancer period + Types of Chronic Conditions + predisposing, enabling, need, and external environment characteristics</i>			
	AOR	95% CI	Sig.
Pre-cancer	Ref		
Post-cancer	1.38	[1.33, 1.43]	***

Notes: Based on 57,489 elderly men, aged 67 years and older, diagnosed with incident prostate cancer between 2002 and 2009 and alive throughout the observation period. Significant differences are based on the log-likelihood test using a repeated measure generalized estimating equations.

AOR: Adjusted Odds Ratio; GEE: Generalized Estimating Equation; AOR: Adjusted Odds Ratio; Sig: Level of Sig: Significance.

*** $p < .001$; ** $.001 \leq p < .01$; * $.01 \leq p < .05$

Appendix 4. 4 Sensitivity Analysis: Non-cancer hospitalization definition 2-Predicted Probabilities with 95% Confidence Intervals for Types of Chronic Conditions From GEE analysis on Non-Cancer Related Hospitalizations Elderly Medicare Beneficiaries with Incident Prostate Cancer Surveillance, Epidemiology and End Results (SEER)-Medicare Linked Database-2000-2010

	Pre-cancer		Post-cancer		Changes in	Additive
	P	95% CI	P	95% CI	Probabilities	Effect
<i>Model 1, adjusted for pre- and post-cancer period</i>						
Overall***	0.035	[0.034, 0.036]	0.047	[0.046, 0.048]	0.012	
<i>Model 2, adjusted for pre- and post-cancer period + Types of Chronic Conditions</i>						
Overall***	0.028	[0.027, 0.029]	0.038	[0.037, 0.039]	0.010	
Types of Chronic Conditions***						
None	0.018	[0.017, 0.018]	0.031	[0.030, 0.032]	0.013	Ref
CM only	0.044	[0.043, 0.046]	0.077	[0.075, 0.079]	0.033	0.020
MH only	0.032	[0.027, 0.037]	0.055	[0.047, 0.063]	0.023	0.010
RESP only	0.029	[0.026, 0.031]	0.05	[0.045, 0.054]	0.021	0.008
CM + MH	0.075	[0.069, 0.081]	0.127	[0.117, 0.137]	0.052	0.039
CM + RESP	0.087	[0.084, 0.091]	0.146	[0.141, 0.151]	0.059	0.046
All Three	0.150	[0.138, 0.162]	0.239	[0.222, 0.256]	0.089	0.076
<i>Model 3 adjusted for pre- and post-cancer period + Types of Chronic Conditions + predisposing, enabling, need, and external environment characteristics</i>						
Overall***	0.027	[0.026, 0.028]	0.036	[0.036, 0.038]	0.009	
Types of Chronic Conditions***						
None	0.016	[0.015, 0.016]	0.021	[0.020, 0.022]	0.008	Ref
CM only	0.039	[0.038, 0.041]	0.053	[0.052, 0.055]	0.014	0.008
MH only	0.026	[0.022, 0.030]	0.036	[0.030, 0.041]	0.010	0.004
RESP only	0.021	[0.019, 0.023]	0.029	[0.026, 0.032]	0.008	0.002
CM + MH	0.056	[0.051, 0.061]	0.075	[0.069, 0.082]	0.020	0.014
CM + RESP	0.066	[0.062, 0.069]	0.088	[0.084, 0.092]	0.023	0.017
All Three	0.107	[0.097, 0.116]	0.141	[0.129, 0.153]	0.035	0.029

Notes: Based on 57,489 elderly men, aged 67 years and older, diagnosed with incident prostate cancer between 2002 and 2009 and alive throughout the observation period. Significant differences are based on the log-likelihood test using a repeated measure generalized estimating equations.

Abbreviations: CM: Cardio-metabolic conditions; MH: Mental health conditions; RESP: Respiratory conditions; Sig: Level of Significance;

*** $p < .001$; ** $.001 \leq p < .01$; * $.01 \leq p < .05$

Chapter 5

Discussion of Findings and Research Implications

5.1 SUMMARY OF FINDINGS & DISCUSSION

With an increase in the cancer-related survival and risk of non-cancer mortality among elderly men with prostate cancer, the Office of Cancer Survivorship (OCS) and Institute of Medicine (IOM) have prioritized the co-management of chronic conditions and cancer. The current study, which focuses on the role of chronic conditions in cancer treatment, cancer and non-cancer outcomes, is timely, unique and in alignment with the scope of the OCS and IOM. In the current study, one in two elderly (≥ 67 years) fee-for-service Medicare beneficiaries with incident prostate cancer had a pre-existing chronic condition, consistent with the published studies. Among those with pre-existing chronic conditions, the cardio-metabolic conditions were highly prevalent (53.8%). These findings suggest that elderly men with prostate cancer have a significant illness burden.

In the current study, types of pre-existing chronic conditions were not associated with cancer stage at diagnosis. One in 10 elderly Medicare beneficiaries had advanced prostate cancer at diagnosis. Elderly men with none of three types of chronic conditions were *more likely* to be diagnosed with advanced prostate cancer as compared to those with all the three types of chronic conditions. No statistically significant associations between other types of chronic conditions and the risk of advanced stage prostate cancer were observed. These findings suggest that *the strategies for reducing the risk of advanced prostate cancer at diagnosis should focus on elderly men with none of three common types of chronic conditions.*

The initial prostate cancer treatment rates were high even among elderly men with incident localized prostate cancer. In the study cohort, three in four elderly Medicare beneficiaries diagnosed with incident localized prostate cancer received either RP, RT or hormone therapy during the first six-month after cancer diagnosis. Although there is no evidence that the initial cancer treatment can be beneficial the in long-term for elderly men with prostate cancer and pre-existing chronic conditions, many received treatment, suggesting *an overuse of RP and RT among elderly men with localized incident prostate cancer.*

The types of chronic conditions were associated with some types of the initial cancer treatment. As compared to elderly men with all the three types of chronic conditions, those with none of three types of

chronic conditions were more likely to receive RP/RT, men in all other chronic condition categories (except “mental health and respiratory conditions” and “only mental health conditions”) were more likely to receive RT. There were no differences in the receipt of hormone therapy by the types of chronic conditions. Again, prior research has shown that elderly men with cardio-metabolic conditions may not benefit from cancer treatment as these men are at high risk for non-cancer related mortality (8, 50). *These findings reinforce the need for specific clinical guidelines for the treatment of cancer in presence of particular types of chronic conditions.*

The types of chronic conditions were associated with bowel, sexual and urinary dysfunction. As compared to those with all the three types of conditions, elderly men with none of the three types of chronic conditions or only respiratory conditions or only cardio-metabolic were less likely to have bowel and urinary dysfunctions. Whereas, as compared to elderly men with all the three types of conditions, those with none of the three types of chronic conditions, and only respiratory conditions were more likely to have sexual dysfunctions. *The reasons for why these particular combinations are associated with lower risk of bowel and urinary dysfunctions were not known. Future research needs to explore the possible pathophysiological link between types of chronic conditions and bowel and urinary dysfunction.*

The treatment of pre-existing T2DM with metformin during the year before the incident prostate cancer diagnosis reduced the risk for advanced prostate cancer at diagnosis. Among elderly men with prostate cancer and T2DM, metformin use during the year before diagnosis of incident prostate cancer was associated with a statistically significant reduction in the risk of advanced prostate cancer at diagnosis, after controlling for the observed selection bias between metformin users and non-users and other independent variables. This finding is consistent with the pre-clinical evidence. If the findings are replicated by other observational studies and RCTs, metformin can be used as a preventive therapy for reducing the risk of advanced prostate cancer.

Metformin users were more likely to receive RP as the initial cancer treatment as compared to non-users. *The reasons for a higher rate of RP among metformin users are not clear. Future research needs to explore the reasons as to why metformin users were more likely to receive aggressive treatments.*

Prostate cancer diagnosis was associated with an increased risk of non-cancer hospitalizations among elderly men with incident prostate cancer. Elderly Medicare beneficiaries with incident prostate cancer had higher rates of non-cancer hospitalizations during the post-cancer period as compared to the pre-cancer period, even after controlling for a comprehensive list of risk factors. The highest rates of non-cancer hospitalizations were observed during first four months after the diagnosis of prostate cancer. *Collectively, these findings suggest the need for further research on the relationship between the appropriate management of pre-existing chronic conditions during the pre-cancer period and the risk of non-cancer hospitalizations during the post-cancer period. Along with cancer care, better surveillance efforts and closer monitoring of chronic conditions may be needed, especially at the time of incident cancer diagnosis among elderly men, to reduce the risk of excess non-cancer hospitalizations.*

The magnitude of the relationship between the diagnosis of prostate cancer and non-cancer hospitalizations varied by the types of pre-existing chronic conditions. Those with all the three types of conditions, both cardio-metabolic conditions and respiratory conditions, and both cardio-metabolic and mental-health conditions had a greater increase in the risk of non-cancer-hospitalizations (between the pre-cancer and post-cancer period) as compared to those with none of the three types of chronic conditions. *The study also has a key methodological implication for estimating cancer-related healthcare utilization. Typically, cancer-related annual healthcare utilizations among men with prostate cancer are estimated by subtracting the total healthcare utilization in a year before cancer diagnosis from the total utilization after in a year after cancer diagnosis (5-9). Such method of estimating cancer-related healthcare utilizations may overestimate prostate-cancer-related utilizations as elderly men with incident prostate cancer had higher rates of non-cancer hospitalizations during post-cancer as compared to pre-cancer period.*

5.2 IMPLICATIONS FOR FUTURE RESEARCH

Historically, the role of chronic conditions in cancer has been examined using comorbidity indices or the number of chronic conditions. The current study is the first of its kind to provide comprehensive information on the role of specific types of chronic conditions and their combinations in prostate cancer diagnosis, treatment, and cancer and non-cancer outcomes. The study findings provide some actionable evidence that can be utilized in real-world treatment decisions. One of the major research implications is to

conduct future studies among individuals with other types of cancers with better survival profile such as the localized breast, colon, rectum, melanoma, testis, thyroid, urinary bladder and uterine corpus cancers.

In the current study it was observed that elderly men without the commonly prevalent chronic conditions had advanced prostate cancer at diagnosis. Future research studies should examine the impact of less common conditions such as inflammatory related conditions, smoking associated disorders, sexually transmitted disease on prostate cancer risk, as these conditions also share common risk factors for developing prostate cancer.

The current study found a reduced risk of advanced prostate cancer diagnosis with metformin use among elderly men with T2DM and prostate cancer. Well-designed pragmatic trials are needed to provide evidence on the effectiveness of metformin use.

The SEER authority advised against the use of the prostate specific antigen (PSA) as the PSA levels were not accurately recorded over the years. In the current study, PSA levels could not be incorporated to examine cancer stage at diagnosis. Therefore, future research should focus on the reliability and validity of using the PSA levels from the real-world electronic medical records.

As the elderly men with prostate cancer at higher risk for non-cancer hospitalizations during the post-cancer period as compared to the pre-cancer period, future studies should examine the reasons behind the increased risk.

5.3 STUDY LIMITATIONS

The current study has some limitations. First, the study cohort was restricted to elderly men enrolled in fee-for-service Medicare services only residing in the SEER-regions, therefore, study findings cannot be generalized to younger men, enrolled in managed care plans or commercial plans, and those residing in non-SEER regions. In addition, in the second aim, our study restricted to elderly men with a history of diabetes, the findings cannot be generalized to those with incidence of prostate cancer and no prior history of diabetes. The clinical severity of the chronic conditions could not be measured. Furthermore, the current study utilized the registry-linked administrative claims data which have either no information or limited validity of codes to identify body-mass index, exercise, and smoking status, which

may be associated severity, advanced prostate cancer at diagnosis, the initial treatment receipt and clinical outcome among elderly men with prostate cancer. In addition, the types of chronic conditions were considered as incurable conditions. The cardio-metabolic conditions and respiratory conditions can be considered as incurable conditions, however, the mental-health conditions such as depression can be cured with proper medications and other clinical approaches. Therefore, the chronic condition classification might overestimate the presence of such conditions. Given this limitation, the presence of each of those conditions was identified in the immediate periods before diagnosis of cancer.

Despite these limitations, the current study contributed to the nascent literature on the role of selected chronic conditions and their combinations on the stage of cancer, the initial cancer treatment, cancer- and non-cancer outcomes among elderly men with incident prostate cancer using the largest population-based cancer registries-Medicare-linked database of the US.

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