ASSOCIATION BETWEEN ADJUVANT CHEMOTHERAPY AND NEPHROTOXICITY AND KIDNEY FUNCTION MONITORING IN ELDERLY BREAST CANCER PATIENTS

A DISSERTATION
SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
OF THE UNIVERSITY OF MINNESOTA
BY

SHULING LI

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

ADVISOR: AARON R. FOLSOM, MD

MAY 2013

Acknowledgements

I would like to acknowledge my dissertation committee of Aaron Folsom, MD, Kristin Anderson, PhD, Beth Virnig, PhD, and Allan Collins, MD, FACP, for their guidance and support of this project. Their experience and expertise on epidemiologic study design, cancer epidemiology, administrative Medicare claims data, and nephrology was enormously helpful through the completion of my dissertation. They all shaped my thinking and guided me to where I am today in their own way. I would particularly like to express gratitude towards my academic and thesis advisor Dr. Folsom for his continuous support, wise advice and valuable suggestions that guided me throughout my PhD study and the dissertation process.

I am very fortunate to work at the Chronic Disease Research Group/Minneapolis Medicare Research Foundation. My special thanks go to Dr. Collins, who inspired the ideas for this dissertation and supported me in both my academic and working careers; David Gilbertson, PhD, for his support and encouragement through the years as I tried to juggle studying, working, and completing my dissertation; and Jiannong Liu, PhD, for his encouragement and tremendous help with various methodological issues and giving me the final push to end this long and challenging journey.

I would also like to thank several colleagues who supported me in various aspects throughout this process, including SEER-Medicare data acquisition and processing, questions related to administrative Medicare data and coding issues, document editing, and words of encouragement. They are Shu-Cheng Chen, Dana Knopic, Roger Johnson, Daniel Sheets, Jim Ebben, Xinyue Wang, Jim Kaufmann, Nan Booth, Delaney Berrini, Suying Li, and Craig Solid.

Finally, I must acknowledge all of my family and friends for their support and encouragement. To my husband Feng Yan and my daughter Ruhan Yan, thank you for your continuous love and support. To my parents, thank you for your understanding and support. To my dear sister Shumei Li, thank you for your encouragement and taking care of our parents while I am thousands of miles away from home. To my longtime friend Shu Ning, thank you for your continuous encouragement and wisdom, and for just listening.

Dedication

This dissertation is dedicated to my husband Feng Yan (严峰), my daughter Ruhan Yan (严茹涵), my sister Shumei Li (李淑梅), and my parents Huanzhi Cao (曹焕芝) and Chunxian Li (李春贤).

Abstract

Background: Chronic kidney disease (CKD) and cancer are major public health problems in the elderly population. With the development of cancer screening and efficacious treatments including chemotherapy, the number of cancer survivors has been increasing. In elderly cancer patients, little information is available on CKD as a late effect of chemotherapy or on risk of acute kidney injury (AKI) associated with chemotherapy. Furthermore, little is known about patterns of clinical practice regarding renal function monitoring in this population after completion of cancer treatment, especially patients treated with potential nephrotoxic chemotherapeutic agents.

Objectives: The purpose of this study was to evaluate the association between adjuvant chemotherapy (CHEMO) and risks of AKI and CKD and rate of renal function monitoring in elderly women diagnosed with early stage breast cancer.

Methods: The study was a 1:1 individually matched, retrospective cohort design including women diagnosed with stages I-III breast cancer at ages 66-89 years 1992-2007 in Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data. Sequential matching on time-dependent propensity score at the day of CHEMO initiation was performed. Follow-up (F/U) began on the CHEMO initiation date of the treated patient for each matched pair. AKI was identified in the first 6 months of F/U, while CKD and renal function monitoring were examined until December 31, 2009. The associations between CHEMO and risks of AKI and CKD were evaluated using Cox proportional hazards models. The associations between CHEMO and rate of renal function monitoring was examined using interval Poisson regression models with the cutoffs of F/U intervals $\leq$ 1 year, > 1-$\leq$ 2 years, and > 2-< 18 years.

Results: A total of 28,048 patients were included in the matched study cohorts. CHEMO was associated with a 2.7-fold increased risk of AKI within 6 months after initiation (HR 2.7, 95% CI 1.8-4.1), despite a very low overall incidence rate (16 and 6 per 1,000 person-years in patients treated with CHEMO and not treated, respectively). To find a possible explanation to this association, distribution of other diseases coded on hospital claims in AKI patients was examined and showed that septicemia occurred in 40% of CHEMO treated patients with AKI and in only 17% of untreated patients with AKI. No significant association was found between CHEMO and risk of CKD in the maximum 18-year follow-up (HR 1.00, 95% CI 0.93-1.07). The rate of urine albumin testing was low, ranging from 59/1,000 person-years in the first year of F/U for untreated patients to 94/1,000 person-years after 2 years of F/U for treated patients. In the first and second year F/U, no significant differences were found in rate of testing in CHEMO treated patients compared with untreated patients (RR 1.00, 95% CI 0.86-1.18 in first year F/U; RR 1.07, 95% CI 0.92-1.25 in second year F/U). After 2 years of F/U, rate of urine albumin testing was 12% higher in treated patients (RR 1.12, 95% CI 1.03-1.20).

Conclusion: CHEMO is associated with increased risk of AKI. This association may be partially explained by septicemia caused by infection/neutropenia due to use of myelosuppressive chemotherapeutic agents, which highlights the importance of preventing serious complications of CHEMO in preventing AKI. The findings of no association between CHEMO and risk of CKD do not suggest a late nephrotoxic effect of chemotherapeutic agents commonly used to treat breast cancer in the adjuvant setting, or provide evidence for the need for a clinical practice guideline for CKD screening specifically in elderly breast cancer patients treated with CHEMO. Future studies on CKD as a late effect of cancer treatment for other solid tumors commonly treated with known or potential nephrotoxic agents are warranted.

Table of Contents

List of Tables

List of Figures

Chapter 1 Introduction

Chronic kidney disease (CKD) is a major worldwide public health problem.[1;2] In the United States, CKD prevalence increased from 10% based on National Health and Nutrition Examination Surveys (NHANES) 1988-1994 to 13% based on NHANES 1999-2004. Approximately 26 million adults currently have CKD.[3] In 2012, the United States Renal Data System (USRDS) reported that the prevalence of recognized CKD in the Medicare population aged 65 years or older increased from 2.7% in 2000 to 9.2% in 2010 (Figure 2.2, p.55).[4] Cardiovascular disease, premature death, and kidney failure are the three primary adverse consequences of CKD.[1;5-8]

CKD is also common in adult patients with cancer.[4;9] As the U.S. population continues to age, the number of newly diagnosed elderly cancer patients will expand. Chemotherapy has been recognized to be efficacious in cancer treatment and its use has been increasing over the past several decades. Although they benefit patients overall, chemotherapeutic drugs can damage healthy cells along with cancerous cells, causing side effects. Some common side effects associated with chemotherapy generally resolve when the treatment ends. However, organ damage and functional disabilities caused by the disease, the treatment, or both may occur months or years after the treatment is completed. With the development of effective cancer screening and treatment, many patients with cancers are cured and live for extended periods of time after the completion of treatment. Many studies have shown that chemotherapeutic agents are associated with

a wide range of late effects such as cardiotoxicity,[12-17] pulmonary toxicity,[18-20] cognitive dysfunction and neurotoxicity,[21-25] and other chronic conditions.[26-36]

Studies of CKD as a late effect of chemotherapy are available,[37-42] but have mainly focused on childhood cancer survivors. Few studies in the literature have evaluated the incidence of CKD and the association between chemotherapy and risk of CKD in elderly cancer patients. Additionally, since renal function is expected to deteriorate with increasing age,[43] elderly cancer patients receiving chemotherapy treatment may have an increased risk of acute kidney injury (AKI), which could be precipitated by drug toxicity or complications from infections. Although AKI induced by chemotherapeutic agents has been extensively investigated, most studies have been limited to case reports, small cohort studies, or clinical trials.[44-50] Because elderly cancer patients are usually underrepresented in clinical trials, little information is available on the occurrence of AKI as an adverse outcome of chemotherapy treatment in elderly cancer patients. To date, no population-based study has estimated the incidence of AKI and the magnitude of association between nephrotoxic chemotherapeutic agents and the risk of AKI in elderly cancer patients. Furthermore, clinical practice guidelines for chemotherapy treatment recommend that renal function be assessed prior to each cycle for potential dose modification to avoid myelosuppression from several known nephrotoxic agents.[51] For surveillance and management of nephrotoxicity among cancer survivors, however, the clinical practice guidelines are available only for asymptomatic pediatric cancer survivors. There is currently no guideline for surveillance and management of nephrotoxicity in adult cancer survivors. Little is known about patterns of

clinical practice regarding renal function monitoring in elderly cancer patients after completion of cancer treatment, especially patients treated with nephrotoxic chemotherapeutic agents.

I conducted three retrospective cohort studies to evaluate the association between adjuvant chemotherapy and risk of AKI and CKD and rate of renal function monitoring among elderly women with breast cancer. I chose breast cancer for my dissertation based on the following considerations. First, breast cancer is one of the most commonly occurring cancers in the U.S., with over 207,090 new diagnoses reported in 2010.[52] Second, breast cancer has a high survival rate, representing the largest proportion of female cancer survivors (41%), and of all cancer survivors (22%), on January 1, 2008.[53] Finally, evidence regarding the nephrotoxicity of chemotherapeutic agents commonly used in the treatment of breast cancer is lacking.

The current study addresses three primary objectives and two secondary objectives:

<u>Primary objectives:</u>

1. To examine whether adjuvant chemotherapy is associated with increased risk of AKI during the treatment period among elderly breast cancer patients.

2. To evaluate whether adjuvant chemotherapy is associated with increased risk of CKD among elderly breast cancer patients.

3. To compare the use of laboratory tests to monitor kidney function during the post-treatment period among elderly breast cancer patients treated with adjuvant

chemotherapy with the use of these tests among patients not treated with adjuvant chemotherapy.

Secondary objectives:

1. To examine whether the strength of association between adjuvant chemotherapy and risk of AKI during the treatment period varies among major types of chemotherapy regimens in elderly women with breast cancer.

2. To evaluate whether the strength of association between adjuvant chemotherapy and risk of CKD varies among major types of chemotherapy regimens in elderly women with breast cancer.

These objectives were accomplished through the use of the linked Surveillance, Epidemiology and End-Results (SEER)-Medicare data.

The rest of the thesis is organized into five chapters. Chapter 2 presents a literature review of chemotherapy-related nephrotoxicity and the significance of the proposed study. In this chapter, I first focus on chemotherapy, describing the classification of chemotherapeutic agents, factors related to use of chemotherapy, and toxicities. Then, I move on to nephrotoxicity, describing its definition, clinical manifestations focusing on AKI and CKD, pathogenesis, and current literature on chemotherapy-induced nephrotoxicity. Next, I briefly describe the clinical practice guidelines for surveillance and management of nephrotoxicity. I conclude Chapter 2 by discussing the significance of the proposed study. Chapter 3 describes the study designs and analytical methods to address each objective. Chapter 4 presents the study findings. Chapter 5 summarizes and interprets the main study findings, discusses the strength and

limitations of the study, discusses the implications, and proposes two future research ideas. Finally, Chapter 6 presents the conclusions.

Chapter 2 Literature Review

2.1 Chemotherapy

2.1.1 Definition

Chemotherapy is a type of cancer treatment that uses a single drug or combinations of drugs to slow or stop the rapid growth of cancer cells by impacting cell division. Depending on the type and stage of the cancer, chemotherapy can be used prior to surgery to shrink a tumor enough to make surgical removal possible (neoadjuvant therapy) or after surgery, alone or coupled with radiation therapies, to destroy any undetected cancer cells that may have migrated to other parts of the body (adjuvant therapy). Sometimes, chemotherapy is administered to manage the pain or pressure caused by cancer (palliative care).

2.1.2 Classification of Chemotherapeutic Agents

Chemotherapeutic agents can be classified into the following groups based on their mechanisms:

1) Alkylating agents directly damage DNA to prevent the cancer cell from reproducing. These agents attach an alkyl group, resulting in linking nucleobases in the DNA double helix, which prevents DNA replication and cell division. These agents work in all phases of the cell cycle. Examples include cisplatin, carboplatin, cyclophosphamide (Cytoxan®), and ifosfamide. Of these alkylating agents, cyclophosphamide, coupled with two other agents, is commonly used in breast cancer treatment in the adjuvant setting.

2) Anti-metabolites interfere with DNA and RNA growth by substituting for the normal building blocks of RNA and DNA. These agents damage cells during the S phase. Examples used in breast cancer treatment include 5-fluorouracil (5-FU) and methotrexate.

3) Anti-tumor antibiotics interfere with enzymes involved in DNA replication. These agents work in all phases of the cell cycle and are widely used for a variety of cancers. Examples used in breast cancer treatment include doxorubicin (Adriamycin®) and epirubicin.

4) Plant alkaloids are plant-derived chemicals that can stop or inhibit enzymes from making proteins needed for cell reproduction. These drugs work during the M phase of the cell cycle, but can damage cells in all phases. Thus, they are used to treat many different types of cancer including breast, lung, myelomas, lymphomas, and leukemias. Examples used in breast cancer treatment include the taxanes (paclitaxel and docetaxel).

2.1.3 Factors Related to Use of Chemotherapy

In general, the type and stage of cancer, previous treatment with chemotherapy, and comorbid conditions (diabetes or heart disease) determine the use of chemotherapy. Patients with pre-existing CKD may need dose adjustment for nephrotoxic agents. Morimoto et al showed that factors related to increased likelihood of receiving chemotherapy in women with breast cancer include younger age, white race, good general health and few comorbid conditions, more severe clinical disease, good response to previous treatment, and breast cancer that is estrogen or progesterone receptor negative.[54]

2.1.4 Toxicities

Although they benefit patients overall, chemotherapeutic drugs can damage healthy cells along with cancerous cells, causing side effects. The most common side effects associated with chemotherapy include hair loss, fatigue, nausea, and vomiting, which generally resolve when the treatment ends. However, the organ damage and functional disabilities caused by the disease, the treatment, or both may occur months or years after the treatment is completed. With advances in the early diagnosis and effective treatment of cancer, many cancer patients are either cured of their cancer or live with it as a chronic disease.[55-58] Patients who survived the initial cancer treatments are likely to experience the late consequences of these treatments.

Many studies have shown that chemotherapeutic agents are associated with a wide range of late effects such as cardiotoxicity,[12-17] pulmonary toxicity,[18-20] nephrotoxicity,[37-42] cognitive function and neurotoxicity,[21-25] premature menopause,[26] sexual impairment,[27;28] infertility,[29] chronic fatigue,[30;31] and second malignancies.[32-34] In addition, significant adverse psychosocial outcomes after the completion of treatment occur in many survivors and their families, affecting quality of life.[35;36]

2.2 Nephrotoxicity

2.2.1 Definition

Nephrotoxicity is the development of functional or structural kidney damage caused by toxic chemicals, medications, or other treatments.[59] The damage in kidney function includes glomerular or tubular dysfunction, impairment of blood pressure

control, and renal endocrine dysfunction. The damage in kidney structure includes microscopic morphologic lesions such as glomerular or tubular abnormalities and gross morphologic lesions such as the small (atrophic) kidneys associated with chronic renal failure.

The kidneys are a pair of vital organs that regulate the volume, osmolarity, electrolyte content, concentration, and acidity of body fluids; excrete metabolic end products, mostly urea and creatinine; eliminate foreign substances, such as drugs and toxic substances; and release three important hormones: 1) renin, which regulates blood pressure; 2) erythropoietin, which stimulates the bone marrow to make red blood cells; and 3) calcitriol, the active form of vitamin D, which helps maintain the calcium and phosphate balance in the body.[60]

The kidneys are often exposed to potential toxic insults because urinary excretion is one of the major routes of elimination of many chemotherapeutic agents and their metabolites. Therefore, patients with cancer are frequently at risk for renal dysfunction either related to the malignancy itself or to its treatment. Some kidney damage is transient and reversible after the treatment ends, but high doses of certain chemotherapy agents or prolonged use of standard doses may cause permanent damage.

2.2.2 Clinical Manifestations

Nephrotoxicity induced by chemotherapeutic agents may manifest itself as tubulopathies, AKI, nephritic/nephrotic syndrome, and CKD. Only AKI and CKD are discussed.

2.2.2.1 Acute Kidney Injury

Definition

AKI (formerly referred to as acute renal failure) is a complex disorder that can be acquired in both community and hospital settings with clinical manifestations ranging from a relatively modest increase in serum creatinine level to anuric renal failure requiring dialysis. The definition of AKI varies widely in published studies in which AKI is defined based on serum creatinine changes, absolute levels of serum creatinine, changes in blood urea nitrogen or urine output, or the need for dialysis.[61] In the absence of a standard definition, AKI is generally defined as an abrupt and sustained decline in glomerular filtration rate (GFR) with or without a decrease in urine output occurring over hours or days.[62]

Staging/classification

In 2004, the Acute Dialysis Quality Initiative (ADQI) group published a classification system for AKI to establish a uniform definition. AKI is classified in five categories (Table 1), including three degrees of increasing severity based on changes in serum creatinine levels within 1 to 7 days or urine output within 48 hours (risk, injury, and failure) and two clinical outcomes (loss and end-stage disease), known as the RIFLE criteria.[63] AKI is both abrupt (within 1-7 days) and sustained (more than 24 hours).

Table 2-1 Risk, injury, failure, loss, and end-stage kidney disease (RIFLE) classification for acute kidney injury

Category	Serum Creatinine Level or Renal Function	Urine Output
Risk	Increased serum creatinine 1.5 times baseline	< 0.5mL/kg/hour for more than 6 hours
Injury	2 times baseline	< 0.5mL/kg/hour for more than 12 hours
Failure	3 times baseline, or serum creatinine level at least 4 mg/dL [354 μmol/l] with absolute increase exceeding 0.5 mg/dL [44 μmol/l]	< 0.3mL/kg/hour for more than 24 hours, or anuria for more than 12 hours
Loss	Complete loss of kidney function for longer than 4 weeks	
End-stage	End-stage kidney disease for longer than 3 months	

(Note: adapted from Figure 1, p. R206)[63]

In 2007, the Acute Kidney Injury Network (AKIN) recommended a modified diagnostic criteria and staging system for AKI based on accumulating evidence that small increments in serum creatinine are associated with adverse outcomes.[64] AKI is defined by an abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of ≥ 0.3 mg/dL (≥ 26.4 μmol/L), a percentage increase in serum creatinine of ≥ 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 mL/kg per hour for more than 6 hours). Based on this definition, AKIN modified the RIFLE criteria so that patients meeting the proposed definition of AKI could be staged (Table 2-2). This new classification system removed the "loss" and "failure" categories from the RIFLE criteria and retained them as outcomes. The new system also proposed the diagnosis of AKI based on changes in serum creatinine over the course of 48 hours, instead of 1 week as in the RIFLE criteria.

Table 2-2 AKIN classification/staging system for acute kidney injury

Stage	Serum Creatinine Criteria	Urine Output Criteria
1	Increase in serum creatinine to ≥ 0.3 mg/dL (26.4 μmol/l) or increase to ≥ 150% to 200% (1.5- to 2-fold) from baseline	< 0.5 mL/kg per hour for more than 6 hours
2	Increase in serum creatinine to > 200% to 300% (2- to 3-fold) from baseline	< 0.5 mL/kg per hour for more than 12 hours
3	Increase in serum creatinine to > 300% (3-fold) from baseline (or serum creatinine ≥ 4.0 mg/dL [≥ 354 μmol/l] with an acute increase of at least 0.5 mg/dL [44 μmol/l])	< 0.3 mL/kg per hour for 24 hours or anuria for 12 hours

(Note: adapted from Table 2)[64]

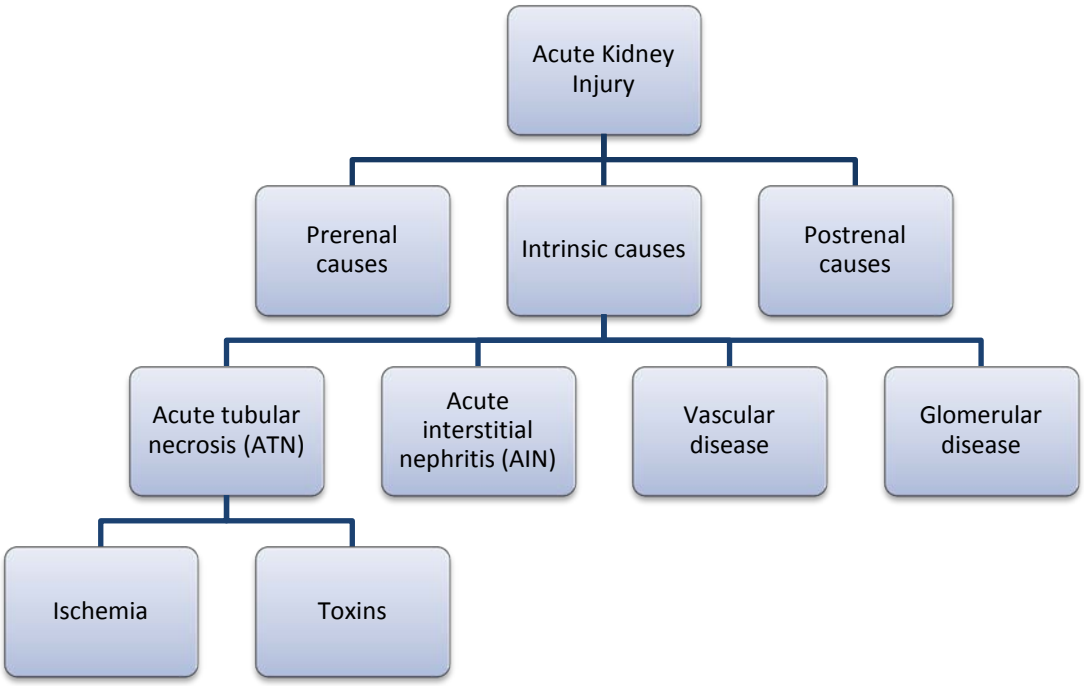
Epidemiology

AKI is a complex disorder and a serious complication of many disease and treatments. The incidence of AKI varies greatly depending on the clinical settings, ranging from 1% in patients at admission to the hospital, to 2% to 5% during the hospitalization, and up to 4% to 15% after cardiopulmonary bypass.[65] Multiple studies have shown that AKI is more common in the elderly population, and incidence of AKI increases with older age.[66-69] In 2012, the USRDS reported that the rates of hospitalization for first AKI in 2010 for Medicare patients age 66-69, 70-74, 75-79, 80-84, and 85 years and older were 13.6, 18.1, 24.9, 34.2, and 46.9 per 1,000 patient years, respectively (Figure 6.3, p.100).[4] AKI is also common in cancer patients. Data from several studies of critically ill cancer patients demonstrated that the incidence of AKI ranged from 12% to 49% during the intensive care unit stay, and 9% to 32% required dialysis.[70] AKI induced by chemotherapeutic agents is discussed in detail in Section 2.2.4.1.

Causes

The multiple causes of AKI can be classified as prerenal, intrinsic, or postrenal according to the underlying pathophysiology, presented in Figure 2-1.

Figure 2-1 Main categories of acute kidney injury



(Note: adapted from Figure 1, p. 459[71] and Figure 1, p.1449[65]).

Prerenal AKI is usually caused by any reduction in blood flow to the kidneys and represents 40% to 80% of cases.[72;73] Diseases that may cause prerenal AKI in the outpatient setting include vomiting, diarrhea, poor fluid intake, fever, use of diuretics, and heart failure. Hospital-acquired prerenal AKI is often due to cardiac failure, liver dysfunction, cardiac surgery, or septic shock.[65] Since the renal parenchyma typically

remains intact, renal function returns to normal if the underlying cause has been corrected.

Postrenal AKI results from mechanical obstruction of the urinary outflow tract distal to the bladder and represents 5% to 15% of cases.[72;73] Postrenal AKI is often present in the outpatient setting and is most commonly caused by prostatic hypertrophy; cancers of cervix, prostate, bladder, or colon; and kidney stones.[65] It is crucial to identify and correct the causes of postrenal AKI quickly because the duration of obstruction negatively affects the potential for recovery of renal function.[74]

Intrinsic or intrarenal AKI refers to any injuries affecting renal parenchyma and represents 10% to 30% of cases.[72;73] According to the area of kidney parenchyma involved, intrinsic AKI can be further categorized into four groups: acute tubular necrosis (ATN), acute interstitial nephritis, vascular disease, and glomerular disease. ATN is the most common cause of intrinsic AKI and usually occurs after an acute ischemic or toxic event. Many clinical conditions can cause generalized or localized reduction in renal blood flow leading to ischemic ATN; these include sepsis, small-vessel renal vascular disease, large-vessel renal vascular disease, intravascular volume depletion and hypotension, decreased effective intravascular volume, medications, and hepatorenal syndrome.[65] Of these conditions, sepsis is the most frequent cause of ischemic ATN. Toxic ATN results from direct tubular damage from nephrotoxins such as aminoglycoside antibiotic, radio-contrast agents, chemotherapeutic agents, and other drugs. Acute interstitial nephritis is most often caused by an allergic reaction to a drug[75]

and accounts for approximately 2% to 3% of AKI.[71] Vascular and glomerular diseases are not common causes of AKI.

Risk factors

AKI mostly occurs in connection with another medical condition or event. Advanced age is a major risk factor for many forms of AKI.[76] Clinical conditions that increase the risk of AKI include preexisting renal insufficiency (e.g., GFR of less than 60 mL/min/1.73 m^2), intravascular volume depletion, diabetes, congestive heart failure, peripheral artery disease, high blood pressure, liver disease, atheroembolism, and sepsis.[65;77] Treatment-related factors that increase the risk of AKI include cardiovascular surgery, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE-Is/ARBs), aminoglycosides, radio-contrast agents, and nephrotoxic chemotherapeutic agents.[65;78]

Adverse outcomes

AKI is associated with an increased risk of premature death. The reported mortality rates for AKI vary greatly depending on the precipitating factors, ranging from approximately 7% among patients with community-acquired AKI[79] to more than 80% among patients with postoperative AKI.[80;81] Age is a major risk factor for in-hospital death in both young and elderly patients. In the 2009 Annual Data Report, the USRDS analyzed in-hospital mortality in patients with AKI hospitalizations 2006-2007 using a large employer group health plan dataset and the Medicare 5% sample dataset (Table 8.d)[82] In commercially insured patients, the adjusted odds ratio of in-hospital death

during an AKI hospitalization is 1.48 (95% confidence interval [CI]: 1.18-1.87) in patients aged 55-64 years compared with those aged 20-44 years. In Medicare fee-for-service patients, the adjusted odds ratio is 1.41 (95% CI 1.30-1.52) in patients aged 80 years and older compared with those aged 66-70 years.

AKI is usually considered to be reversible without long-term effect on kidney function after the underlying cause has been treated. However, in some cases, CKD or end-stage renal disease (ESRD) may develop. Several studies have shown that patients who survived AKI are at an increased risk for CKD and/or ESRD.[83-86] Patients with pre-existing CKD are likely to progress in CKD stage after an AKI episode. In the 2012 Annual Data Report, the USRDS compared CKD status before and after an AKI hospitalization in Medicare fee-for-service enrollees with an AKI hospitalization in 2010 (Figure 6.21, p.106).[4] In this analysis, Medicare claims with qualifying International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes for CKD were assembled in the 1 year prior and 1 year following the AKI admission date. CKD stage was defined through the ICD-9-CM diagnosis code 585.X. A significant change in CKD status was observed after an AKI hospitalization. Of patients with stages 1-2 CKD before the hospitalization, 42.8% were reclassified as having stages 3-5 CKD within 1 year after discharge. Of patients with stages 3-5 CKD at baseline, 12.6% were later registered in the ESRD program.

Diagnosis

AKI can be verified through a spot check for protein or albumin in the urine. A more sensitive test for protein or albumin in the urine involves laboratory measurement

and calculation of the protein-to-creatinine or albumin-to-creatinine ratio (ACR). Recent guidelines recommend estimating GFR using prediction equations based on serum creatinine, age, sex, race, and body size. The two most commonly used equations in adults include the Cockcroft-Gault equation[87] and the simplified Modification of Diet in Renal Disease (MDRD) Study equation.[88]

Although estimated GFR is used to clinically assess the degree of kidney impairment and to follow the disease progression, it provides no information on the cause of AKI. The cause of AKI is usually determined through urinalysis, measurement of urinary protein excretion. Sometimes, imaging tests such as ultrasound and computerized tomography and/or kidney biopsy are necessary to determine the exact cause of the kidney failure.[65]

2.2.2.2 Chronic Kidney Disease

Definition

CKD is characterized by a progressive course with ongoing loss of kidney function. According to the National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI) Clinical Practice Guidelines,[1] the criteria for diagnosis of CKD are either kidney damage or GFR less than 60 mL/min/1.73 m^2 body surface area, with or without kidney damage, for 3 or more months. Kidney damage is defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either pathological abnormalities or markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests.

Staging/Classification

According to the K/DOQI guidelines, CKD is classified in five stages, based on estimated GFR and irrespective of diagnosis (Table 2-3).

Table 2-3 NKF classification of chronic kidney disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or better GFR	≥ 90
2	Kidney damage with mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	15-29
5	Kidney failure	< 15 (or dialysis)

(Note: adapted from Table 33, p. S65)[1]

Epidemiology

CKD is a worldwide public health problem. In the U.S., the prevalence of CKD increased from 10% based on NHANES 1988-1994 to 13% based on NHANES 1999-2004. Approximately 26 million adults currently have CKD.[3] Data from NHANES 1999-2004 also demonstrated that prevalence of CKD stages was 1.8%, 3.2%, 7.7%, and 0.35% for stage 1 to stage 4, respectively.[3] In 2012, the USRDS reported that the prevalence of recognized CKD among Medicare patients aged 65 years or older increased from 2.7% in 2000 to 9.2% in 2010 (Figure 2.2, p.55)[4] Using a Medicare claims-based definition, the USRDS reported that the incidence of recognized CKD among Medicare patients aged 65 years or older increased almost 4 times during 1995-2008, from 1.2% in 1995 to 4.3% in 2008 (Figure 2.4, p.57).[89]

CKD is also common in adult cancer patients.[9] A recent study of 4,684 adults (mean age 58 years) undergoing treatment for solid tumors in 15 French centers (the Renal Insufficiency and Anticancer Medications [IRMA] study) found that 50% to 60% had creatinine clearance below 90 mL/min/1.73 m^2, which defines stage 2 CKD according to the K/DOQI guidelines.[9] However, this study did not investigate whether this high prevalence of reduced GFR related to the cancer itself or to cancer treatment. In 2012, the USRDS reported that the prevalence of recognized CKD in Medicare cancer patients age 65 years or older was 15.8% (Table 2a, p.54).[4] These apparently much different CKD prevalence estimates may be explained by the different definitions of (creatinine clearance in the IRMA study, Medicare claims-based definition in the USRDS study) and timing of evaluation (during treatment in the IRMA study, pre-specified calendar year in the USRDS study). The incidence of CKD associated with cancer treatment is discussed in Section 2.2.4.2.

Causes

The exact cause of CKD is not always identified. However, any condition or disease that damages blood vessels or other structures in the kidneys may cause CKD. The two leading causes of CKD are diabetes and hypertension, which account for up to two-thirds of all CKD cases.[1] High blood sugar levels caused by diabetes could damage blood vessels in the kidneys. If the blood sugar level remains high, this damage gradually reduces kidney function. Uncontrolled high blood pressure is a leading cause of heart attacks, strokes, and CKD. Also, blood pressure often rises with CKD. High blood

pressure may further damage kidney function when another medical condition initially caused the disease.

Other conditions that can damage the kidneys and cause CKD include 1) kidney diseases and infections, such as polycystic kidney disease, pyelonephritis, and glomerulonephritis; 2) obstructions caused by renal artery stenosis, kidney stones, enlarged prostate gland in men, and cancers of bladder and kidney; 3) lupus and other diseases affecting the body's immune system; and 4) long-term use of medicines that can damage the kidney, such as NSAIDs and certain antibiotics.

Risk factors

The NKF defined risk factors for susceptibility to and initiation and progression of CKD (Table 39-40).[1] Clinical factors for susceptibility to and initiation of CKD include diabetes, hypertension, autoimmune diseases, systemic infections, urinary tract infections, urinary stones, lower urinary tract obstruction, neoplasia, family history of CKD, recovery from AKI, reduction in kidney mass, exposure to certain drugs, and low birth weight. Sociodemographic factors for susceptibility to and initiation of CKD include older age, US ethnic minority status, exposure to certain chemical and environmental conditions, and low income/education. The risk factors for progression of CKD include higher level of proteinuria, higher blood pressure level, poor glycemic control in diabetes, and smoking.

Adverse outcomes

Cardiovascular disease, premature death, and kidney failure are the three primary adverse consequences of CKD.[1] Studies have shown that patients with CKD are 20 to 50 times more likely than non-CKD patients to die than to survive to more advanced CKD stages or ESRD.[5-7] In a study using a large health plan dataset, Go et al showed that lower levels of GFR are associated with higher incidence of cardiovascular events.[5] In another study using the Medicare claims data,[7] Collins et al demonstrated that patients with CKD without documented cardiovascular disease were 60% more likely than patients without CKD to acquire cardiovascular diagnosis codes and services over a 1-year period. In a recent meta-analysis including 105,872 individuals from 14 studies with urine ACR measurements and 1,128,310 individuals from 7 studies with urine protein dipstick measurements, Matsushita et al demonstrated that estimated GFR and albuminuria were both associated with risk of all-cause mortality and cardiovascular mortality.[8]

Diagnosis

CKD can be diagnosed by chronically reduced GFR and persistent proteinuria. In addition, renal hematuria, pyuria, glycosuria, and other kidney abnormalities defined by radiologic or pathologic studies are used to diagnose CKD.

2.2.3 Pathogenesis of Nephrotoxicity of Selected Chemotherapeutic Agents

Chemotherapeutic agents cover a wide range of drugs that target different types of cancers. Of these drugs, several are inherently nephrotoxic, including cisplatin,

carboplatin, ifosfamide, and high-dose methotrexate ($\geq$ 1 g/m^2), while others may be nephrotoxic based on preliminary understanding of the mechanism. Only chemotherapeutic agents commonly given in the adjuvant setting for the treatment of breast cancer and known as nephrotoxic or potentially nephrotoxic are discussed below, including methotrexate, cyclophosphamide, and doxorubicin.

2.2.3.1 Methotrexate

Methotrexate (MTX) is an anti-folate drug that inhibits the metabolism of folic acid. MTX and its metabolites are eliminated predominantly by the kidneys, through glomerular filtration and tubular secretion. After intravenous administration, 70% to 100% of the drug appears in the urine in the first 24 hours.[62]

Several mechanisms have been proposed for MTX-induced nephrotoxicity: precipitation of MTX and its metabolites in the distal tubules producing obstructive uropathy and tubular necrosis,[90-92] direct toxic effect of MTX on the renal tubules,[93] and possibly, alteration of GFR.[94] Among these mechanisms, tubular precipitation is the most commonly accepted mechanism.

2.2.3.2 Cyclophosphamide

Cyclophosphamide (CP) is one of the commonly used and highly effective cytotoxic drugs of the alkylating agents. CP is initially oxidized to active and inactive metabolites that are excreted by the kidneys.[95] The 24-hour urinary excretion of intact parent compound is 1% to 14%.

CP has been known for its association with urotoxic side effects, such as hemorrhagic cystitis, but not with tubular injury.[96] The pathogenic mechanisms of CP-induced nephrotoxicity remain unknown, but earlier and recent animal studies have shown that oxidative stress is thought to play a role in the pathogenesis of CP-induced renal damage.[97-102]

2.2.3.3 Doxorubicin

Doxorubicin (DOX) is an anthracycline antibiotic agent. Following systemic administration, it is rapidly and extensively metabolized by the liver to doxorubicinol. The main route of excretion is through bile, while urinary elimination accounts for approximately one-sixth of total excretion.[103]

Anthracycline agents are mostly known for their cardiotoxicity.[12-14;16;17] The molecular mechanism responsible for the pathogenesis of DOX-induced renal injury is not clearly defined. Animal studies have suggested that the possible mechanisms of DOX-induced renal toxicity may be alterations of the permeability of the glomerular capillary wall and glomerular atrophy[104;105] or the consequence of free radical formation, iron-dependent oxidative damage of biological macromolecules, and membrane lipid peroxidation.[105-108]

2.2.4 Current Literature on Chemotherapy-Induced Nephrotoxicity

2.2.4.1 Acute Kidney Disease

AKI has been reported following administration of high dose MTX in case reports, cohort studies, and clinical trials. Ahmad et al reported that a 47-year-old man

with chondrosarcoma of the pelvis with pulmonary metastasis presented sustained AKI within 2 days after starting the second course of high dose MTX therapy and died 12 days after receiving MTX.[44] Renal histological studies showed severe tubulointerstitial damage consistent with MTX toxicity. Another study by Jaffe and Traggis reported that 6 of 41 patients who received high-dose methotrexate for osteogenic sarcoma developed nephrotoxicity and two of these episodes were fatal.[45] In a review of 20 published clinical trials of 3,887 patients with osteosarcoma who received high-dose MTX, approximately 1.8% developed nephrotoxicity that was either Grade ≥ 2 (World Health Organization criteria) or significant enough to be reported at some time during treatment.[46]

AKI has also been reported following administration of intermediate doses of MTX.[47;48] Stark et al reported that four men aged 42-67 years developed renal failure in 5-7 days after receiving 200 mg/m^2 MTX for high-grade lymphoma despite normal serum creatinine prior to chemotherapy.[48]

Low-dose MTX treatment has not been believed to have significant renal effects. However, studies have shown that nephrotoxicity can occur at low MTX doses. In a study of 13 patients with classic or definite rheumatoid arthritis receiving low-dose MTX treatment with 15 mg oral MTX weekly, Seideman et al found a significant decrease in GFR ($P < 0.05$) in all patients after 4-8 weeks of treatment.[49] In another study of 13 patients with advanced carcinomas, Condit et al reported that MTX in doses of 0.5-3 mg/kg resulted in elevated blood urea nitrogen (BUN) and creatinine in 5 patients. Three of these patients had persistent azotemia at the time of death. Post-mortem examination of the kidneys showed extensive necrosis of the tubular epithelial cells.[50]

Although earlier and recent animal studies have shown that doxorubicin caused significantly increased levels of kidney markers including BUN, serum creatinine, urine protein, and urine albumin,[107;109;110] and damage of glomerular structure,[107;109] only one case report links anthracyclines with renal failure in humans.[111] The renal biopsy in this patient demonstrated pathologic lesions resembling those in rats treated with the related anthracycline, daunorubicin. In the absence of other case reports linking anthracyclines with renal failure, the nephrotoxic potential of doxorubicin in humans seems low.

Similar to doxorubicin, cyclophosphamide causes renal toxic reactions in experimental animal models,[97-102] but there have been no reports of this problem in humans.

To date, two population-based studies address incidence of AKI in adult breast cancer patients.[112;113] In a recent Danish population-based cohort study of 46,880 incident cancer patients of all ages diagnosed 1999-2006,[112] Christiansen et al examined the incidence rate and cumulative incidence of AKI at 1 year and 5 years of follow-up and found that the 1-year risk of AKI was highest among patients with kidney cancer, liver cancer, or multiple myeloma and lowest among patients with testis cancer, breast cancer, or malignant melanoma. Of 3,938 breast cancer patients with a baseline creatinine measurement, the 1-year incidence rate of AKI, defined as > 50% increase in serum creatinine compared with baseline level, was 48 per 1,000 person-years (95% CI 41-56 per 1,000 person-years) and the 1-year risk of AKI was 4.5% (95% CI 3.9%-5.2%). Langeberg et al conducted a retrospective cohort study using a large national commercial claims database.[113] Among 13,150 women diagnosed with breast cancer 2000-2007, aged

18-64 years at diagnosis, with no history of renal insufficiency, the cumulative incidence of AKI, defined using at least one inpatient or two outpatient claims with ICD-9-CM code 584.XX or 586.XX, within a year after cancer diagnosis was 0.3% in all patients and 1.0% in patients who received nephrotoxic chemotherapy.

Most studies in the literature so far focus on reporting incidence of AKI. Few studies have evaluated the occurrence of AKI in elderly cancer patients and the association between chemotherapeutic agents and risk of AKI.

2.2.4.2 Chronic Kidney Disease

Few studies in the literature have evaluated the incidence of CKD and the association between chemotherapy and risk of development of CKD in elderly cancer patients. Current understanding of the incidence of CKD and the association between cytotoxic chemotherapeutic agents and risk of CKD in cancer patients comes mainly from studies in childhood cancer survivors.[37-42] Data from the UK Renal Registry Report indicated that 1.9% of cases of established renal failure in children were owing to malignancy (whereas malignancy occurs in only about 0.17% of children) and 0.8% was caused by drug nephrotoxicity.[40] A report from the Childhood Cancer Survivor Study (CCSS) in North America showed that severe chronic renal disease (grade 3 to 4 World Health Organization criteria) was uncommon, being present in only 0.8% of long-term survivors aged 18 years or older who had completed at least 5 years of treatment. However, this incidence was significantly more common than in their siblings (0.2%, relative risk 8.1, 95% CI 2.9-23.1).[38] Another CCSS study of over 10,000 survivors of

childhood cancer reported that 0.5% had developed renal failure or required dialysis, with a relative risk to siblings of 8.9 (95% CI: 2.2-36.6).[41]

2.3 Clinical Practice Guidelines for Surveillance and Management of Nephrotoxicity

For childhood cancer survivors, the Children's Oncology Group Long-Term Follow-Up Guidelines (COG LTFU Guidelines) for Survivors of Childhood, Adolescent, and Young Adult Cancers were developed through the collaborative effects of the Children's Oncology Group Late Effects Committee, Nursing Discipline, and Patient Advocacy Committee.[114] The COG LTFU Guidelines are risk-based, exposure-related clinical practice guidelines designed for asymptomatic survivors beginning with routine medical follow-up 2 or more years after completion of cancer treatment. The guideline recommends that all asymptomatic survivors undergo baseline screening including blood pressure measurement, serum electrolytes including Ca, Mg, and P, BUN/creatinine, and urinalysis and annual follow-up exams including blood pressure measurement and urinalysis. Referral to a nephrologist should be prompted in the presence of progressive renal insufficiency, proteinuria, or hypertension.

For cancer survivors diagnosed and treated as adults, there are no clear guidelines for the optimal intervals and total duration of kidney function monitoring. The currently available clinical guidelines are designed for each specific cancer type and intended to provide guidance for cancer treatment and follow-up of the survivor's primary disease. The National Comprehensive Cancer Network (NCCN) has developed more than 100

clinical practice guidelines for about 95% of the clinical situations presented by cancer patients.[51] Although the guidelines for chemotherapy treatment recommend that renal function should be assessed prior to each cycle for potential dose modification for several nephrotoxic agents,[51] there is no survivorship guideline for monitoring kidney function in cancer survivors. The NCCN guidelines for breast cancer follow-up include a physical exam every 4-6 month for 5 years, then every 12 months, and a mammogram every 12 months (and 6-12 month post-radiation therapy if breast conserved).

The American Society of Clinical Oncology (ASCO) guidelines for breast cancer follow-up and management[115] include regular physical examinations (every 3-6 months for the first 3 years after the first treatment, every 6-12 months for years 4 and 5, and every year thereafter), mammograms (1 year after the first mammogram that led to diagnosis, but no earlier than 6 months after radiation therapy, every 6-12 months thereafter), breast self-examination (monthly), and pelvic examination. The following tests are not currently recommended by ASCO for regular follow-up care because they have not been shown to lengthen the life of breast cancer patients: complete blood count, liver enzymes, chest x-ray, bone scan, liver ultrasound, computed tomography, fluorodeoxyglucose-positron-emission tomography scan, breast magnetic resonance imaging test, and breast cancer tumor markers.

In 2007, the ASCO Cancer Survivorship Expert Panel published extensively reviewed evidence of cardiac and pulmonary late effects. The intent of this rigorous review was to establish an evidence-based clinical guideline for survivorship care. After

the review, the panel concluded that the evidence was not sufficient to support an evidence-based clinical practice guideline for survivorship care.[116]

The 2006 Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference on CKD was convened to discuss six major topics regarding CKD classification, CKD screening and surveillance, public policy for CKD, cardiovascular disease and its risk factors as risk factors for development and progression of CKD, association of CKD with chronic infections, and association of CKD with cancer.[2] The meeting proposed three recommendations for cancer patients: "1) all cancer patients should be screened for CKD at diagnosis, at initiation, and change of cancer therapy. Tests for CKD should include a urinalysis (for hematuria and proteinuria) and a measure of kidney function (serum creatinine to estimate GFR); 2) kidney sparing interventions should be utilized in patients with kidney and uroepithelial cancers; 3) screening for CKD is recommended in subjects cured of cancer who are at risk for CKD, because of the type of cancer, its complications, its treatment, or other risk factors for CKD not related to cancer."

2.4 Significance of Current Study

Cancer is a disease that mainly affects the elderly. Approximately 60% of patients diagnosed with cancer are aged ≥ 65 years.[10;11] As the U.S. population continues to age, the number of newly diagnosed elderly cancer patients will expand. Since renal function is expected to deteriorate with increasing age,[43] elderly cancer patients who receive chemotherapy treatment have an increased risk of AKI. Although AKI induced by

chemotherapeutic agents has been extensively investigated, most studies have been limited to case reports, small cohort studies, or clinical trials.[44-50] Since elderly cancer patients are usually underrepresented in clinical trials, little information is available on the occurrence of AKI as an adverse outcome of chemotherapy treatment in elderly cancer patients. To date, no population-based study has estimated the incidence of AKI and the magnitude of association between nephrotoxic chemotherapeutic agents and the risk of AKI in elderly cancer patients.

Most AKI episodes caused by cancer treatment are reversible. However, initial acute toxicity caused by some cytotoxic chemotherapy agents can progress to CKD with the development of chronic tubulointerstitial nephritis, papillary necrosis, or prolonged proteinuria.[117] With the development of effective cancer screening and treatment, many patients with cancers are cured and live for extended periods after the completion of treatment, and may have an elevated risk for CKD as a late effect of chemotherapy treatment. Studies of CKD as a late effect of chemotherapy have mainly focused on child and adolescent cancer survivors.[37-42] The clinical practice guidelines for survivorship care have been developed for surveillance and management of nephrotoxicity for asymptomatic pediatric cancer survivors. However, little attention has been given to CKD as a late effect of chemotherapeutic agents in adult cancer survivors and there is currently no clinical practice guideline for kidney function monitoring in adult cancer survivors. Patterns of clinical practice regarding renal function monitoring in elderly cancer patients after completion of cancer treatment, especially patients treated with nephrotoxic chemotherapeutic agents, are unknown.

I conducted three retrospective cohort studies using the linked SEER-Medicare data to investigate (1) the association between adjuvant chemotherapy and risk of AKI among elderly women with breast cancer, (2) the association between adjuvant chemotherapy and risk of CKD among elderly women with breast cancer, and (3) clinical practice patterns of kidney function monitoring among elderly breast cancer patients after completion of treatment by adjuvant chemotherapy status.

I chose breast cancer for the proposed body of work based on the following considerations. First, breast cancer is a major public health issue. In the U.S., breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer death in women. An estimated 207,090 women were diagnosed with breast cancer (28% of all female cancer cases and 13.5% of all incident cancers) and 39,840 died of breast cancer (15% of all female cancer deaths and 7% of all cancer deaths) in 2010.[52]

Second, breast cancer has a high survival rate. Approximately 89% of breast cancer patients survive for more than 5 years, and the 5-year relative survival is higher among women with a less advanced stage at diagnosis (98% for localized disease) and among women diagnosed with breast cancer at age 40 or older (90%).[118] With advances in early detection and effective treatment of cancer, the number of cancer survivors increased in the U.S. from approximately 3 million in 1971 to 12 million in 2007.[119] Breast cancer survivors represented the largest proportion of female cancer survivors (41%) and of all cancer survivors (22%) on January 1, 2008.[53]

Finally, the evidence of nephrotoxicity for chemotherapeutic agents commonly used in the treatment of breast cancer is lacking. Though nephrotoxicity caused by high-

dose MTX has been extensively investigated, low-dose MTX is usually used in conjunction with cyclophosphamide and 5-FU (CMF regimen) in treating breast cancer patients in the adjuvant setting. Whether low-dose MTX could cause nephrotoxicity remains unknown. In addition, recent animal studies suggested that doxorubincin, another widely used anthrocycline agent in breast cancer treatment, may induce renal damage through oxidative stress. No population-based studies have evaluated nephrotoxcity induced by doxorubincin.

Chapter 3 Methods

3.1 Data source

This study used a database developed by the U.S. National Cancer Institute (NCI) and the Center for Medicare & Medicaid Services (CMS). The NCI-sponsored Surveillance, Epidemiology, and End Results (SEER) program includes population-based tumor registries that routinely collect information on all newly diagnosed cancer (incident) cases in SEER areas since January 1, 1973. In 1991, when the SEER data were initially linked to Medicare, the SEER areas included the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah, and the metropolitan areas of Detroit, San Francisco-Oakland, Atlanta, and Seattle-Puget Sound, representing approximately 10% of the U.S. population. In 1992, two registries from Los Angeles County and the San Jose-Monterey areas became available, increasing the SEER representation to approximately 14% of the U.S. population. In 2000, four registries from Kentucky, Louisiana, New Jersey, and the remainder of California were added, increasing the SEER area coverage to approximately 25% of the U.S. population. The SEER registries collect information about each incident cancer case from multiple reporting sources such as hospitals, outpatient clinics, laboratories, private medical practitioners, nursing/convalescent homes/hospices, autopsy reports, and death certificates.[119] The information collected includes demographic characteristics such as age, sex, race, and marital status; cancer-related characteristics such as tumor location, size, histology, American Joint Committee on Cancer (AJCC) stage, axillary node status, grade, and estrogen receptor status; and type of treatment

provided within 4 months of diagnosis, follow-up of vital status, and cause of death, if applicable.

The CMS-sponsored Medicare program is the primary health insurer for 97% of the U.S. population aged ≥ 65 years. All Medicare beneficiaries receive Part A (hospital insurance) coverage for inpatient care, skilled nursing facilities, home health, and hospice care. Ninety-five percent of beneficiaries also subscribe to Part B (medical insurance) coverage for physician services, outpatient care, durable medical equipment, and in some cases home health.[119]

The linkage of SEER and Medicare data is conducted by NCI and CMS based on an algorithm involving a match of Social Security number, name, sex, and date of birth.[120] The SEER data available as part of SEER-Medicare files are in the Patient Entitlement and Diagnosis Summary File (PEDSF), which includes all SEER data, Medicare eligibility, Medicare demographic variables, reason for Medicare entitlement, and health maintenance organization (HMO) enrollment for each individual in the SEER data who has been matched with Medicare enrollment records. The Medicare data available as part of SEER-Medicare files are claims from Medicare Provider Analysis and Review (MedPAR) short-stay hospital, MedPAR skilled nursing facility, home health agency, hospital outpatient, physician, and hospice providers. All Medicare files include information on demographics, date(s) of service, diagnostic codes, and procedure codes, in addition to the amounts of charges and reimbursement. The SEER-Medicare 2010 linkage data include cancer cases reported to SEER from 1973 through 2007 and all associated Medicare claims from 1991 (1998 for incident cases 2003 to 2005 and 2000

for incident cases 2006 to 2007) to 2009. Medicare hospitalization claims are available back to 1986.

3.2 Study Population, Inclusion and Exclusion Criteria

The study population includes women who were diagnosed with unilateral breast cancer from 1992 to 2007, surgically treated, aged 66-89 years at the time of diagnosis, and continuously enrolled in Medicare both Part A and Part B during the month of diagnosis and the 12 months before the month of diagnosis.

The study population excludes women who participated in an HMO during the month of diagnosis or the 12 months before diagnosis because Medicare claims data are often incomplete for these patients; women who were diagnosed with AJCC stage 0 or stage IV disease because adjuvant chemotherapy treatment is the focus of the study; women who had liver disease because liver disease affects chemotherapy use; women who had claims evidence of AKI, CKD, or ESRD before diagnosis of primary breast cancer because AKI and CKD are the two main outcomes under study; and women who had a prior breast cancer or other cancer, had claims evidence of cancer in situ or metastasis, had claims evidence of cancer treatment including radiotherapy, chemotherapy, breast-conserving surgery, or mastectomy, to ensure that breast cancer is the first primary cancer and that patients are treatment naive at the time of study.

3.3 Study Design

The study used a 1:1 individually matched, retrospective cohort design to compare the risk of AKI and CKD and to evaluate kidney function monitoring between

chemotherapy-treated and untreated breast cancer patients. Breast cancer patients with advanced stages or hormone receptor negative tumors were more likely to receive chemotherapy. Other non-tumor related factors may also affect decisions about chemotherapy treatment in elderly patients, including age, race, and presence of comorbid conditions, which are also risk factors for AKI and CKD.[1;65;76;77] Matching may reduce treatment selection bias because of factors that may have influenced physicians or patients to choose chemotherapy and may be related to the outcomes.[121]

Because time from the first cancer-directed surgery to initiation of adjuvant chemotherapy varies among patients treated with chemotherapy, and the underlying hazard of AKI and CKD may not be constant after surgery, time-dependent matching at the day of chemotherapy initiation was used. For all patients who met the study inclusion and exclusion criteria, initiation of adjuvant chemotherapy was identified within 6 months (183 days) after the date of first surgery. Cox proportional hazards modeling was used to estimate the probability of initiating adjuvant chemotherapy at each day of follow-up for each patient. At each time point when one or more patients initiated adjuvant chemotherapy, patients who received chemotherapy on that day were individually matched using the Greedy Match algorithm[122] with patients who had the same or similar probability of receiving chemotherapy but had not yet initiated chemotherapy on that day. Detailed information on time-dependent matching is described in Section 3.5.1.

The assembled matched cohorts were used in the analyses for all three objectives with different follow-up start and end dates defined for each study objective. For

objectives 1 and 2, follow-up began on the chemotherapy initiation date of the matched treated patient for each matched pair. For objective 1, follow-up ended at AKI occurrence, CKD diagnosis, death, change in Medicare both Part A and Part B enrollment, participation in an HMO, development of second non-breast cancer, or 6 months after the follow-up start date, whichever came the earliest. For patients in the matched untreated cohort, follow-up time was also censored at initiation of chemotherapy after first surgery. For objective 2, follow-up time was not censored at AKI occurrence and the follow-up end date was extended to December 31, 2009, if no other censoring events occurred.

Because objective 3 was to compare utilization of kidney function monitoring tests between chemotherapy-treated and untreated patients after completion of treatment, the period of time when patients were under chemotherapy treatment should not be considered. Therefore, for patients who were treated with chemotherapy, the follow-up period began on the day following completion of the adjuvant chemotherapy course. Since the chemotherapy course duration varied, time from the matching date to follow-up start date was different among treated patients. To ensure that similar time elapsed for patients in the matched untreated cohort, the follow-up start date for the untreated cohort was the date of matching plus the median course duration (112 days). Thus, on average, an equal time period elapsed after the matching date between the two cohorts. Follow-up ended at diagnosis of CKD, development of a second non-breast primary cancer, death, change in Medicare both Part A or Part B enrollment, participation in an HMO, or December 31, 2009, whichever occurred the earliest. For patients who received

chemotherapy for treatment of recurrence or non-breast primary cancer, the duration of the subsequent chemotherapy course(s) was excluded from the follow-up period because kidney function was likely monitored during the treatment. Because lab tests were likely performed a few days before or on the day of chemotherapy treatment to examine patient health status, one week before the initiation of a subsequent chemotherapy course was also excluded to avoid counting pre-chemo kidney function testing as kidney function monitoring after treatment. Comorbid conditions were re-evaluated for all patients during the 12 months before follow-up began to control for residual confounding in the analysis stage. The outcome of interest was the total number of laboratory tests assessing renal function for each type. If the renal-related laboratory test occurred on the same day as CKD diagnosis, the laboratory test was not considered because it may be the diagnostic test for CKD, not screening for CKD.

3.4 Definitions of Study Variables

3.4.1 Chemotherapy

Chemotherapy exposure was identified using a constellation of *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes and procedure codes, Current Procedure and Terminology (CPT) codes, Healthcare Common Procedure Coding System (HCPCS) codes, revenue codes, and Diagnosis-Related Groups (DRG) codes in Medicare inpatient, outpatient, and physician claims. Hospital claims contain ICD-9-CM diagnosis codes, ICD-9-CM procedures codes, and DRG codes that were used to identify chemotherapy administration, but not specific

agents. Chemotherapeutic agents were identified through HCPCS codes reported on outpatient and physician claims. Chemotherapy administration in an outpatient setting was identified through ICD-9-CM diagnosis and procedure codes and revenue codes reported on outpatient claims, and through ICD-9-CM diagnosis codes and CPT codes reported on physician claims. Codes used to identify receipt of chemotherapy are detailed in Table A.1 in Appendix A.

Three chemotherapy regimens were studied: anthracycline-based, CMF, and taxane-based. These regimens were defined by the following hierarchy order: anthracyclines->CMF->taxane. Anthracycline-based chemotherapy was defined if patients received doxorubicin or eprirubicin whether or not other agents were also given. A CMF regimen was defined if patients received cyclophosphamide, methotrexate, and 5-fluorouracil in the absence of doxorubicin or eprirubicin. Taxane-based chemotherapy was defined if patients received docetaxel or paclitaxel in the absence of anthracyclines and CMF. Using this hierarchy order, three major types of chemotherapy were defined mutually exclusively because patients treated with an anthracycline-based regimen could have also received cyclophosphamide, 5-fluorouracil, or a taxane in addition to an anthracycline. Further, use of non-anthracycline-containing taxane-based chemotherapy has rapidly increased after 2005 due to the concern about cardiotoxicity associated with anthracycline-based chemotherapy.[123] Patients who received none of the three regimens were grouped into “other” category. Codes used to define specific chemotherapy agents in these regimens are presented in Tables A.2 in Appendix A.

Patients were identified as having received chemotherapy if they had a claim

carrying a general chemotherapy procedure code, a diagnosis code for chemotherapy administration, or a HCPCS code for a specific agent. For inpatient claims for chemotherapy, chemotherapy date was defined as date of admission. For outpatient and physician claims, chemotherapy date was defined as date of service.

Chemotherapy course was defined from the first chemotherapy claim within the study period (12-month baseline period before diagnosis plus the follow-up period after diagnosis) until the last chemotherapy claim with a less than 60-day gap between two consecutive claims based on the method described in a previous publication[124] with slight modification. If a chemotherapy claim occurred 60 days or more after the date of service of the prior chemotherapy claim, that was considered the first claim of the next chemotherapy course. Adjuvant chemotherapy was defined as chemotherapy initiation within 6 months following the first cancer-directed surgery.

Use of Medicare claims data to identify patients receiving chemotherapy was anticipated to have a high level of accuracy and completeness because chemotherapy is covered by Medicare and because of the nature of chemotherapy treatment (expensive, lengthy, and more likely administered in an outpatient setting).[126] The facility/provider receives reimbursement for both drug costs and drug administration fees, and is therefore motivated to report accurately.

3.4.2 Acute Kidney Injury

AKI was identified through ICD-9-CM diagnosis codes and ICD-9-CM procedure codes, revenue codes, and CPT codes indicating dialysis in the MedPAR short-stay hospital, outpatient, and physician claims. In the baseline period, patients with AKI

occurring in either the inpatient or the outpatient setting were identified and excluded from the study. In the follow-up period, AKI occurring in the inpatient setting was the event of interest to evaluate the association between adjuvant chemotherapy and risk of AKI. The date of AKI was defined as the hospital admission date for AKI. Codes used to identify patients with AKI are detailed in Table B1 of Appendix B.

The accuracy of ICD-9-CM codes for identifying patients with AKI has been assessed by Waikar et al[127] using the linked administrative and laboratory data from 97,705 adult discharges from three Boston hospitals in 2004. They reported that ICD-9-CM diagnosis codes for AKI (584.5-584.9) had a sensitivity of 35.4%, specificity of 97.7%, positive predictive value (PPV) of 47.9%, and negative predictive value (NPV) of 96.1%, and the ICD-9-CM procedure codes for dialysis had a sensitivity of 90.4%, specificity of 93.8%, PPV of 94.0%, and NPV of 90.0%.

3.4.3 Chronic Kidney Disease

CKD was identified through ICD-9-CM diagnosis codes in Medicare claims based on a previously published methodology that has been validated for identification of diabetic patients using Medicare claims.[128] Patients were considered to have CKD if they had at least one MedPAR short-stay hospital, MedPAR skilled nursing facility or home health agency claim, or at least two hospital outpatient or physician/supplier claims on different dates within a 12-month interval carrying the ICD-9-CM diagnosis codes for chronic renal insufficiency, diabetic nephropathy, hypertensive nephropathy, AKI, or miscellaneous other renal disease. The diagnosis codes for AKI were included in identifying CKD only in the presence of additional claims with other qualifying diagnosis

codes for CKD. The earliest date of claims with the qualifying diagnosis codes was defined as the CKD index date. Table B.2 in Appendix B lists the ICD-9-CM diagnosis codes used to identify CKD.

The method used to identify CKD patients in this study is based on a previously published methodology that has been validated for the identification of diabetic patients using Medicare claims.[128] Application of the same method to identify patients with CKD in Medicare beneficiaries with breast cancer has not been validated. However, two studies have examined the validity of using similar renal-related ICD-9-CM diagnosis codes to identify patients with CKD stages 3-5 in two patient groups.[129;130] The results showed similar specificity (93%), 74% to 89% PPV, 27% to 42% sensitivity, and 37% to 78% NPV.

Of note, CKD patients identified using the methodology described above tend to have clinically apparent kidney disease for which the providers submit claims for clinical care services. Therefore, patients identified as having CKD using the claims-based definition represent patients with recognized CKD from the diagnoses codes in the Medicare claims and are likely to be in later stages of kidney disease and not to have mild kidney disease.[7]

3.4.4 Assessment of Kidney Function

In this study, kidney function monitoring includes laboratory blood testing of serum creatinine to determine whether the kidneys are functioning normally, and urine testing for albumin and albumin-to-creatinine ratio (ACR) to detect whether there is early damage to the kidneys. These measures were identified through CPT codes in the carrier

and outpatient claims. For services identified in the carrier claims, date of laboratory test was defined as the "line first expense date." For services identified in the outpatient claims, date of service was defined as the "claim from" date. Codes used to identify renal laboratory tests and renal imaging procedures are presented in Appendix C.

For the tests of serum creatinine and urine albumin, only one type of laboratory test was counted if the claim showed more than one CPT code indicating the same type of laboratory test on the same service day. Urinary ACR assessment required CPT codes for both albumin and creatinine to be present on the claim on the same service day.

Validation studies of renal-related laboratory tests are not available. However, coding of laboratory tests in Medicare was anticipated to have a high level of accuracy. The facility/provider receives reimbursement for performing the tests, and is therefore motivated to report accurately.

3.4.5 Other Study Variables

Risk factors and potential confounders were selected based on the literature. Information on patient demographics, other patient characteristics, breast cancer-related clinical factors, and radiation therapy following breast cancer diagnosis were abstracted from the SEER registry database, while information on surgery type, comorbid conditions, cancer in situ, other primary cancer, metastatic cancer, and radiotherapy during the baseline period was obtained from the Medicare claims. The various data elements and the definitions are listed below.

Demographics and other patient characteristics

Patient demographic and other characteristics were identified in SEER registry data and included age defined on cancer diagnosis (66-69, 70-74, 75-79, 80-84, and 85-89 years), race (white, black, other), year of diagnosis (1992-2007), marital status (married, unmarried, unknown), and SEER areas (Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta/rural Georgia, Kentucky, Louisiana, New Jersey, California).

Breast cancer-related clinical factors

Breast cancer-related characteristics were obtained from SEER registry data and included AJCC stage (I, II, III), tumor grade (well-differentiated, moderately differentiated, poorly differentiated, unknown/missing), tumor size (< 2 cm, ≥ 2 cm, missing), hormone receptor status (estrogen receptor positive and/or progesterone receptor positive, estrogen receptor negative and progesterone receptor negative, unknown), histology (ductal, lobular, mixed, other), lymph node status (negative, positive, missing), and laterality (left, right).

Breast cancer-related treatment

Surgery type (breast-conserving surgery, mastectomy) was identified based on ICD-9-CM procedure codes and CPT codes in Medicare claims data within 4 months after cancer diagnosis.[131] SEER registry data code the most extensive procedure following an established hierarchy. If a patient underwent three procedures in the following order: biopsy->lumpectomy->mastectomy, mastectomy was coded as the type

of surgery. Using this method, surgery type was defined by the most extensive surgery in claims data. If the surgery was performed in hospital, date of surgery was defined as the admission date. If the surgery was performed in an outpatient setting, date of surgery was defined based on the service date. Table B.5 in Appendix B presents the ICD-9-CM procedure codes and CPT codes for breast-conserving surgery and mastectomy.

Radiotherapy (yes, no) for breast cancer treatment was identified in the SEER registry database and included beam radiation, radioactive implants, radioisotopes, or other radiation. Radiotherapy (yes, no) during the 12-month interval before breast cancer diagnosis was identified from Medicare claims carrying the following codes: CPT codes (77401-77499, 77520-77525, 77750-77799, G0256, G0261), ICD-9-CM procedure codes (92.21-92.29), revenue center codes (0330, 0333), DRG codes (409), and ICD-9-CM V codes (V58.0, V66.1, V67.1).

Comorbid conditions

Comorbid conditions were identified from Medicare claims during the 12-month interval before cancer diagnosis and the 12-month interval before chemotherapy initiation using a previously published methodology,[128] and include the following conditions (yes, no): atherosclerotic heart disease (ASHD), cerebrovascular accidents/transient ischemic attack (CVA/TIA), chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), dysrhythmia, diabetes mellitus, gastrointestinal (GI) disorders, other cardiovascular diseases, peripheral vascular disease (PVD), and hypertension. Table B.3 in Appendix B list the ICD-9-CM diagnosis codes used to identify each comorbid condition.

Cancer in situ, primary cancer, and metastatic cancer

Cancer in situ, primary cancer, and metastatic cancer were identified from Medicare claims during the 12-month interval before the diagnosis of the first primary breast cancer using a previously published methodology.[128] Table B.4 in Appendix B presents the ICD-9-CM diagnosis codes for these conditions.

Second non-breast primary cancer

Second non-breast primary cancer after the diagnosis of the first primary breast cancer was identified in SEER registry data.

3.5 Statistical Analysis

All statistical analyses were performed using SAS 9.1.3 software (SAS Institute, Cary, NC) unless otherwise indicated.

3.5.1 Sequential Matching on Time-Dependent Propensity Score

The following steps were used to perform sequential matching on time-dependent propensity score. First, the probability (i.e., propensity score) of initiating adjuvant chemotherapy on each day within 6 months (183 days) after the date of first cancer-directed surgery was estimated using the Cox proportional hazards model.[132] All patients who met the study inclusion and exclusion criteria were followed from the date of first surgery to initiation of adjuvant chemotherapy; occurrence of AKI; diagnosis of CKD, liver disease, or non-breast primary cancer; change of Medicare Part A or Part B enrollment status; participation in an HMO; death; or 6 months (183 days) after the date of first surgery, whichever came earliest. The following patient and tumor characteristics,

which may affect the choice of chemotherapy and outcome, were included in the Cox model as predictors: age, race, marital status, tumor stage, tumor grade, tumor size, node status, estrogen/progesterone receptor status, comorbid conditions, radiation therapy, mastectomy status, year of diagnosis, and SEER area.

Then, at each time point when one or more patients initiated adjuvant chemotherapy, patients who received chemotherapy were individually matched using the Greedy Match algorithm[122] with patients who had the same or similar probability of initiating chemotherapy but had not yet initiated at that time point. Because the probability of initiating adjuvant chemotherapy during the 6-month period ranged from 0 to 1, the estimated daily probability would be much smaller. Thus, the matching algorithm was performed 8->2 digits to improve precision. On the day a patient initiated chemotherapy, this patient was first matched on 8 digits of the probability to a patient who had not yet initiated chemotherapy. If an appropriate match could not be formed, then a 7-digit match on the probability was attempted. This process was continued down to a 2-digit match on probability for patients who remained unmatched. If a treated patient could not be matched to any untreated patient on 2 digits, the treated patient was removed from the analysis. If more than one patient initiated chemotherapy at the same time point, these treated patients were ordered randomly and matching took place in order. If more than one untreated patient could be matched to a treated patient, the matched untreated patient was randomly selected. Patients who were matched to treated patients at an earlier time point were not included for future matching unless they initiated adjuvant chemotherapy later. Therefore, it is possible that patients in the

matched treatment cohort could also appear in the matched no-treatment cohort. The correlation was addressed in the analysis stage using the robust variance estimation. Because patterns of care for breast cancer patients and recognition of AKI and CKD in the Medicare claims database may change over years, matching was performed by year of cancer diagnosis. The SAS Macro program by Parsons was used to form matched pairs.[133]

Finally, balance in baseline characteristics between the treatment cohort and the matched no-treatment cohort was assessed using the standardized difference[134] with the following equation:

$$\text{Standardized difference} = \frac{|P_t - P_c|}{\sqrt{\frac{P_t(1-P_t)+P_c(1-P_c)}{2}}}$$

where P_t and P_c denote the proportion of a given level of a categorical baseline variable in the treatment and the matched no-treatment cohorts, respectively.

A standardized difference of less than 0.1 (10%) represents a rule-of-thumb for an acceptable balance in covariate distribution between treated and untreated subjects.[135-137]

3.5.2 Patient Baseline Characteristics

The distributions of patient characteristics were summarized for all patients, for patients who did and did not receive adjuvant chemotherapy before matching, and for patients in each study cohort after matching. Since all patient characteristics were defined as categorical variables, standard descriptive statistics such as counts and percentages were used to summarize the distributions. The chi-square test was used to compare frequency distributions of baseline characteristics between chemotherapy-treated and

untreated cohorts before matching. Standardized difference was used to evaluate balance in baseline characteristics before and after matching.

The distribution of patient characteristics was also reported for patients who received each of the four types of chemotherapy including anthracycline-based, CMF, taxane-based, and others.

3.5.3 Objective 1 Adjuvant Chemotherapy Treatment and Risk of AKI

Counts and proportions of patients who were admitted to hospital for AKI and rate of AKI during the 6-month follow-up period were summarized for treated and matched untreated cohorts. Mean and median follow-up time was also examined.

The cumulative incidence of AKI during the 6-month follow-up period was assessed using the Kaplan-Meier method. Cumulative incidence curves were stratified by adjuvant chemotherapy status. Differences in the cumulative incidence curves between the two cohorts were evaluated using the log-rank test.

Since baseline patient characteristics were expected to be balanced in the matched cohorts, a Cox proportional hazards model with adjuvant chemotherapy use as the only independent variable was used to estimate the hazards ratio of AKI hospitalization for patients who received adjuvant chemotherapy compared with those who did not. Robust variance estimation was used to incorporate intra-patient correlation between the treatment and matched no-treatment cohorts.[138]

Because a matched cohort study design may not achieve the perfect balance in patient baseline characteristics between the treated and matched untreated cohorts as a

randomized clinical trial would, the association between adjuvant chemotherapy and risk of AKI was reexamined including all factors listed in Section 3.4.5 in the Cox model.

The analyses were repeated by regimen type (anthracycline-based, CMF, taxane-based, others) with the matched untreated cohort as the comparison group to evaluate the effect of regimen type on risk of AKI with adjustment for patient baseline characteristics.

3.5.4 Objective 2 Adjuvant Chemotherapy Treatment and Risk of CKD

3.5.4.1 Primary Analyses

Counts and proportions of patients with claims evidence of incident CKD and incidence rate of CKD during the follow-up period were summarized by adjuvant chemotherapy status. Incidence rate of CKD was defined as the ratio of the number of patients with claims evidence of CKD diagnosis divided by the total person-years at risk. The cumulative incidence of recognized CKD was assessed using the Kaplan-Meier method. Cumulative incidence curves were stratified by adjuvant chemotherapy use. Differences in the cumulative incidence curves between the two cohorts were evaluated using the log-rank test.

A Cox proportional hazards model with adjuvant chemotherapy as the only independent variable was used to evaluate the association between adjuvant chemotherapy and risk of CKD. A robust covariance estimator was included in the Cox model to account for within-pair correlation.[138] The assumption of proportionality of the hazards was assessed graphically with a Schoenfeld residual plot to determine whether a horizontal line was present in the graph. As explained in Section 3.5.3, the effect of

adjuvant chemotherapy on risk of CKD was reexamined with all factors listed in Section 3.4.5 included in the Cox model.

The analyses were repeated by regimen types (anthracycline-based, CMF, taxane-based, others) with the untreated cohort as the comparison group to evaluate the effect of regimen type on risk of incident CKD with adjustment for patient baseline characteristics.

3.5.4.2 Sensitivity Analysis

Initiation of adjuvant chemotherapy as a time-varying covariate

All patients who met the inclusion and exclusion criteria were included in this analysis. Initiation of adjuvant chemotherapy within 6 months after the first surgery was defined as a time-varying variable. The time-varying Cox proportional hazards model with robust covariance estimate was used to estimate the hazards ratio of CKD for patients who received adjuvant chemotherapy compared with patients who did not.

Competing risk analyses

In the primary analyses, death was one of the censoring events for time to CKD, under the assumption that patients who die are subject to the same risks of CKD after death as those remaining under observation. By this method, the estimated relative hazard of CKD for patients who received adjuvant chemotherapy compared with patients who did not represents the risk of CKD associated with chemotherapy ignoring anything that happened before CKD onset.

In reality, although chemotherapy may increase the risk of CKD, this risk for patients who are likely to die before they develop CKD may not be of concern. For this

purpose, death is a competing event with CKD. To evaluate the effect of chemotherapy on risk of CKD during the time interval when patients remained alive, a competing risk analysis was performed for patients in the matched cohorts. The estimated relative hazard of CKD for adjuvant chemotherapy compared with no adjuvant chemotherapy reflects the association between chemotherapy and risk of CKD when patients were alive.

The cumulative incidence method was used to report the observed event probabilities of CKD and death. A Cox regression model was used with the Fine-Gray method[139] to assess competing risk and adjust for all factors listed in Section 3.4.5.

Subgroup analyses by course duration

Associations between adjuvant chemotherapy and risk of CKD were re-examined for subgroups of patients who received shorter chemotherapy treatment (≤ 1 week) and patients who received longer treatment (> 1 week).

3.5.5 Objective 3 Utilization of Kidney Function Monitoring Tests

Since the follow-up start date in this study was no longer the date of initiation of adjuvant chemotherapy for patients in the treatment cohort and the matched date for patients in the no-treatment cohort, the balance in patient characteristics achieved from matching may not be preserved. The distributions of patient characteristics were reexamined. Differences in patient characteristics between the treatment and no-treatment cohorts were evaluated using the chi-square test.

The cumulative percentage of patients receiving at least one laboratory test related to renal function during the follow-up period was assessed using the Kaplan-Meier

method for patients who were and were not treated with adjuvant chemotherapy. Differences in assessment of renal function between the two study cohorts were tested using the log-rank test. In this analysis, time to the first laboratory test was the event of interest. Thus, follow-up also ended at the date of first laboratory test for patients whose kidney function was assessed.

Following the initial comparison of time to first renal function assessment between patients who did and did not receive adjuvant chemotherapy, the frequency of renal function assessment was examined in three intervals during the follow-up period. The cutoffs of follow-up intervals were ≤ 1 year, > 1-≤ 2 years, and > 2-< 18 years. All patients who survived the previous interval were included in the analysis for the subsequent interval. In this analysis, the total number of tests per patient (i.e., multiple events) was the outcome of interest. For each interval, person-time was defined from the beginning of the interval to the end of the interval or the end of follow-up. The unadjusted rate of renal-related testing was calculated as the ratio of the total number of kidney function laboratory tests divided by the total person-years of follow-up and measured as number of tests per 1,000 patient-years. The rate ratio of renal function testing in chemotherapy-treated patients compared with untreated patients was estimated using an interval Poisson regression model with adjustment for baseline characteristics including patient demographics, comorbid conditions, and tumor characteristics.

Analyses were performed for each laboratory test.

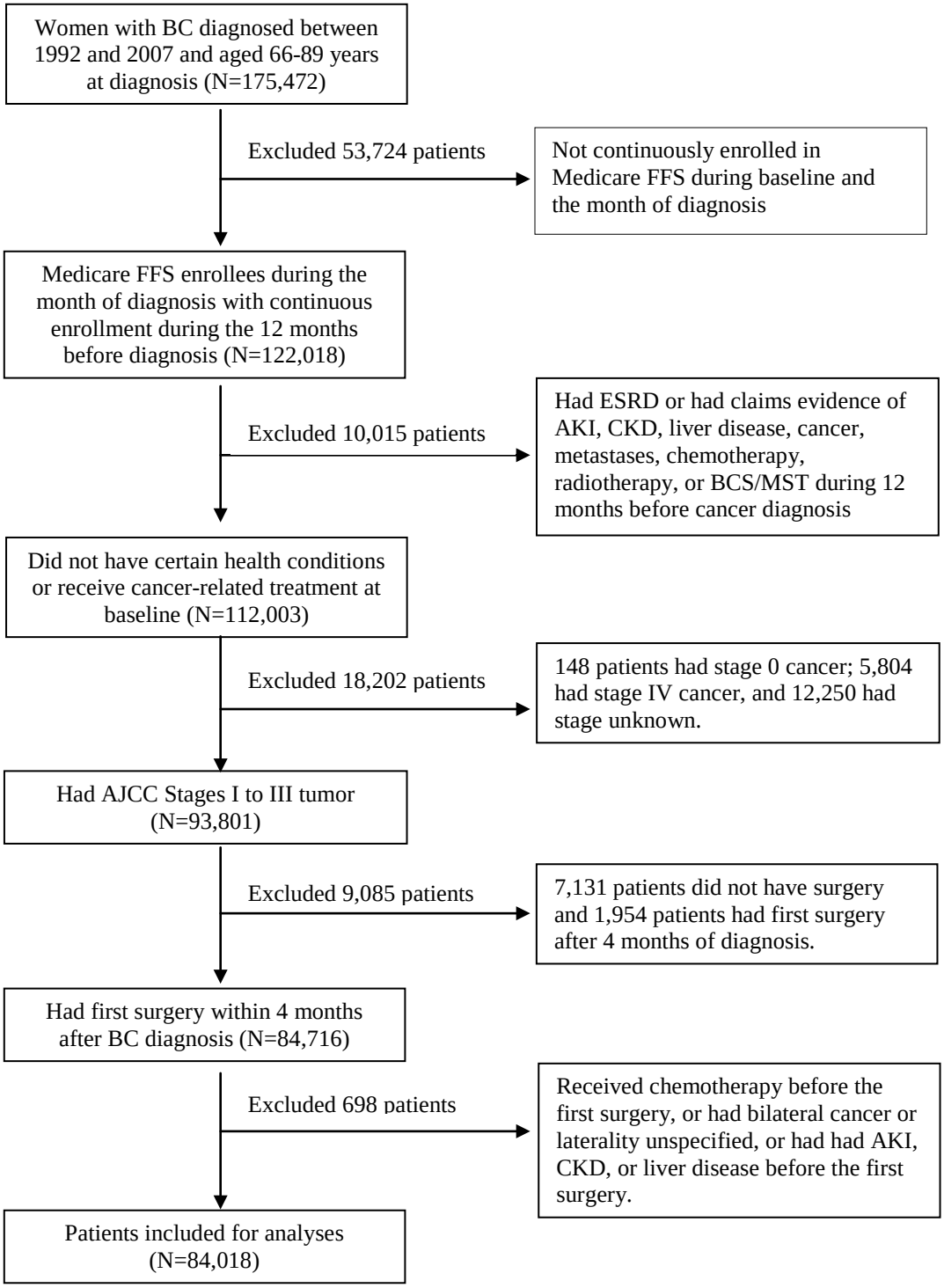
Chapter 4 Results

This chapter is divided into four components. The first presents patient characteristics for the study cohorts before and after time-dependent matching. The remaining three components sequentially present the results of objectives 1, 2, and 3.

4.1 Patient Baseline Characteristics

A total of 175,472 women with breast cancer diagnosed between 1992 and 2007 and aged 66 to 89 years at diagnosis were identified in SEER-Medicare linkage data. Of these women, 84,018 met the study inclusion and exclusion criteria. Figure 4-1 illustrates the process of patient selection.

Figure 4-1 Flow diagram for selection of patients. AKI, acute kidney injury; BC, breast cancer; BCS, breast-conserving surgery; CKD, chronic kidney disease; FFS, fee-for-service; MST, mastectomy



Of women included in the study, 14,725 (17.5%) received adjuvant chemotherapy. Demographic characteristics, tumor characteristics, and comorbid conditions differed substantially between patients who were and were not treated with adjuvant chemotherapy. Patients who received adjuvant chemotherapy, compared with patients who did not, were younger, more often black, diagnosed at later stages, more likely to be hormone receptor negative, more likely to undergo mastectomy, more likely to have diabetes at baseline, and less likely to have cardiovascular disease or other comorbid conditions at baseline (Table 4-1).

Of 14,725 patients treated with adjuvant chemotherapy, 14,024 (95.2%) could be individually matched to untreated patients at the time of chemotherapy initiation. Of these patients, 3,982 (28.4%) were also present in the matched no-chemotherapy cohort. A total of 516 patients (3.7%) in the matched no-chemotherapy cohort also initiated adjuvant chemotherapy at a later time after matching, but could not be matched to an untreated patient at the time of chemotherapy initiation.

After matching, differences in baseline characteristics between chemotherapy-treated and no-chemotherapy patients were greatly reduced. Standardized differences were computed for each of the baseline variables before and after matching. The standardized differences after matching were less than 10% for all levels of baseline characteristics, indicating a good balance achieved through matching between the distribution of patient characteristics in the matched chemotherapy and no-chemotherapy cohorts (Table 4-1).

Table 4-1 Patient characteristics by adjuvant chemotherapy status before and after matching

		Before Matching			After Matching		
	All BC	No CHEMO	Any CHEMO	SD	No CHEMO	Any CHEMO	SD
Sample size, n	84,018	69,293	14,725		14,024	14,024	
Age at diagnosis, yr.							
66-69	21.5	17.8	38.8	0.480	35.4	37.8	0.050
70-74	27.6	26.1	34.3	0.179	35.1	34.6	0.010
75-79	25.4	26.6	19.6	0.168	21.2	20.1	0.027
80-84	17.3	19.6	6.2	0.409	6.1	6.4	0.012
85-89	8.3	9.8	1.1	0.392	2.2	1.1	0.086
Race							
White	90.2	90.8	87.6	0.101	88.1	87.8	0.008
Black	5.8	5.3	7.8	0.101	7.6	7.7	0.003
Other	4.0	3.9	4.5	0.031	4.3	4.5	0.008
Marriage status							
Single	52.3	53.8	44.8	0.181	45.8	45.0	0.016
Married	44.6	42.9	52.3	0.188	51.1	52.1	0.019
Unknown	3.2	3.3	2.9	0.021	3.1	2.9	0.010
Year of diagnosis							
1992	4.4	4.8	2.6	0.117	2.7	2.7	
1993	4.2	4.6	2.5	0.114	2.5	2.5	
1994	4.1	4.4	2.7	0.096	2.7	2.7	
1995	4.2	4.5	2.6	0.106	2.6	2.6	
1996	3.9	4.2	2.6	0.093	2.6	2.6	
1997	4.2	4.3	3.3	0.051	3.4	3.4	
1998	4.1	4.1	3.9	0.010	3.9	3.9	
1999	4.2	4.2	4.4	0.011	4.4	4.4	
2000	7.5	7.3	8.6	0.047	8.6	8.6	
2001	9.0	8.7	10.5	0.062	10.5	10.5	
2002	8.9	8.6	10.2	0.054	10.2	10.2	
2003	8.4	8.3	9.1	0.027	9.0	9.0	
2004	8.5	8.3	9.3	0.035	9.3	9.3	
2005	8.3	8.1	9.4	0.044	9.3	9.3	
2006	8.1	7.8	9.4	0.056	9.3	9.3	
2007	7.8	7.6	9.0	0.053	8.9	8.9	
SEER area							
California	31.7	32.0	30.3	0.037	30.6	30.6	0.000
Connecticut	10.1	10.4	8.4	0.070	8.6	8.4	0.009
Detroit	10.8	10.5	12.3	0.057	12.1	12.1	0.002
Hawaii	1.8	1.8	2.1	0.025	1.9	2.1	0.014
Iowa	10.8	11.3	8.5	0.093	8.6	8.7	0.006
New Mexico	3.1	3.2	2.5	0.038	2.5	2.6	0.007
Seattle	3.6	3.7	3.4	0.017	3.5	3.4	0.008
Utah	3.8	3.6	4.3	0.035	4.2	4.3	0.005
Atlanta/rural Georgia	4.6	4.6	4.6	0.001	4.5	4.6	0.003
Kentucky	5.4	5.3	5.8	0.022	6.2	5.7	0.019
Louisiana	4.3	4.0	5.5	0.067	5.4	5.4	0.002
New Jersey	10.0	9.6	12.3	0.087	11.9	12.1	0.006
AJCC stage							
Stage I	57.4	65.6	19.0	1.069	18.9	19.8	0.022

Stage II	35.8	30.2	62.6	0.689	66.0	62.7	0.070
Stage III	6.7	4.3	18.3	0.456	15.0	17.5	0.067
Size, cm							
< 2	60.2	65.3	36.1	0.611	36.6	36.6	0.002
≥ 2	37.4	32.3	61.6	0.616	61.3	61.1	0.004
Unknown	2.4	2.5	2.3	0.012	2.0	2.3	0.018
Positive lymph node							
Negative	62.6	68.5	34.7	0.721	36.9	36.0	0.019
Positive	24.3	16.6	60.7	1.016	57.8	59.2	0.028
Unknown	13.0	14.8	4.6	0.351	5.2	4.8	0.022
Grade							
Well	21.7	24.3	9.2	0.411	10.7	9.6	0.036
Moderately	40.8	42.0	35.0	0.143	37.3	35.7	0.033
Poorly	25.3	20.9	46.0	0.553	42.0	44.8	0.058
Undifferentiated	1.3	1.2	2.0	0.063	1.7	2.0	0.016
Unknown	11.0	11.7	7.7	0.133	8.4	8.0	0.015
Histology							
Ductal	69.1	68.5	71.8	0.071	70.1	71.6	0.032
Lobular	10.0	9.9	10.4	0.016	11.4	10.6	0.024
Mixed	10.5	10.5	10.3	0.005	10.6	10.4	0.008
Unknown	10.4	11.1	7.5	0.124	7.9	7.4	0.017
ER/PR status							
ER + and/or PR +	73.9	77.0	59.3	0.387	64.0	60.5	0.071
ER- and PR-	12.6	8.9	30.1	0.556	24.6	28.6	0.091
Unknown	13.5	14.1	10.6	0.108	11.4	10.8	0.019
Laterality, right	51.1	51.0	51.9	0.018	51.1	51.8	0.014
Surgery type/RT							
BCS with RT	37.6	39.5	28.7	0.231	31.8	29.1	0.059
BCS without RT	15.7	16.2	13.6	0.071	11.6	13.6	0.061
Mastectomy	46.7	44.3	57.7	0.271	56.6	57.3	0.014
Comorbid conditions							
ASHD	14.7	15.3	11.8	0.103	12.2	11.7	0.015
CHF	6.5	7.0	4.1	0.127	4.5	4.1	0.020
CVA/TIA	5.8	6.2	4.1	0.097	4.3	4.1	0.010
Dysrhythmia	12.7	13.5	9.0	0.142	9.8	9.0	0.025
PVD	7.5	8.0	5.1	0.115	5.6	5.2	0.018
Cardiac, other	10.9	11.3	9.2	0.070	9.9	9.2	0.023
Anemia	9.0	9.3	7.8	0.055	8.1	7.7	0.017
COPD	10.4	10.6	9.1	0.053	9.3	9.0	0.009
Diabetes	16.3	16.1	17.5	0.039	17.9	17.3	0.015
GI disorder	2.4	2.5	2.0	0.034	2.2	2.0	0.011
Hypertension	54.6	54.8	53.6	0.025	54.0	53.3	0.013

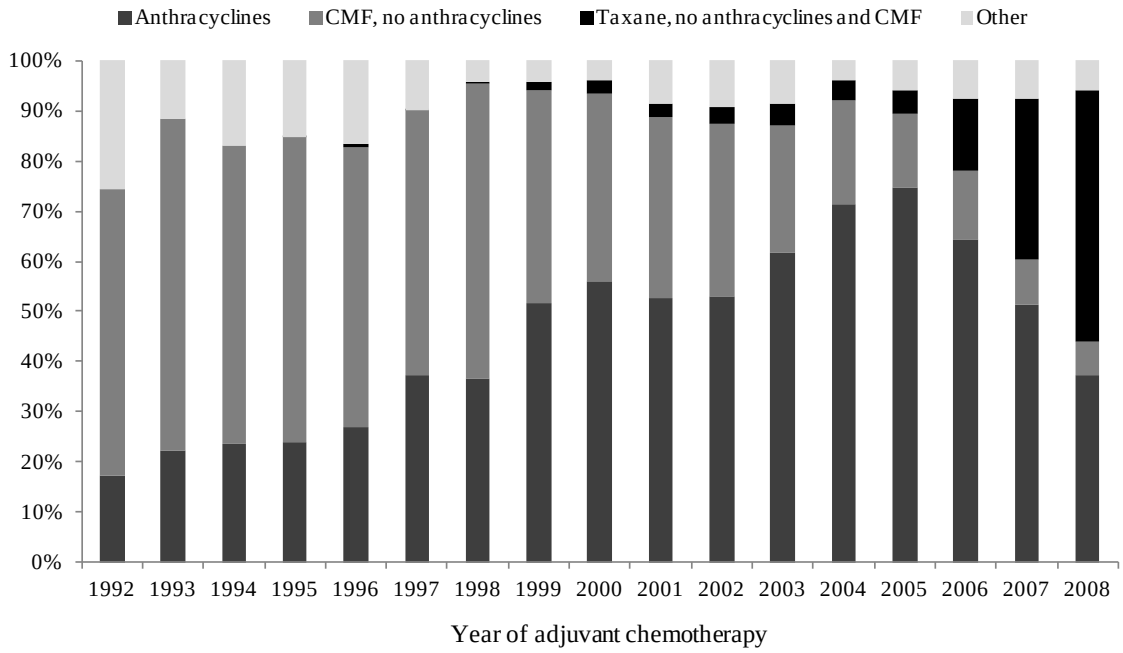
Note: Values are percentages unless otherwise indicated. Before matching, patient characteristic comparisons between chemotherapy treatment and no-treatment cohorts were statistically significant ($P < 0.05$) for all variables. Cox proportional hazards modeling including all the factors listed in this table as independent variables was used to estimate the probability of initiating adjuvant chemotherapy at each day within 6 months after first breast-conserving surgery or mastectomy for each patient. At each time point when one or more patients initiated adjuvant chemotherapy, patients who received chemotherapy on that day were individually matched using the Greedy Match algorithm performed 8->2 digits with those who had the same or similar probability but had not yet initiated chemotherapy on that day. A standardized difference of less than 0.1 (10%) represents a rule-of-thumb for an acceptable balance in covariate distribution between treated and untreated subjects.

Abbreviation: AJCC, American Joint Committee on Cancer; ASHD, atherosclerotic heart disease; BC, breast cancer; BCS, breast-conserving surgery; CHF, congestive heart failure; CHEMO, chemotherapy; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; ER, estrogen receptor; GI, gastrointestinal; PR, progesterone receptor; PVD, peripheral vascular disease; SD, standardized difference.

Of patients in the matched treatment cohort, 53.2%, 31.3%, 7.3%, and 8.1% received an anthracycline-based regimen, CMF (without anthracyclines), a taxane-based regimen (without anthracyclines and CMF), and other chemotherapy, respectively. Among 1,140 patients who received other chemotherapy, 769 (67%) received one or more different chemotherapeutic agents that could not be classified as one of the three major regimen types, and for 371 (33%) no chemotherapeutic agents were reported on Medicare claims. Trastuzumab, approved by the U.S. Food and Drug Administration (FDA) on November 16, 2006, as part a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel for the adjuvant treatment of women with node-positive, HER2-overexpressing breast cancer, was used most often with a taxane-based regimen (29.1%), followed by other chemotherapy (11.2%), an anthracycline-based regimen (5.1%), and CMF (0.3%). The proportion of trastuzumab use in patients treated with adjuvant chemotherapy was low (< 2.5%) before 2005, but increased rapidly from 12.5% in 2005 to about 20% in 2008.

Figure 4-2 presents the trends in use of the major types of chemotherapy by year of initiation. Use of anthracycline-based chemotherapy increased steadily from 1992 to 2005, and decreased after 2005. CMF regimens had been the major choice of treatment in the 1990s; more than half of chemotherapy-treated patients received CMF, but use decreased rapidly after 1999 and occurred for only 7% of patients who initiated adjuvant chemotherapy in 2008. Use of non-anthracycline-containing taxane-based chemotherapy was not common before 2005, but increased sharply from 4.4% in 2005 to 50% in 2008.

Figure 4-2 Trends in use of major chemotherapy regimen types by year of initiation of adjuvant chemotherapy



The balance in the distribution of patient characteristics between the matched chemotherapy-treatment and no-treatment cohorts was apparently not preserved for each type of adjuvant chemotherapy compared with no treatment (Table 4-2). Compared with patients in the matched untreated cohort, patients receiving anthracycline-based chemotherapy were younger, diagnosed at a later stage, more likely to have positive lymph nodes, more likely to be hormone receptor negative, and less likely to have comorbid conditions at baseline. Conversely, patients receiving anthracycline-free taxane-based chemotherapy, were older, more likely to have negative lymph nodes, and more likely to have comorbid conditions.

Table 4-2 Baseline characteristics of the matched no-chemotherapy and chemotherapy cohorts by type of chemotherapy

	Matched No CHEMO	Matched CHEMO				*P*
		Anthracyclines	CMF	Taxane	Others	
Sample size, n	14,024	7,465	4,389	1,030	1,140	
Trastuzumab use		5.1	0.3	29.1	11.2	
Age at diagnosis, yr.						<0.001
66-69	35.4	44.7	30.3	30.1	28.3	
70-74	35.0	34.7	35.3	35.3	30.1	
75-79	21.2	17.1	24.2	21.4	22.8	
80-84	6.1	3.1	9.1	11.0	14.0	
85-89	2.2	0.4	1.3	2.2	4.7	
Race						0.48
White	88.1	87.9	88.3	86.2	87.4	
Black	7.6	7.6	7.2	8.7	8.8	
Other	4.3	4.5	4.6	5.0	3.9	
Marriage status						<0.001
Single	45.8	42.7	47.2	45.5	51.1	
Married	51.1	54.5	49.7	50.9	46.6	
Unknown	3.1	2.9	3.1	3.6	2.3	
Year of diagnosis						<0.001
1992	2.7	0.8	5.0		7.7	
1993	2.5	1.1	5.3		3.9	
1994	2.7	1.2	5.1		5.6	
1995	2.6	1.2	5.0	*	5.1	
1996	2.6	1.4	4.6	*	4.9	
1997	3.4	2.4	5.7	*	3.6	
1998	3.9	2.7	7.1	*	2.2	
1999	4.4	4.4	5.9	*	2.0	
2000	8.6	9.0	10.3	2.9	4.8	
2001	10.5	10.4	11.8	4.2	11.2	
2002	10.2	10.2	11.0	4.8	12.1	
2003	9.0	10.7	7.2	5.0	8.9	
2004	9.3	12.8	5.6	5.1	4.6	
2005	9.3	12.6	4.3	7.8	8.3	
2006	9.3	10.9	3.6	23.8	7.4	
2007	8.9	8.0	2.6	44.4	7.7	
SEER area						<0.001
California	30.6	30.9	27.2	39.0	33.9	
Connecticut	8.6	7.0	12.2	4.8	6.1	
Detroit	12.1	11.3	14.9	7.5	11.1	
Hawaii	1.9	2.0	2.5	*	2.6	
Iowa	8.6	8.5	10.2	3.9	8.7	
New Mexico	2.5	2.4	2.4	**	4.6	
Seattle	3.5	3.3	3.1	5.9	3.1	
Utah	4.2	4.2	5.1	2.3	3.6	
Atlanta/rural Georgia	4.5	4.1	5.2	5.1	4.8	
Kentucky	6.2	6.7	4.1	7.1	3.9	
Louisiana	5.4	6.6	2.3	7.9	6.9	

New Jersey	11.9	12.9	10.7	14.0	10.5	
AJCC stage						<0.001
I	18.9	16.2	23.5	25.2	24.6	
II	66.0	62.9	66.2	52.5	56.6	
III	15.0	20.9	10.3	22.3	18.8	
Size, cm						<0.001
< 2	36.6	34.8	39.7	35.9	36.3	
≥ 2	61.3	62.5	58.8	62.1	60.0	
Unknown	2.0	2.7	1.4	1.9	3.7	
Positive lymph node						<0.001
Negative	36.9	31.4	41.7	44.3	36.6	
Positive	57.8	64.2	54.3	49.6	54.2	
Unknown	5.2	4.3	4.0	6.1	9.2	
Grade						<0.001
Well	10.7	9.7	10.1	7.2	9.0	
Moderately	37.3	36.6	34.2	36.0	34.7	
Poorly	42.0	45.6	42.7	50.9	42.7	
Undifferentiated	1.8	1.9	2.2	1.8	1.9	
Unknown	8.4	6.2	10.9	4.2	11.6	
Histology						<0.001
Ductal	70.1	71.0	71.2	76.2	72.3	
Lobular	11.4	10.7	11.2	8.3	9.6	
Mixed	10.6	11.2	9.7	8.7	9.6	
Unknown	7.9	7.1	7.9	6.8	8.6	
ER/PR status						<0.001
ER + and/or PR +	64.0	62.6	57.6	57.2	61.6	
ER- and PR-	24.6	27.9	29.2	36.1	24.5	
Unknown	11.4	9.5	13.2	6.7	13.9	
Laterality, right	51.1	52.3	50.6	52.2	53.2	0.22
Surgery type/RT						<0.001
BCS with RT	31.8	30.3	26.8	30.4	29.4	
BCS without RT	11.6	13.6	13.3	16.5	12.4	
Mastectomy	56.6	56.1	59.9	53.1	58.2	
Comorbid conditions						
ASHD	12.2	9.8	14.0	14.0	13.0	<0.001
CHF	4.5	2.6	5.4	6.9	6.3	<0.001
CVA/TIA	4.3	3.8	3.9	5.0	5.3	0.09
Dysrhythmia	9.8	7.4	10.3	12.8	11.8	<0.001
PVD	5.6	4.6	5.1	7.8	6.8	<0.001
Cardiac, other	9.9	8.4	9.6	12.8	9.6	<0.001
Anemia	8.1	7.2	7.3	9.2	10.4	<0.001
COPD	9.3	8.9	8.6	11.2	9.1	0.13
Diabetes	17.9	16.7	17.6	21.4	17.1	0.004
GI disorder	2.2	1.8	2.2	1.7	2.6	0.22
Hypertension	54.0	52.6	52.2	65.7	50.9	<0.001

Note: Values are % unless otherwise indicated.

Abbreviation: AJCC, American Joint Committee on Cancer; ASHD, atherosclerotic heart disease; BCS, breast-conserving surgery; CHF, congestive heart failure; CMF, cyclophosphamide, methotrexate, and fluorouracil; CHEMO, chemotherapy; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; ER, estrogen receptor; GI, gastrointestinal; PR, progesterone receptor; PVD, peripheral vascular disease.

* Values for cells with ten or fewer patients are suppressed.

** Value is suppressed to avoid deriving other cell with ten or fewer patients.

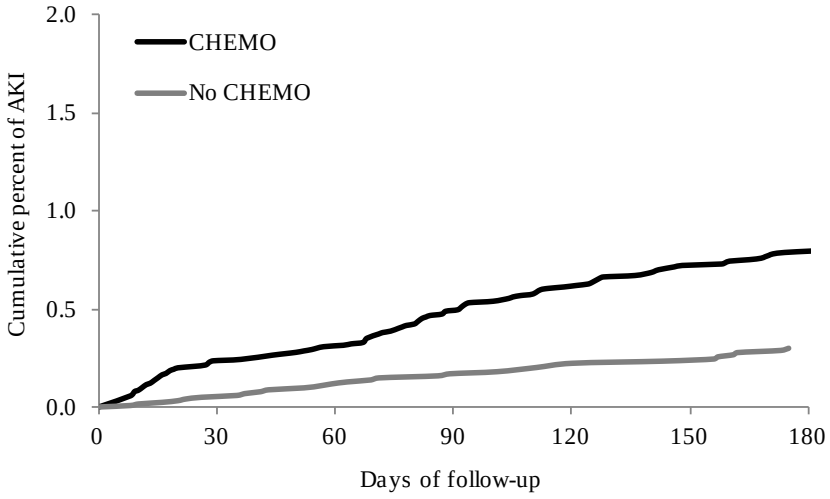
4.2 Objective 1 – Adjuvant Chemotherapy and Risk of Acute Kidney Injury

4.2.1 Any Chemotherapy and Risk of Acute Kidney Injury

The mean (standard deviation [SD]) follow-up time was 179.5 (23.5) days for the chemotherapy treated cohort and 130.1 (75.1) days for the matched no-chemotherapy cohort. During the maximum 6-month follow-up period, AKI occurred in 140 (0.5%) patients, 0.78% of patients who received adjuvant chemotherapy (n = 110) and 0.21% of patients who did not (n = 30). The AKI rate measured as number of patients who developed AKI divided by total patient-years at risk was 15.9 per 1,000 patient-years in the treatment cohort and 6.0 per 1,000 patient-years in the no-treatment cohort.

Figure 4-3 presents Kaplan-Meier estimated cumulative percent of patients developing AKI during the follow-up period by chemotherapy use. During the follow-up period, risk of AKI was consistently higher for patients receiving than not receiving adjuvant chemotherapy ($P < 0.0001$). The cumulative percentages of patients with AKI at days 30, 90, and 180 were 0.24%, 0.50%, and 0.80% for patients receiving adjuvant chemotherapy, compared with 0.05%, 0.17%, and 0.30% for no-chemotherapy patients.

Figure 4-3 Cumulative percent of patients developing AKI during the 6-month follow-up period, by adjuvant chemotherapy status



Number of patients at risk

Days of follow-up	0	30	60	90	120	150	180
CHEMO	14024	13885	13792	13672	13584	13495	13416
No CHEMO	14024	10915	9821	9421	9219	9093	8986

A Cox proportional hazards model was performed to evaluate the risk of incident AKI following adjuvant chemotherapy. Patients who received adjuvant chemotherapy were almost 3 times (hazards ratio [HR] 2.73, 95% confidence interval [CI] 1.82-4.09; $P < 0.001$) more likely to develop incident AKI than patients who did not. Adjustment for patient demographics, tumor characteristics, and comorbid conditions had miniscule impact on the estimated HR described above, indicating good balance achieved through matching in the distribution of baseline variables between treated and untreated patients (Table 4-3). Significant predictors for incident AKI following chemotherapy initiation

included increasing age at diagnosis, black race, breast-conserving surgery without radiation therapy, and atherosclerotic heart disease (Table 4-3).

Table 4-3 Adjusted hazard ratios for the association of adjuvant chemotherapy, demographics, tumor characteristics, and comorbid conditions with incident acute kidney injury

Variable	Hazard ratio	95% CI	*P*
Chemotherapy	2.69	(1.79, 4.06)	<0.001
Age at diagnosis, yrs.			
66-69	Reference		
70-74	1.33	(0.83, 2.13)	0.24
75-79	1.95	(1.21, 3.15)	<0.01
80-84	2.03	(1.09, 3.79)	0.03
85-89	2.65	(1.05, 6.66)	0.04
Race			
White	Reference		
Black	1.83	(1.15, 2.94)	0.01
Other	0.98	(0.37, 2.56)	0.96
Marriage status			
Married	Reference		
Single	1.19	(0.83, 1.70)	0.35
Unknown	1.32	(0.55, 3.15)	0.53
Diagnosis year			
1992	Reference		
1993	4.31	(0.48, 38.75)	0.20
1994	1.64	(0.15, 18.19)	0.69
1995	2.89	(0.30, 28.07)	0.36
1996	2.92	(0.30, 28.35)	0.35
1997	2.09	(0.21, 20.32)	0.53
1998	1.91	(0.20, 18.62)	0.58
1999	2.16	(0.24, 19.60)	0.50
2000	3.12	(0.39, 24.69)	0.28
2001	2.51	(0.31, 20.03)	0.39
2002	1.28	(0.15, 11.21)	0.82
2003	5.14	(0.67, 39.38)	0.11
2004	3.17	(0.40, 24.90)	0.27
2005	3.91	(0.50, 30.30)	0.19
2006	4.75	(0.62, 36.60)	0.13
2007	6.85	(0.90, 52.13)	0.06
SEER area			
California	Reference		
Connecticut	0.76	(0.37, 1.59)	0.47
Detroit	1.63	(1.00, 2.66)	0.05
Hawaii	1.33	(0.35, 5.06)	0.68
Iowa	0.43	(0.15, 1.21)	0.11
Kentucky	0.95	(0.45, 1.99)	0.89
Louisiana	1.25	(0.67, 2.33)	0.48
New Jersey	0.75	(0.43, 1.32)	0.32
New Mexico	0.62	(0.15, 2.58)	0.51
Seattle	0.23	(0.03, 1.68)	0.15
Utah	0.70	(0.22, 2.27)	0.55
Atlanta/rural Georgia	0.15	(0.02, 1.06)	0.06
AJCC stage			

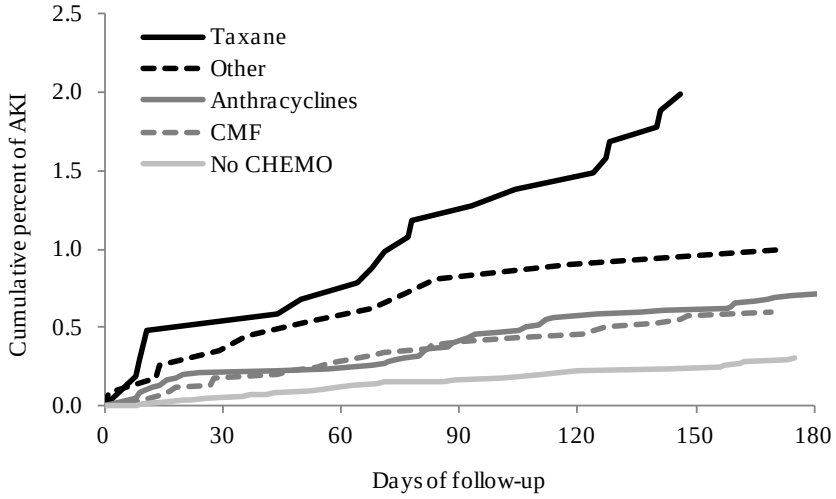
Stage I	Reference		
Stage II	0.85	(0.42, 1.71)	0.64
Stage III	1.19	(0.52, 2.72)	0.68
Tumor size, cm			
< 2	Reference		
≥ 2	1.52	(0.94, 2.45)	0.09
Unknown	0.92	(0.25, 3.32)	0.89
Positive lymph nodes			
Negative	Reference		
Positive	1.44	(0.87, 2.38)	0.15
Unknown	1.50	(0.73, 3.10)	0.27
Grade			
Well	Reference		
Moderately	1.53	(0.71, 3.30)	0.28
Poorly	2.13	(0.99, 4.56)	0.05
Undifferentiated	1.58	(0.33, 7.58)	0.57
Unknown	1.82	(0.69, 4.80)	0.23
Histology			
Ductal	Reference		
Lobular	0.80	(0.43, 1.51)	0.50
Mixed	0.58	(0.30, 1.13)	0.11
Unknown	0.88	(0.45, 1.72)	0.70
ER/PR status			
ER + and/or PR +	Reference		
ER- and PR-	0.71	(0.46, 1.08)	0.11
Unknown	0.96	(0.56, 1.64)	0.87
Laterality			
Left	Reference		
Right	1.03	(0.74, 1.43)	0.87
Surgery type/RT			
BCS and RT	Reference		
BCS, no RT	2.24	(1.31, 3.84)	<0.01
Mastectomy	1.27	(0.80, 2.03)	0.31
Comorbid conditions			
ASHD	1.81	(1.19, 2.75)	<0.01
CHF	1.66	(0.97, 2.86)	0.07
CVA/TIA	1.29	(0.72, 2.32)	0.39
Dysrhythmia	1.26	(0.78, 2.03)	0.35
PVD	1.20	(0.70, 2.06)	0.52
Cardiac, other	1.15	(0.71, 1.86)	0.57
Anemia	1.00	(0.60, 1.66)	1.00
COPD	0.88	(0.52, 1.50)	0.65
Diabetes	1.42	(0.97, 2.08)	0.07
GI disorder	1.36	(0.55, 3.40)	0.51
Hypertension	1.19	(0.80, 1.77)	0.40

Abbreviation: AJCC, American Joint Committee on Cancer; ASHD, atherosclerotic heart disease; BCS, breast-conserving surgery; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; ER, estrogen receptor; GI, gastrointestinal; PR, progesterone receptor; PVD, peripheral vascular disease; RT, radiation therapy.

4.2.2 Regimen Type and Risk of Acute Kidney Injury

Figure 4-4 presents Kaplan-Meier estimated cumulative percentages of patients who received anthracyclines, CMF, taxane, and other chemotherapy developing AKI during the follow-up period compared with no-chemotherapy patients. During the 6-month follow-up period, rates of AKI were consistently higher for patients who received taxane-based chemotherapy, followed by rates for patients who received other chemotherapy. Cumulative incidence of AKI was similar for patients treated with anthracyclines and CMF. The estimated 6-month cumulative incidence of AKI was 2.0%, 1.0%, 0.7%, and 0.6% for patients treated with taxane, other chemotherapy, anthracyclines, and CMF, respectively, compared with 0.3% in no-chemotherapy patients ($P < 0.0001$).

Figure 4-4 Cumulative percent of patients developing AKI during the 6-month follow-up period, by regimen



Number of patients at risk

Days of follow-up	0	30	60	90	120	150	180
Anthracycline	7465	7399	7361	7306	7266	7224	7186
CMF	4389	4359	4328	4291	4263	4239	4216
Taxane	1030	1014	1005	990	981	966	955
Other	1140	1113	1098	1085	1074	1066	1059
No CHEMO	14024	10915	9821	9421	9219	9093	8986

The association between adjuvant chemotherapy and risk of AKI varied across regimen types (Table 4-4). After adjustment for baseline characteristics and trastuzumab use, patients treated with taxane-based chemotherapy were about 4 times more likely to develop AKI than untreated patients (HR 4.17, 95% CI 2.23-7.79); this relationship was the most profound association among the four types of treatment. Patients who received other chemotherapy were about 3 times more likely to develop AKI than patients who did not receive adjuvant chemotherapy (HR 3.01, 95% CI 1.47-6.16). The hazards ratio of AKI was similar for patients treated with anthracycline-based chemotherapy (HR 2.54,

95% CI 1.60-4.06) and CMF (HR 2.22, 95% CI 1.30-3.82) compared with no-chemotherapy patients.

The effect of trastuzumab use on risk of AKI was evaluated among patients who received adjuvant chemotherapy (Table 4-4). After adjustment for baseline characteristics and types of chemotherapy, use of trastuzumab was associated with a 6% increased risk of AKI, but this association was not significant ($P = 0.87$).

Table 4-4 Association between type of adjuvant chemotherapy and risk of acute kidney injury during the 6-month follow-up

Regimen	Total, n	Patients with AKI, n (%)	Mean (SD) F/U time, days	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Both cohorts[*]							
No chemotherapy	14024	30 (0.21)	130 (75)	Reference		Reference	
Anthracyclines	7465	53 (0.71)	180 (22)	2.46 (1.57, 3.85)	<0.001	2.54 (1.60, 4.06)	<0.001
CMF	4389	26 (0.59)	180 (22)	2.06 (1.22, 3.48)	0.007	2.22 (1.30, 3.82)	0.004
Taxane	1030	20 (1.94)	177 (29)	6.84 (3.88, 12.05)	<0.001	4.17 (2.23, 7.79)	<0.001
Others	1140	11 (0.96)	176 (33)	3.42 (1.72, 6.83)	<0.001	3.01 (1.47, 6.16)	0.003
Treatment cohort[†]							
No trastuzumab	13198	98 (0.74)	180 (23)	Reference		Reference	
Trastuzumab	826	12 (1.45)	179 (27)	1.97 (1.08, 3.59)	0.026	1.06 (0.55, 2.08)	0.85

[*]All patients in the matched chemotherapy treatment and no-treatment cohorts were included in this analysis. Covariates in the model include factors listed in Table 4-1 and trastuzumab use.

[†]All patients in the matched chemotherapy treatment cohort were included in this analysis. Covariates in the model include factors listed in Table 4-1 and type of regimen.

Abbreviation: AKI, acute kidney injury; CI, confidence interval; CMF, cyclophosphamide, methotrexate, and fluorouracil; F/U, follow-up; HR, hazard ratio.

4.2.3 AKI Case Studies

More AKI patients in the chemotherapy cohort than in the matched no-chemotherapy cohort were older and black, and had stage I cancer, negative hormone receptor, and comorbid conditions including CHF, dysrhythmia, diabetes, and hypertension at baseline, but these comparisons were not statistically significant due to small sample size.

AKI was coded as the principal diagnosis on hospital claims in 21.5% of AKI patients who received adjuvant chemotherapy and in 10.3% of AKI patients who did not. Unspecified AKI (ICD-9-CM code 584.9) was the most frequent AKI diagnosis, representing 82.2% of chemotherapy-treated patients with AKI and 86.2% of untreated patients with AKI. AKI with lesion of tubular necrosis (ICD-9-CM code 584.5) was diagnosed in 16.8% of chemotherapy-treated patients with AKI and in 10.3% of untreated patients with AKI.

Among 84 AKI patients who received chemotherapy and for whom AKI was a secondary diagnosis, septicemia (ICD-9-CM code 038.xx) was coded most frequently as the principal diagnosis in 27.4%, followed by disorder of fluid, electrolyte, and acid-base balance (ICD-9-CM code 276.xx) in 9.5%, and other disease of lung (ICD-9-CM code 518.xx) in 6.0%. Among 26 AKI patients who did not receive chemotherapy and for whom AKI was a secondary diagnosis, septicemia was coded most frequently as the principal diagnosis in 15.4%. Disorder of fluid, electrolyte, and acid-base balance, female breast cancer (ICD-9-CM code 276), unspecified pneumonia (ICD-9-CM code 486), other chronic ischemic heart disease (ICD-9-CM code 414), and endocarditis (ICD-9-CM

code 421) were diagnosed in 7.7%, respectively.

Regardless of position on the hospital claims, 96.3% of AKI patients treated with chemotherapy were also diagnosed with disorder of fluid, electrolyte, and acid-base balance, compared with 86.2% of AKI patients not treated with chemotherapy. Septicemia was the second most commonly diagnosed disease in chemotherapy-treated patients with AKI, representing 40.2% of these cases, but it occurred in only 17.2% of AKI patients who did not receive chemotherapy.

4.3 Objective 2 – Adjuvant Chemotherapy and Risk of Chronic Kidney Disease

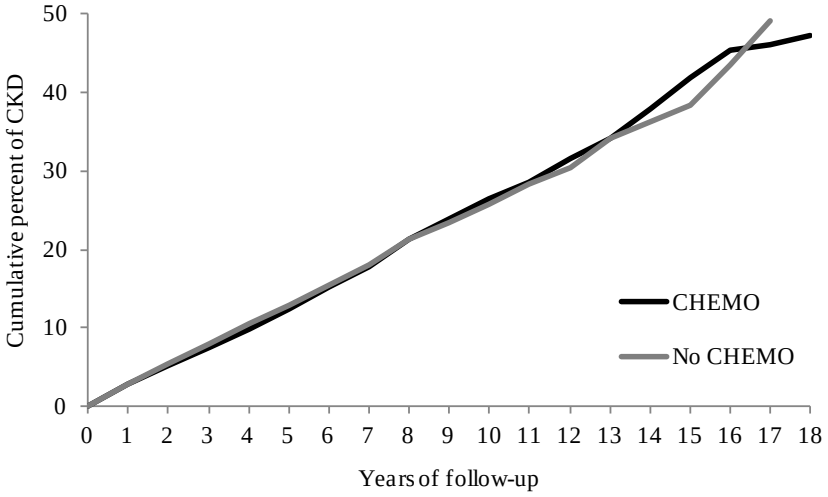
4.3.1 Any Chemotherapy and Risk of CKD

The mean (SD) follow-up time was 5.06 (3.39) years for the chemotherapy-treated cohort and 3.25 (3.6) years for the untreated cohort. During the maximum 18-year follow-up period, CKD occurred in 2,058 patients (14.7%) who received adjuvant chemotherapy and in 1,335 patients (9.5%) who did not. CKD rates (SE) were 29.0 (0.6) per 1,000 patient-years in the treatment cohort and 29.3 (0.8) per 1,000 patient-years in the no-treatment cohort. Among patients in the matched chemotherapy cohort, 20.9% died, 9.4% changed Medicare fee-for-service enrollment status, 6.2% developed a non-breast primary cancer, and nearly 50% were followed until the end of study (December 31, 2009). Among patients in the matched no-chemotherapy cohort, nearly one-third initiated adjuvant chemotherapy within 6 months of first surgery, 6.6% underwent first chemotherapy treatment more than 6 months after first surgery, 12.6% died, 6.3%

changed Medicare fee-for-service enrollment status, 4.2% developed a non-breast primary cancer, and 28.8% were followed until the end of study.

Figure 4-5 shows the Kaplan-Meier estimated cumulative percent of patients developing CKD during the follow-up period by chemotherapy use. Overall, there was no significant difference in the cumulative incidence of CKD between patients who received adjuvant chemotherapy and patients who did not ($P = 0.91$). Within the first 14 years of follow-up, all patients had similar rates of CKD; the 14-year cumulative percentages of patients developing CKD were 37.9% in chemotherapy-treated patients and 36.2% in no-chemotherapy patients. Beyond 14 years, the cumulative incidence of CKD was slightly higher in patients who were treated with adjuvant chemotherapy than in patients who were not. However, these results were based on 274 chemotherapy-treated patients and 200 untreated patients. The cumulative percentages of patients developing CKD by the end of follow-up were 47.2% in chemotherapy-treated patients and 49% in no-chemotherapy patients.

Figure 4-5 Cumulative percent of patients developing chronic kidney disease, by adjuvant chemotherapy status



Number of patients at risk

Years of follow-up	0	1	2	3	4	5	10	15
CHEMO	14024	12881	11441	9416	7633	6109	1164	176
No CHEMO	14024	8461	7294	5923	4734	3744	791	123

A Cox proportional hazards model was performed to evaluate the risk of developing CKD following adjuvant chemotherapy. There was no significant difference between patients who received adjuvant chemotherapy and patients who did not (HR 1.00, 95% CI 0.93-1.07; $P = 0.91$). Adjustment for patient demographics, tumor characteristics, and comorbid conditions did not change this association (Table 4-5). Significant predictors of developing CKD included increasing age at diagnosis, black race, single status, diagnosis at later tumor stage, breast-conserving surgery without radiation therapy and mastectomy regardless of radiation therapy, and presence of comorbid conditions including atherosclerotic heart disease, CHF, dysrhythmia, PVD, anemia, COPD, diabetes, and hypertension (Table 4-5).

Table 4-5 Adjusted hazard ratios for the association of adjuvant chemotherapy, demographics, tumor characteristics, and comorbid conditions with incident chronic kidney disease

	Hazard ratio	95% CI	*P*
Chemotherapy	1.00	(0.93, 1.08)	0.99
Age at diagnosis, yrs.			
66-69	Reference		
70-74	1.20	(1.1, 1.31)	<0.001
75-79	1.35	(1.22, 1.48)	<0.001
80-84	1.68	(1.46, 1.93)	<0.001
85-89	1.78	(1.41, 2.25)	<0.001
Race			
White	Reference		
Black	1.26	(1.12, 1.42)	<0.001
Other	0.91	(0.75, 1.12)	0.36
Marriage status			
Married	Reference		
Single	1.12	(1.04, 1.20)	0.002
Unknown	1.08	(0.89, 1.31)	0.45
Diagnosis year			
1992	Reference		
1993	0.94	(0.71, 1.26)	0.68
1994	1.19	(0.90, 1.57)	0.22
1995	1.23	(0.93, 1.62)	0.15
1996	1.36	(1.03, 1.81)	0.03
1997	1.62	(1.24, 2.10)	<0.001
1998	1.39	(1.07, 1.81)	0.01
1999	1.54	(1.19, 2.00)	0.001
2000	1.86	(1.47, 2.36)	<0.001
2001	2.00	(1.58, 2.54)	<0.001
2002	1.96	(1.54, 2.49)	<0.001
2003	2.30	(1.80, 2.94)	<0.001
2004	2.32	(1.81, 2.98)	<0.001
2005	2.47	(1.91, 3.18)	<0.001
2006	2.42	(1.86, 3.14)	<0.001
2007	2.96	(2.26, 3.88)	<0.001
SEER area			
California	Reference		
Connecticut	1.01	(0.88, 1.16)	0.88
Detroit	1.09	(0.98, 1.22)	0.12
Hawaii	0.94	(0.70, 1.25)	0.66
Iowa	0.86	(0.75, 0.99)	0.03
Kentucky	1.04	(0.89, 1.22)	0.61
Louisiana	1.06	(0.90, 1.24)	0.50
New Jersey	0.90	(0.80, 1.02)	0.10
New Mexico	0.85	(0.67, 1.08)	0.18
Seattle	1.05	(0.85, 1.29)	0.67
Utah	0.72	(0.58, 0.89)	0.002
Atlanta/rural Georgia	1.11	(0.94, 1.31)	0.20
AJCC stage			

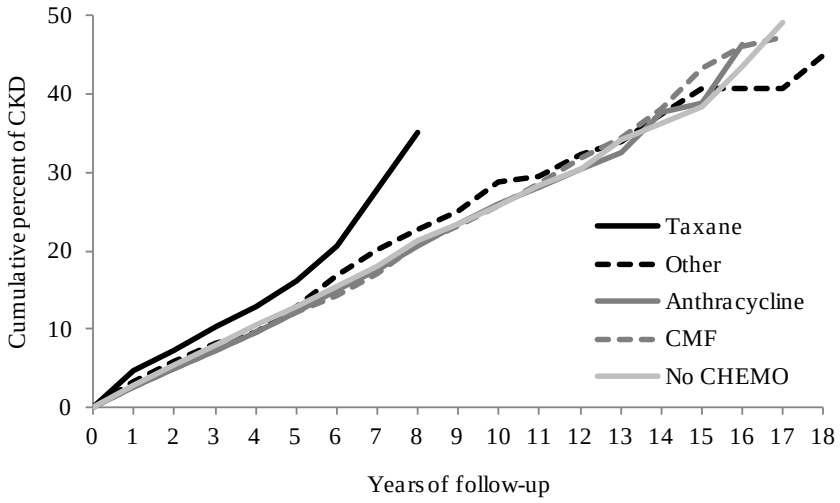
Stage I	Reference		
Stage II	1.10	(0.97, 1.25)	0.15
Stage III	1.30	(1.10, 1.54)	0.002
Tumor size, cm			
< 2	Reference		
≥ 2	1.04	(0.95, 1.14)	0.37
Unknown	1.19	(0.94, 1.50)	0.15
Positive lymph nodes			
Negative	Reference		
Positive	1.03	(0.93, 1.13)	0.60
Unknown	1.20	(1.03, 1.4)	0.02
Grade			
Well	Reference		
Moderately	1.00	(0.89, 1.13)	0.99
Poorly	1.10	(0.97, 1.24)	0.13
Undifferentiated	0.98	(0.73, 1.3)	0.87
Unknown	0.99	(0.85, 1.17)	0.94
Histology			
Ductal	Reference		
Lobular	1.11	(0.99, 1.24)	0.08
Mixed	1.05	(0.94, 1.17)	0.43
Unknown	1.02	(0.9, 1.16)	0.76
ER/PR status			
ER + and/or PR +	Reference		
ER- and PR-	1.00	(0.92, 1.1)	0.97
Unknown	1.05	(0.95, 1.17)	0.35
Laterality			
Left	Reference		
Right	0.95	(0.89, 1.02)	0.13
Surgery type/RT			
BCS and RT	Reference		
BCS, no RT	1.19	(1.06, 1.34)	0.004
Mastectomy	1.22	(1.12, 1.33)	<0.001
Comorbid conditions			
ASHD	1.22	(1.11, 1.34)	<0.001
CHF	1.61	(1.41, 1.84)	<0.001
CVA/TIA	1.05	(0.9, 1.22)	0.55
Dysrhythmia	1.13	(1.01, 1.26)	0.03
PVD	1.22	(1.07, 1.38)	0.003
Cardiac, other	1.10	(0.99, 1.23)	0.09
Anemia	1.30	(1.16, 1.45)	<0.001
COPD	1.13	(1.01, 1.26)	0.04
Diabetes	2.15	(1.99, 2.33)	<0.001
GI disorder	1.14	(0.94, 1.39)	0.19
Hypertension	1.49	(1.38, 1.61)	<0.001

Abbreviation: AJCC, American Joint Committee on Cancer; ASHD, atherosclerotic heart disease; BCS, breast-conserving surgery; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; ER, estrogen receptor; GI, gastrointestinal; PR, progesterone receptor; PVD, peripheral vascular disease; RT, radiation therapy.

4.3.2 Type of Chemotherapy and Risk of CKD

Figure 4-6 shows the Kaplan-Meier estimated cumulative percent of patients developing CKD during the follow-up period by type of chemotherapy. Compared with patients who did not receive adjuvant chemotherapy, rates of CKD were significantly higher for patients who received taxane-based chemotherapy ($P = 0.0005$); rates were similar for patients who received an anthracycline-based regimen, CMF, and other types of chemotherapy ($P = 0.71$).

Figure 4-6 Cumulative percent of patients developing chronic kidney disease, by type of adjuvant chemotherapy



Number of patients at risk

Years of follow-up	0	1	2	3	4	5	10	15
Anthracycline	7465	6921	6219	5173	4115	3147	369	38
CMF	4389	4063	3660	3206	2763	2370	652	108
Taxane	1030	903	692	321	166	115	*	*
Other	1140	994	870	716	589	477	138	30
No CHEMO	14024	8461	7294	5923	4734	3744	791	123

*Value for cell with ten or fewer patients is suppressed.

Table 4-6 presents the association between adjuvant chemotherapy and risk of developing CKD by regimen and trastuzumab use. Because the interaction term in the model for regimen and trastuzumab use and risk of CKD was not significant ($P = 0.70$), the effect of regimen on risk of CKD was evaluated after adjustment for patient baseline characteristics and trastuzumab use. Compared with patients who did not receive adjuvant chemotherapy, patients treated with CMF and patients treated with other chemotherapy were 4% more likely to develop CKD; patients treated with anthracycline-based regimens were 4% less likely and patients treated with taxane-based regimens were 9% less likely to develop CKD. Though the association between adjuvant chemotherapy and risk of developing CKD varied across regimen types, these associations were not statistically significant.

The effect of trastuzumab use on risk of CKD was evaluated among patients treated with adjuvant chemotherapy. Compared with patients who did not receive trastuzumab, patients who did were 18% more likely to develop CKD (HR 1.18, 95% CI 0.94-1.47), but this association was not significant.

Table 4-6 Type of adjuvant chemotherapy and trastuzumab use and associated risks of chronic kidney disease

Treatment	Total, *n*	Patients w/ CKD, *n* (%)	Mean (SD) F/U time, years	Rate of CKD (1000 pt/yrs)	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Both cohorts[*]								
No chemotherapy	14024	1335 (9.5)	3.3 (3.6)	29.3	Reference		Reference	
Anthracyclines	7465	1001 (13.4)	4.8 (3.0)	27.7	0.97 (0.89, 1.05)	0.46	0.96 (0.88, 1.04)	0.31
CMF	4389	762 (17.4)	6.0 (3.9)	29.1	0.97 (0.89, 1.06)	0.55	1.04 (0.95, 1.14)	0.44
Taxane	1030	114 (11.1)	2.8 (1.8)	39.4	1.44 (1.19, 1.75)	0.0002	0.91 (0.74, 1.12)	0.38
Others	1140	181 (15.9)	5.1 (4.0)	31.2	1.05 (0.90, 1.23)	0.55	1.04 (0.89, 1.22)	0.60
Treatment cohort[†]								
No trastuzumab	13198	1956 (14.8)	5.2 (3.4)	28.5	Reference		Reference	
Trastuzumab	826	102 (12.3)	2.9 (1.6)	42.7	1.65 (1.35, 2.02)	<.0001	1.18 (0.94, 1.47)	0.15

[*]All patients in the matched chemotherapy-treatment and no-treatment cohorts were included in this analysis. Covariates in the model include factors listed in Table 4-1 and trastuzumab use.

[†]All patients in the matched chemotherapy-treatment cohort were included in this analysis. Covariates in the model include factors listed in Table 4-1 and type of regimen.

Abbreviation: CI, confidence interval; CKD, chronic kidney disease; CMF, cyclophosphamide, methotrexate, and fluorouracil; F/U, follow-up; HR, hazard ratio; SD, standard deviation.

4.3.3 Sensitivity Analyses

4.3.3.1 Adjuvant Chemotherapy as Time-Varying Variable

Of 84,018 patients who met the study inclusion and exclusion criteria, 14,725 received adjuvant chemotherapy. With initiation of adjuvant chemotherapy defined as a time-varying variable, the unadjusted hazard ratio of CKD was 0.98 (95% CI 0.93-1.02). After adjustment for patient demographics, tumor characteristics, and baseline comorbid conditions, adjuvant chemotherapy was associated with a 4% decreased risk of developing CKD compared with no adjuvant chemotherapy, and this association was not significant (HR 0.96, 95% CI 0.91-1.02; $P = 0.19$).

4.3.3.2 Competing Risk Analyses

The risk of CKD associated with adjuvant chemotherapy based on the competing risk analyses was qualitatively unchanged. The unadjusted hazards ratio of CKD for patients who received adjuvant chemotherapy compared with patients who did not was 0.99 (95% CI 0.92-1.06; $P = 0.77$). After adjustment for patient baseline characteristics, the hazards ratio was 1.03 (95% CI 0.96-1.11; $P = 0.42$).

4.3.3.3 Subgroup Analyses by Duration of Chemotherapy Course

Among 14,024 patients who received adjuvant chemotherapy, 612 (4.4%) received ≤ 1 week of adjuvant chemotherapy; 584 (95%) of these received one treatment cycle only. Baseline characteristics differed substantially between patients in the shorter and in the longer chemotherapy subgroups. More patients in the shorter than in the longer treatment subgroup were aged 80 years or older (19% vs. 7%) and black (10% vs. 8%),

and had stage I tumors (33% vs. 19%), tumor size smaller than 2 cm (41% vs. 36%), negative lymph nodes (45% vs. 36%), and diabetes (20% vs. 17%) and cardiovascular disease (16% vs. 12% for ASHD; 15% vs. 9% for dysrhythmia; 9% vs. 4% for CHF).

The association between adjuvant chemotherapy and risk of CKD varied across the subgroups of patients who received ≤ 1 week and > 1 week of chemotherapy compared with matched untreated patients. Patients who received ≤ 1 week of chemotherapy treatment had a 39% increased risk of CKD (HR 1.39, 95% CI 1.01-1.91; $P = 0.042$) compared with matched untreated patients, and this association was significant. Patients who received chemotherapy for > 1 week had a 3% reduced risk of CKD (HR 0.97, 95% CI 0.90-1.04; $P = 0.35$), but this association was not significant.

4.4 Objective 3 – Utilization of Kidney Function Monitoring

4.4.1 Patient Characteristics

Of 28,048 patients in the matched cohorts, 23,096 were available for evaluation of kidney function monitoring, 13,818 (98.5% of 14,024) in the adjuvant chemotherapy cohort and 9,278 (66.2% of 14,024) in the no-treatment cohort. The mean (SD) follow-up time was 4.65 (3.40) years for patients in the chemotherapy cohort and 4.57 (3.43) years for patients in the no-treatment cohort.

Since the follow-up start date in this study was no longer the date of initiation of adjuvant chemotherapy for patients in the treatment cohort and the matched date for patients in the no-treatment cohort, the balance in patient characteristics achieved from matching may not be preserved. Table 4-7 presents the distributions of selected patient

characteristics with significant differences between patients who received adjuvant chemotherapy and patients who did not. Patients who received chemotherapy, compared with patients who did not, were younger, more often black, diagnosed at a later stage, more likely to be hormone receptor negative, more likely to undergo mastectomy, and less likely to have cardiovascular disease at baseline.

Table 4-7 Baseline patient characteristics

	No CHEMO		CHEMO		
	n	%	*n*	%	*P*
Total	9278	100.0	13818	100.0	
Age at diagnosis, yrs.					<0.001
66-69	2817	30.4	5231	37.9	
70-74	3255	35.1	4780	34.6	
75-79	2205	23.8	2775	20.1	
80-84	712	7.7	880	6.4	
85-89	289	3.1	152	1.1	
Race					0.02
White	8269	89.1	12152	87.9	
Black	634	6.8	1044	7.6	
Other	375	4.0	622	4.5	
Marriage status					0.003
Single	4343	46.8	6214	45.0	
Married	4633	49.9	7203	52.1	
Unknown	302	3.3	401	2.9	
SEER registry					<0.001
California	2926	31.5	4232	30.6	
Connecticut	818	8.8	1155	8.4	
Detroit	1017	11.0	1669	12.1	
Hawaii	143	1.5	290	2.1	
Iowa	889	9.6	1215	8.8	
New Mexico	239	2.6	355	2.6	
Seattle	336	3.6	466	3.4	
Utah	382	4.1	599	4.3	
Atlanta/rural Georgia	442	4.8	633	4.6	
Kentucky	589	6.4	798	5.8	
Louisiana	488	5.3	740	5.4	
New Jersey	1009	10.9	1666	12.1	
AJCC stage					<0.001
I	2296	24.8	2739	19.8	
II	5964	64.3	8674	62.8	
III	1018	11.0	2405	17.4	
Size, cm					<0.001
< 2	3737	40.3	5053	36.6	
≥ 2	5326	57.4	8674	62.8	
Unknown	215	2.3	315	2.3	
Positive lymph node					<0.001
Negative	4151	44.7	4972	36.0	
Positive	4530	48.8	8195	59.3	
Unknown	597	6.4	651	4.7	
Grade					<0.001
Well	1189	12.8	1335	9.7	
Moderately	3658	39.4	4928	35.7	
Poorly	3451	37.2	6184	44.8	
Undifferentiated	145	1.6	271	2.0	
Unknown	835	9.0	1100	8.0	
Histology					<0.001
Ductal	6404	69.0	9893	71.6	

Lobular	1057	11.4	1471	10.7	
Mixed	1031	11.1	1436	10.4	
Unknown	786	8.5	1018	7.4	
ER/PR status					<0.001
ER + and/or PR +	6408	69.1	8375	60.6	
ER- and PR-	1734	18.7	3952	28.6	
Unknown	1136	12.2	1491	10.8	
Surgery type/RT					<0.001
BCS with RT	3297	35.5	4040	29.2	
BCS without RT	1040	11.2	1873	13.6	
Mastectomy	4941	53.3	7905	57.2	
Comorbid conditions					
ASHD	1175	12.7	1609	11.6	0.02
CHF	430	4.6	562	4.1	0.04
CVA/TIA	434	4.7	560	4.1	0.02
Dysrhythmia	972	10.5	1249	9.0	<0.001
PVD	551	5.9	710	5.1	0.009
Cardiac disease, other	944	10.2	1264	9.2	0.009

Abbreviation: AJCC, American Joint Committee on Cancer; ASHD, atherosclerotic heart disease; BCS, breast-conserving surgery; CHF, congestive heart failure; CHEMO, chemotherapy; CVA/TIA, cerebrovascular accident/transient ischemic attack; ER, estrogen receptor; PR, progesterone receptor; PVD, peripheral vascular disease.

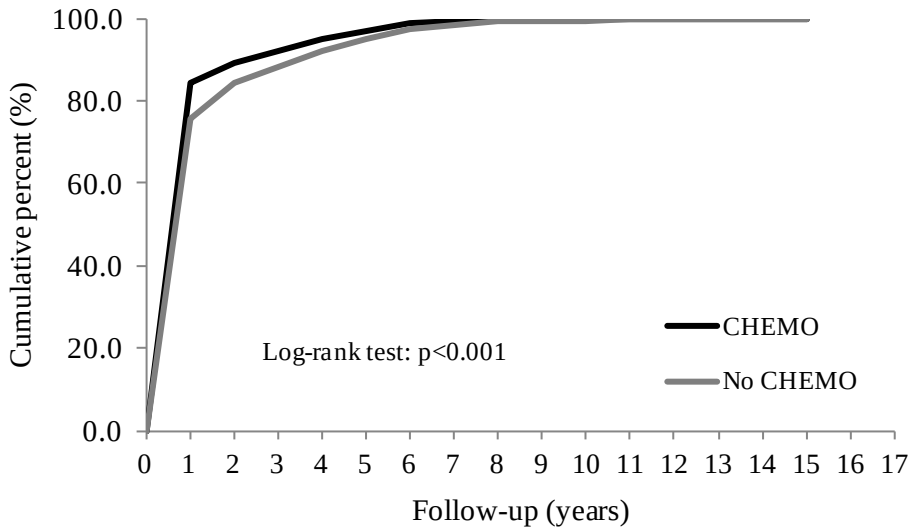
4.4.2 Monitoring Renal Function

Serum Creatinine

Serum creatinine assessment is the most commonly used test for evaluation of kidney function.

Figure 4-7 displays the cumulative percentage of patients receiving at least one serum creatinine assessment during the after-treatment period by adjuvant chemotherapy status. Almost 85% of chemotherapy-treated patients and 76% of untreated patients received at least one serum creatinine assessment within the first year of follow-up. After 5 years of follow-up, the cumulative percentages had increased to 97% for patients treated with adjuvant chemotherapy and 95% for untreated patients.

Figure 4-7 Cumulative percentages of patients receiving at least one serum creatinine assessment during the post-treatment period



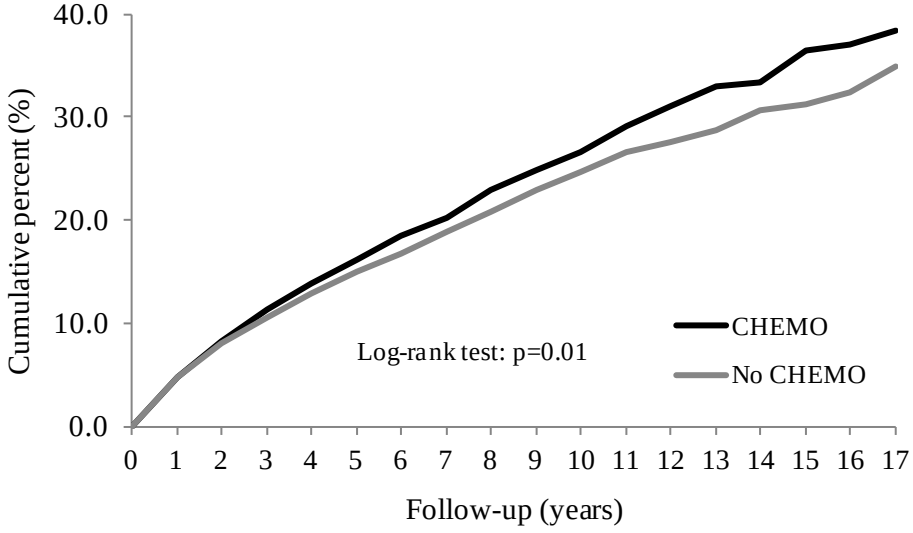
Patients treated with adjuvant chemotherapy were more frequently tested for serum creatinine level than untreated patients, especially within the first year after treatment, and the differences in testing rates between the two patient cohorts steadily decreased as follow-up time increased (Table 4-8). The rate of serum creatinine assessment for patients who received adjuvant chemotherapy was 4.2 tests per patient in the first year post-treatment, 3.5 tests per patient in the second year post-treatment, and 3.2 tests per patient per year after 2 years post-treatment, compared with a roughly constant rate of 2.4 tests per patient per year for no-chemotherapy patients. After adjustment for various possible confounders, rates of serum creatinine testing for chemotherapy-treated patients, compared with untreated patients, were 68%, 43%, and

32% higher in the first year, second year, and after 2 years post-treatment, respectively (Table 4-8).

Urine Albumin

Although urine albumin assessment is one of the most important tests for detecting early kidney damage, it was used less frequently than serum creatinine tests. The 1-year cumulative percent of patients receiving at least one urine albumin test was less than 5% for both adjuvant chemotherapy-treated and untreated patients (Figure 4-8). After 5 years of follow-up, the cumulative percent had increased to 16.2% in chemotherapy-treated patients and 15.0% in untreated patients. Even after 10 years of follow-up, the cumulative percent reached only 26.6% and 24.7% in treated and untreated patients, respectively.

Figure 4-8 Cumulative percentage of patients receiving at least one urine albumin assessment during the post-treatment period

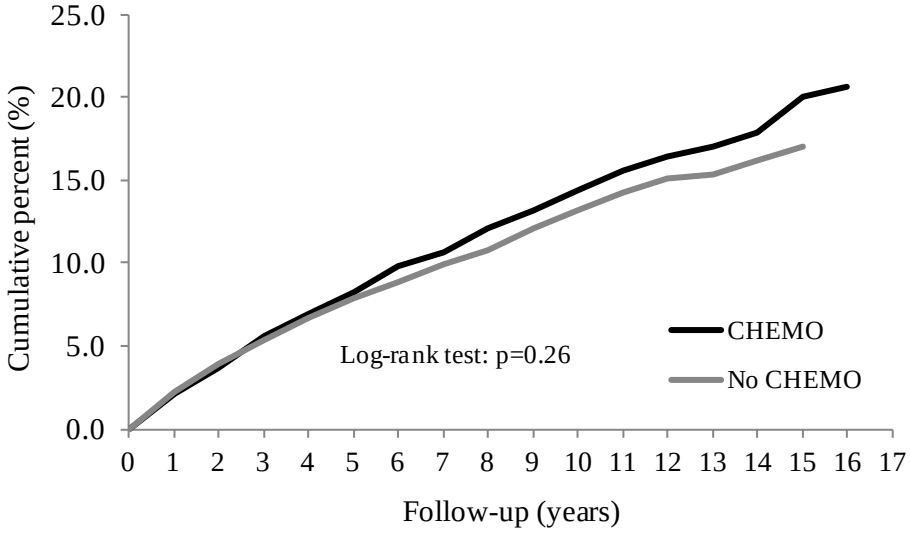


The rate of urine albumin assessment was low during each follow-up interval, but it increased steadily with increasing follow-up time after treatment for patients in both study cohorts, with a higher rate in chemotherapy-treated than in untreated patients (Table 4-8). The rates of urine albumin assessment during the first year, second year, and after 2 years post-treatment were 61.2, 76.4, and 93.9 per 1,000 person-years, respectively, for chemotherapy treated patients, compared with 59.2, 69.4, and 81.2 per 1,000 person-years for untreated patients. After adjustment for baseline characteristics, the differences in rates of urine albumin testing between chemotherapy-treated and untreated patients were not statistically significant for the first and second years post-treatment (Table 4-8). Beyond the first 2 years post-treatment, however, the rate of urine albumin testing was 12% higher for chemotherapy-treated than for untreated patients, and this difference was significant (RR 1.12, 95% CI 1.03-1.20; $P = 0.005$).

Urine Albumin-to-Creatinine Ratio

Urine ACR, which requires both albumin and creatinine to be measured in a random urine sample, was less frequently used than urine albumin testing to detect early kidney damage. The cumulative percentages of patients receiving at least one urine ACR test at 1 year, 5 years, and 10 years after treatment were 2.1%, 8.2%, and 14.3%, respectively, in patients treated with adjuvant chemotherapy, compared with 2.3%, 7.9%, and 13.2% in untreated patients (Figure 4-9).

Figure 4-9 Cumulative percentage of patients receiving at least one urine albumin-to-creatinine ratio assessment during the post-treatment period



Rates of urine ACR assessment were slightly lower for patients who received adjuvant chemotherapy than for patients who did not during the first and second years after completion of treatment, but higher beyond the first 2 years post-treatment (Table

4-8). Rates of urine ACR assessment during the first year, second year, and after the first 2 years post-treatment were 25.5, 32.5, and 42.9 per 1,000 person-years, respectively, for chemotherapy-treated patients, compared with 27.2, 33.1, and 33.4 per 1,000 person-years for untreated patients. After adjustment for baseline characteristics, the differences in rates of urine albumin testing between chemotherapy-treated and untreated patients were not statistically significant for the first or the second year post-treatment (Table 4-8). Beyond the first 2 years post-treatment, however, the rate of urine albumin testing was 21% higher for chemotherapy-treated than for untreated patients, and this difference was significant (RR 1.21, 95% CI 1.08-1.35; $P < 0.001$).

Table 4-8 Assessment of kidney function in surgically treated breast cancer patients during post-treatment period by follow-up intervals

Laboratory tests/Follow-up intervals	CHEMO			No CHEMO				
	Total, n (% pts. tested)	Total tests performed	Rate*	Total, n (% pts. tested)	Total tests performed	Rate*	RR (95% CI)†	*P*
Serum creatinine								
≤ 1 year	13818 (81.8)	52847	4205.6	9278 (73.0)	21338	2463.3	1.68 (1.54, 1.83)	<0.001
> 1-≤ 2 years	12367 (82.8)	39687	3544.1	8110 (75.3)	18320	2432.3	1.43 (1.30, 1.57)	<0.001
> 2-< 18 years	10607 (92.9)	131408	3240.3	6840 (89.4)	62184	2368.9	1.32 (1.26, 1.39)	<0.001
Urine albumin								
≤ 1 year	13818 (4.6)	769	61.2	9278 (4.4)	513	59.2	1.00 (0.86, 1.18)	0.95
> 1-≤ 2 years	12367 (5.4)	856	76.4	8110 (5.2)	523	69.4	1.07 (0.92, 1.25)	0.37
> 2-< 18 years	10607 (14.6)	3808	93.9	6840 (12.9)	2131	81.2	1.12 (1.03, 1.20)	0.005
Urine ACR								
≤ 1 year	13818 (2.0)	321	25.5	9278 (2.1)	236	27.2	0.90 (0.72, 1.12)	0.33
> 1-≤ 2 years	12367 (2.4)	364	32.5	8110 (2.6)	249	33.1	0.95 (0.76, 1.17)	0.60
> 2-< 18 years	10607 (7.6)	1739	42.9	6840 (6.5)	878	33.4	1.21 (1.08, 1.35)	<0.001

* Rate presented as total number of tests performed per 1,000 patient-years.

† An interval Poisson model was used to estimate the adjusted rate ratio of laboratory testing for kidney disease for patients in the adjuvant chemotherapy-treated cohort compared with patients in the untreated cohort. Patient demographic characteristics, comorbid conditions at baseline, and tumor characteristics were included in the model.

Abbreviation: ACR, Albumin-to-creatinine ratio; CHEMO, chemotherapy; CI, confidence interval; RR, rate ratio.

Chapter 5 Discussion

5.1 Summary of Major Findings

To my knowledge, this is the first population-based study to systematically assess the acute and chronic nephrotoxic effects related to use of adjuvant chemotherapy and post-treatment kidney function monitoring among elderly breast cancer patients. In this study, I found that adjuvant chemotherapy was significantly associated with a 2.7-fold increased risk of AKI within 6 months after chemotherapy initiation, although the overall incidence rate of AKI was markedly low in this population (16 per 1,000 patient-years in chemotherapy-treated patients and 6 per 1,000 patient-years in untreated patients). Moreover, each type of chemotherapy was significantly associated with increased risk of AKI, with the strongest association for taxane-based chemotherapy, the weakest for a CMF regimen, and intermediate association for anthracycline-based and other types of chemotherapy. Trastuzumab use was associated with a 6% increased risk of AKI, but this association was not statistically significant after adjustment for patient and tumor characteristics.

I found no association between adjuvant chemotherapy and risk of CKD during the maximum of 18 years follow-up. Compared with patients who did not receive adjuvant chemotherapy, patients who received CMF or “other” chemotherapy were 4% more likely to develop CKD, while patients who received anthracyclines and taxanes were 6% and 9% less likely to develop CKD, respectively. However, these associations were not statistically significant. Trastuzumab use was associated with an 18% increased

risk of CKD. This association, however, was not statistically significant after adjustment for patient and tumor characteristics.

During the post-treatment period, serum creatinine level was assessed in elderly breast cancer patients at a rate decreasing from 4.2 tests per patient per year within the first year after treatment to 3.2 tests per patient per year after 2 years after treatment in patients treated with adjuvant chemotherapy, compared with a roughly constant 2.4 tests per patient per year in patients not treated with adjuvant chemotherapy. Although the strength of association between adjuvant chemotherapy and frequency of serum creatinine tests attenuated with increasing follow-up time, the rate of serum creatinine testing remained a significant 32% higher for chemotherapy-treated than for untreated patients even after 2 years of follow-up after adjustment for patient baseline characteristics. In contrast, the rate of urine albumin testing increased steadily with increasing follow-up time for both chemotherapy-treated and untreated patients, but at a much lower rate than serum creatinine testing, ranging from 59 per 1,000 patient-years in the first year of follow-up for untreated patients to 94 per 1,000 patient-years after 2 years of treatment for treated patients. The rate of urine albumin testing was not significantly different between patients treated and not treated with adjuvant chemotherapy within the first 2 years of treatment, but was 12% higher in treated than in untreated patients after 2 years of treatment. The rate of urine ACR testing was about half the rate of urine albumin testing, with no significant difference between treated and untreated patients within the first 2 years of follow-up and a 21% increased rate in treated compared with untreated patients after 2 years of follow-up.

5.2 Comparison with Previous Studies and Interpretation

5.2.1 Effect of Chemotherapy on Risk of AKI

The low incidence rate of AKI in elderly breast cancer patients observed in this study was consistent with two recent population-based studies despite differences in data sources used to identify AKI patients, target populations, and lengths of follow-up.[112;113] In a recent Danish population-based cohort study of 46,880 incident cancer patients of all ages diagnosed 1999-2006, Christiansen et al examined the incidence rate and cumulative incidence of AKI at 1-year and 5-year follow-up, and found that the 1-year risk of AKI was highest among patients with kidney cancer, liver cancer, or multiple myeloma and lowest among patients with testis cancer, breast cancer, or malignant melanoma.[112] Of 3,938 breast cancer patients with a baseline creatinine measurement, the 1-year incidence rate of AKI, defined as a > 50% increase in serum creatinine compared with baseline level, was 48 per 1,000 person-years (95% CI 41-56 per 1,000 person-years) and the 1-year risk of AKI was 4.5% (95% CI 3.9%-5.2%). This study did not examine the incidence rate of AKI in chemotherapy-treated patients or whether the risk of AKI was related to chemotherapy treatment.

Another population-based study by Langeberg et al addressed the incidence of AKI in adult breast cancer patients and in patients treated with chemotherapy using a large national commercial claims database.[113] Among 13,150 women diagnosed with breast cancer 2000-2007 and aged 18-64 years at diagnosis with no history of renal insufficiency, the cumulative incidence of AKI, defined using at least one inpatient or

two outpatient claims with an ICD-9-CM code of 584.XX or 586.XX, within a year after cancer diagnosis, was 0.3% in all patients and 1.0% in patients receiving nephrotoxic chemotherapy. Although this study did not evaluate the association between chemotherapy and risk of AKI with adjustment for patient baseline characteristics, it was evident that patients who received chemotherapy had much higher incidence of AKI than patients who did not.

Although several experimental animal studies have shown the nephrotoxic potential of doxorubicin[107;109;110] and cyclophosphamide,[97-102] data on nephrotoxic potential in humans is limited; only one case report linking anthracyclines with renal failure in humans[111] and two case reports showed that nephrotoxicity can occur in cancer patients treated with low-dose methotrexate.[49;50] Therefore, the strong association between adjuvant chemotherapy and risk of AKI observed in the current study may not be fully explained by the direct nephrotoxic effect on AKI occurrence. Investigation of the distribution of diagnosis codes accompanying the AKI diagnosis code reported on hospital claims among AKI patients showed that septicemia was the second most frequently coded disease at any position on the hospital claims, presenting in 40% of AKI patients who received chemotherapy compared with 17% of AKI patients who did not receive chemotherapy. Among patients with AKI coded as secondary diagnosis, septicemia was the most frequently coded principal diagnosis in 27% of AKI patients treated with chemotherapy compared with 15% of AKI patients not treated. These results suggest a possible etiologic pathway; i.e., myelosuppressive side effects of chemotherapeutic agents used in the adjuvant setting for breast cancer increased risk for

sepsis, which in turns led to AKI. Many chemotherapy agents and regimens recommended in the NCCN guidelines for treating breast cancer are myelosuppressive and associated with higher risk of infection, as manifested by febrile neutropenia.[140] Patients with infection or febrile neutropenia have markedly increased risk for sepsis which is the most common cause of AKI in cancer patients.[70]

5.2.2 Effect of Chemotherapy on Risk of CKD

The null association between adjuvant chemotherapy and risk of CKD development in elderly breast cancer patients found in the current study may suggest little nephrotoxic effect of the chemotherapeutic agents most commonly used in the treatment of breast cancer. Although several experimental animal studies have shown nephrotoxic potential of doxorubicin[107;109;110] and cyclophosphamide,[97-102] only a few case reports linked these agents with nephrotoxicity in cancer patients.[49;50;111] The null association between adjuvant chemotherapy and diagnosis of CKD in elderly breast cancer patients was also observed in two sensitivity analyses: 1) initiation of adjuvant chemotherapy defined as a time-varying variable; and 2) competing risk analysis with death as a competing event for CKD. These sensitivity analyses were performed to evaluate the association between adjuvant chemotherapy and risk of CKD from different aspects. The analysis with initiation of adjuvant chemotherapy defined as a time-varying variable included all 84,018 elderly women with breast cancer who met the study inclusion and exclusion criteria to ensure the largest possible sample size. The result showed a non-significant 4% reduced risk of CKD associated with adjuvant chemotherapy after adjustment for potential confounders. The competing risk analysis examined the effect of

adjuvant chemotherapy on development of CKD during the time interval when patients remained alive. Although patients treated with adjuvant chemotherapy had a 3% increased risk of CKD compared with untreated patients after adjustment for patient baseline characteristics, this association was not significant.

Another possible explanation for the null association between adjuvant chemotherapy and risk of CKD in elderly breast cancer patients is related to the method used to identify CKD patients using ICD-9-CM diagnosis codes in Medicare claims. Previous validation studies of claims-based definitions of CKD suggested that the claims-based method identifies CKD stages 3-5.[129;130] If the chemotherapeutic agents most commonly used in treating breast cancer likely cause mild (i.e., stages 1-2) damage to kidney function, Medicare claims data poorly identify these cases. Therefore, the findings in the present study likely reflect a null association between chemotherapy and risk of advanced stages of CKD.

The results from the analyses of the subgroup of patients who received one cycle of chemotherapy and matched untreated patients showed a significant 40% increased risk of CKD associated with receiving chemotherapy. Adjuvant chemotherapy for breast cancer usually requires 4-8 cycles and may last 3-8 months. For patients who received treatment for less than 1 week, an adverse event likely prevented them from completing the course. Additionally, these patients had more risk factors for CKD (increasing age, black race, diabetes, and cardiovascular disease) than patients whose chemotherapy treatment lasted more than 1 week. Thus, the observed significant 40% increased risk of

CKD in this subgroup may be due to underlying high risk for CKD, and chemotherapy treatment increased the likelihood of adverse responses to chemotherapeutic agents.

The current study demonstrates that increasing age, black race, cardiovascular disease, diabetes, and hypertension were associated with greater risk of CKD in elderly breast cancer patients. These findings were consistent with prior studies of risk factors for CKD.[1]

5.2.3 Monitoring Renal Function

Few studies have examined clinical practice patterns of renal function monitoring and the association between adjuvant chemotherapy and rate of renal function monitoring in elderly breast cancer patients during the post-treatment period. A study by the USRDS examined the trends in 1-year cumulative percent of serum creatinine and urine albumin testing in the elderly Medicare population without CKD 2000-2010[141] The 1-year cumulative percent of patients receiving at least one serum creatinine measurement was 62% in 2000 and increased to 77% in 2010. Compared with the rate of serum creatinine testing in the Medicare population without CKD, serum creatinine assessment in elderly women with breast cancer was more frequent; the 1-year cumulative percent of testing was 84% in patients treated with adjuvant chemotherapy and 76% in patients not treated. This higher rate of serum creatinine testing in breast cancer patients was likely due to regular follow-up physical exams indicated by the NCCN and ASCO guidelines. Because serum creatinine testing is usually part of a panel of tests in basic or comprehensive metabolic panels, frequent assessment of serum creatinine may not necessarily indicate active assessment of kidney function during the physical exams.

Unlike serum creatinine assessment, urine albumin testing must be ordered separately. Therefore, urine albumin testing may represent a true intent to assess kidney disease. The USRDS reported that the 1-year cumulative percent of at least one urine albumin measurement in the elderly Medicare population without CKD was only 2% in 2000, increased to 6% in 2004, and reached 10% in 2010.[141] For elderly women with breast cancer, in contrast, the 1-year cumulative percent of patients receiving at least one urine albumin test after completion of treatment was about 5% regardless of chemotherapy treatment. These comparisons suggest that elderly women with breast cancer did not receive more screening for kidney disease than the general Medicare population without CKD.

The results of the current study comparing the rate of urine albumin testing between patients treated and not treated with adjuvant chemotherapy during each follow-up interval showed that the rate of urine albumin testing was similar for treated and untreated patients within the first 2 years of follow-up, but increased by a significant 12% for treated patients after the first 2 years of follow-up. This finding may imply that treatment and management of the survivor's primary disease is the clinical focus when patients first finish their primary treatment. Although the testing rate in chemotherapy-treated patients was significantly higher than in untreated patients after 2 years after completion of treatment, the rate was markedly low for both treated (94 tests per 1,000 patient-years) and untreated (81 tests per 1,000 patient-years) patients. The findings of a low rate of renal function monitoring regardless of chemotherapy treatment status and no additional risk of CKD associated with adjuvant chemotherapy do not provide sufficient

evidence for the need for a clinical practice guideline for the surveillance and management of nephrotoxicity among elderly women with breast cancer and treated with chemotherapy.

In a subgroup analysis of elderly breast cancer patients with diabetes, the rate of urine albumin testing was greatly increased regardless of chemotherapy status, but there was no association between adjuvant chemotherapy and increased rate of monitoring in each follow-up interval (results are not shown). Since diabetes is an important risk factor for CKD, and NKF K/DOQI guidelines recommend assessment of proteinuria yearly in adults with type 2 diabetes, these results suggest that CKD surveillance of elderly breast cancer patients with diabetes followed the clinical guidelines for the general population at risk for CKD. Adjuvant chemotherapy did not impact the active assessment of kidney disease to any extent in elderly women with breast cancer.

5.3 Strengths and Limitations

This study had several strengths. First, the study population consisted of elderly breast cancer patients with Medicare fee-for-service coverage at the time of diagnosis. This patient group is usually underrepresented in clinical trials due to comorbid conditions or potential survival limitations. Thus, patients included in this study may be fairly representative of elderly breast cancer patients. Second, a propensity-matched cohort study design may reduce treatment selection bias due to factors that may have influenced physicians or patients to choose chemotherapy and may be related to outcomes. Third, information on health conditions and associated treatments was nearly

complete in Medicare claims data because the Medicare program covers all medical services provided to beneficiaries. Fourth, misclassification of chemotherapy treatment, laboratory tests, or cancer-related clinical factors was likely minimal because 1) information on cancer-related clinical factors provided by SEER registries was of high quality; and 2) facilities/providers are motivated to accurately report chemotherapy drug costs and administration fees and laboratory tests and procedures in order to receive reimbursement. Finally, the maximum of 18 years follow-up allowed for more complete assessment of CKD status and adequate evaluation of post-treatment renal function monitoring, which are almost impossible to evaluate in clinical trials of shorter duration.

The limitations of the study should be noted. First, it is a retrospective observational study. Because chemotherapy treatment was not randomly assigned, a causal relationship between chemotherapy use and the risk of AKI and CKD cannot be inferred. Although propensity matching was used to balance baseline characteristics in patients receiving and not receiving chemotherapy, a propensity score-matched cohort study is not equivalent to a randomized clinical trial. Residual confounding likely exists due to unknown and/or unmeasured confounding variables.

Second, misclassifications of AKI and CKD based on Medicare claims are also concerns. Perfect specificity and imperfect sensitivity of a disease ascertainment will not bias the estimated measure of association, although the statistical power for detecting a significant association may be reduced. In the presence of imperfect specificity, however, the estimated measure of association will be biased towards the null hypothesis.[142] Since both AKI and CKD are uncommon events among cancer patients,[4] the degree of

underestimation will be influenced more by the specificity than by the sensitivity of ascertainment of AKI and CKD. As described in Sections 3.4.2 and 3.4.3, the specificity of the claims-based definitions of AKI and CKD used in this study was likely to be greater than 91% and 93%, respectively, but whether they were close to 100% is not clear. Therefore, given such misclassification was likely non-differential, the estimated associations between chemotherapy use and the risk of AKI and CKD may be biased towards to the null hypothesis.

Third, Medicare claims contain limited information on the dosage and intensity of chemotherapy and biochemical data to determine CKD stage. Therefore, presence of a dose-response relationship between adjuvant chemotherapy and development of CKD and whether adjuvant chemotherapy had adverse effects on the development of early CKD could not be addressed in this study.

Fourth, the statistical power to examine the associations between chemotherapy regimen and the risks of AKI and CKD was likely limited.

Finally, the study sample was restricted to elderly incident breast cancer patients with stages I-III and enrolled in Medicare fee-for-service, so it is uncertain that the findings can be extrapolated to younger patients, patients with stage 0 or stage IV, or patients not enrolled in Medicare fee-for-service.

5.4 Implications

Results from the current study have several important implications for clinicians treating elderly breast cancer patients. First, most chemotherapeutic agents used to treat

breast cancer in the adjuvant setting may not have a direct nephrotoxic effect. Instead, these agents cause myelosuppression, which increases the risk of infection and subsequent AKI. Therefore, prevention of serious complications of chemotherapy including sepsis and infection is important in preventing AKI for patients who receive adjuvant chemotherapy. Second, the findings of the current study do not suggest that adjuvant chemotherapy for breast cancer was associated with increased long-term risk of advanced CKD. Therefore, when clinicians discuss with their patients the potential risk of development of CKD after chemotherapy treatment and the choice of chemotherapy treatment, mainly the patient's comorbid conditions and other risk factors for CKD should be considered. Other risk factors for CKD should be managed appropriately based on existing guidelines. Finally, the findings of no statistically significant association between adjuvant chemotherapy and risk of CKD and the rate of renal function monitoring during the post-treatment period for elderly women with breast cancer do not provide sufficient evidence to recommend clinical practice guidelines to routinely screen for CKD after adjuvant chemotherapy treatment in elderly breast cancer patients.

5.5 Future Research

One important area for future research is to investigate whether trastuzumab use is associated with increased risk of CKD. Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody that binds to HER2, the human epidermal growth factor receptor 2 protein. It was first approved by the FDA to treat patients with metastatic breast cancer who had HER2-positive and node-positive tumors. In November 2006,

FDA approval was expanded to the adjuvant setting combining trastuzumab with chemotherapy to treat patients with early stage, node-positive, and HER2-overexpressing breast cancer. In January 2008, FDA approval was revised to include trastuzumab for use as stand-alone treatment (without chemotherapy) in the adjuvant setting. Though use of trastuzumab remains limited to patients with HER2-positive breast cancer, it could be prescribed to patients regardless of lymph node involvement. Along with FDA approval of trastuzumab use in the adjuvant setting, trastuzumab use for early stage breast cancer has been increasing since 2005. Results in the current study showed that trastuzumab use in the adjuvant setting for elderly women with breast cancer increased rapidly from 12.5% in 2005 to about 20% in 2008. Though trastuzumab could improve disease-free survival for breast cancer patients, studies have shown that breast cancer patients treated with trastuzumab chemotherapy are at increased risk for heart failure and/or cardiomyopathy compared with women not treated with chemotherapy.[143] NCCN guidelines recommend cardiac monitoring for trastuzumab-containing regimens at baseline and at 3, 6, and 9 months. The current study found that trastuzumab was associated with an 18% increased risk of CKD among elderly breast cancer patients treated with chemotherapy. Due to the small sample size of patients using trastuzumab (about 800) and limited follow-up time, statistical power was not adequate to fully test an association. With increased trastuzumab use in the adjuvant setting for early stage breast cancer and the growing number of cancer survivors and CKD patients in the U.S., investigation of the long-term effect of trastuzumab on risk of CKD is warranted.

Findings from the current study did not suggest an association between adjuvant chemotherapy and risk of CKD in elderly women with breast cancer, nor did the findings provide evidence to recommend clinical practice guidelines to routinely screen for CKD after adjuvant chemotherapy treatment in elderly breast cancer patients. However, with the development of new chemotherapeutic and biologic agents that may be potentially nephrotoxic and the growing number of cancer survivors and CKD patients in the U.S, studies of CKD as a late effect of cancer treatment for other solid tumors commonly treated with known or potential nephrotoxic agents and are warranted.

Another potential area to consider for future research is using an instrumental variable (IV) approach to reduce bias caused by unknown and/or unmeasured confounders that could not be addressed in this retrospective observational study. The IV approach has been recently introduced to medical research, and application of an IV may reduce bias caused by measured and unmeasured confounders in observational studies. However, the major limitation of the IV method is that a suitable IV is difficult to find due to the strong assumptions,[144] and IV studies require large sample sizes.

Chapter 6 Conclusions

This body of work is, to my knowledge, the first population-based observational study to systematically examine the association of adjuvant chemotherapy with risks of AKI and CKD and rate of renal function monitoring during the post-treatment period among elderly breast cancer patients. Several key findings include:

- Adjuvant chemotherapy and risk of AKI
    - Although the overall incidence rate of AKI was quite low in elderly women with breast cancer (16/1,000 person-years in patients treated with adjuvant chemotherapy and 6/1,000 person-years in patients not treated), adjuvant chemotherapy was significantly associated with a 2.7-fold increased risk of AKI within 6 months after chemotherapy initiation (95% CI 1.8-4.1; $P < 0.001$).
    - The strength of association varied among the main chemotherapy regimens, and was strongest for taxane-based chemotherapy (HR 4.2, 95% CI 2.2-2.8; $P < 0.001$), weakest for CMF regimen (HR 2.2, 95% CI 1.3-3.8; $P = 0.004$, and intermediate for anthracycline-based (HR 2.5, 95% CI 1.6-4.1; $P < 0.001$) and other types of chemotherapy (HR 3.0, 95% CI 1.5-6.2; $P = 0.003$).
    - Septicemia was the second most commonly diagnosed disease in patients who received chemotherapy and developed AKI, representing 40% of these cases, while it occurred in only 17% of patients with AKI who did not receive chemotherapy.

- Adjuvant chemotherapy and risk of CKD
    - Adjuvant chemotherapy was not associated with increased risk of CKD among elderly women with breast cancer (HR 1.00, 95% CI 0.93-1.07; *P* = 0.91). Although the association varied among major chemotherapy regimens, none of the associations were statistically significant.
    - Trastuzumab use was associated with an 18% increased risk of CKD among elderly women with breast cancer who received adjuvant chemotherapy. This association, however, was not statistically significant after adjustment for patient and tumor characteristics.
- Adjuvant chemotherapy and rate of serum creatinine assessment
    - Serum creatinine level was frequently assessed in elderly breast cancer patients, especially those receiving chemotherapy. For patients treated with adjuvant chemotherapy, the rate of testing was as high as 4.2 tests per patient per year within the first year of follow-up and decreased to 3.2 tests per patient per year after 2 years of treatment. By contrast, the rate was roughly constant at 2.4 tests per patient per year during the post-treatment period for no-chemotherapy patients.
    - Although the strength of association between adjuvant chemotherapy and frequency of serum creatinine testing attenuated with increasing follow-up time, the rate remained a significant 32% higher for patients treated with chemotherapy (RR 1.32, 95% CI 1.26-1.39; $P < 0.001$) than

for untreated patients even after 2 years of follow-up after adjustment for patient baseline characteristics.

- Adjuvant chemotherapy and rate of urine albumin assessment
    - The rate of urine albumin testing increased steadily with increasing follow-up time for both chemotherapy-treated and untreated patients, but was much lower than the rate of serum creatinine testing, ranging from 59/1,000 patient-years in first year of follow-up for untreated patients to 94/1,000 patient-years after 2 years of treatment for treated patients.
    - The rate of urine albumin testing was not significantly different between patients treated and not treated with adjuvant chemotherapy within the first 2 years of treatment, but was 12% higher in treated patients after 2 years of treatment (RR 1.12, 95% CI 1.03-1.20; $P = 0.005$).
- Adjuvant chemotherapy and rate of urine ACR assessment
    - The rate of urine ACR testing was about half the rate of urine albumin testing for both chemotherapy-treated and untreated patients.
    - Within the first 2 years of follow-up, there were no significant differences in rate of ACR testing between patients treated and not treated with adjuvant chemotherapy. After 2 years of follow-up, the rate of testing for treated patients was 21% higher than for untreated patients (RR 1.21, 95% CI 1.08-1.35; $P < 0.001$).

In conclusion, this body of work suggests that the increased risk of AKI associated with adjuvant chemotherapy among elderly women with breast cancer is likely explained by the following etiology pathway: myelosuppressive chemotherapeutic agents increased the risk of infection/neutropenia, which increased the risk of septicemia and subsequent risk of AKI. This finding highlights the importance of preventing serious complications of chemotherapy, including infection and sepsis, in preventing AKI for patients who received adjuvant chemotherapy. Additionally, adjuvant chemotherapy in elderly women with breast cancer may not impose additional risk for CKD. This finding suggests that patients' underlying risk factors for CKD such as diabetes, hypertension, etc. should be considered in the discussions between clinicians and patients regarding potential risk of CKD development after chemotherapy treatment and choice of chemotherapy treatment. Finally, although renal function should be assessed prior to each cycle for potential dose modification for several nephrotoxic agents, the findings do not provide sufficient evidence of the need for a clinical practice guideline for CKD screening among elderly breast cancer survivors treated with adjuvant chemotherapy. However, with the development of new chemotherapeutic agents and the growing number of cancer survivors and CKD patients in the U.S., studies may be needed of CKD as a late effect of chemotherapy for other solid tumors and of the cost-benefit of clinical practice guidelines on surveillance and nephrotoxic management in survivors of other type of cancers diagnosed and treated in adults.

References

(1) National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. *Am J Kidney Dis* 2002;39:S1-S266.

(2) Levey AS, Atkins R, Coresh J et al. Chronic kidney disease as a global public health problem: approaches and initiatives - a position statement from Kidney Disease Improving Global Outcomes. *Kidney Int* 2007;72:247-259.

(3) Coresh J, Selvin E, Stevens LA et al. Prevalence of chronic kidney disease in the United States. *JAMA* 2007;298:2038-2047.

(4) U.S. Renal Data System. *USRDS 2012 Annual Data Report: Atlas of Chronic Kidney Disease & End-Stage Renal Disease in the United States*. 2012 ed. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2012.

(5) Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296-1305.

(6) Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004;164:659-663.

(7) Collins AJ, Li S, Gilbertson DT, Liu J, Chen SC, Herzog CA. Chronic kidney disease and cardiovascular disease in the Medicare population. *Kidney Int* 2003;64 (Suppl 87):S24-S31.

(8) Matsushita K, van d, V, Astor BC et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010;375:2073-2081.

(9) Launay-Vacher V, Oudard S, Janus N et al. Prevalence of Renal Insufficiency in cancer patients and implications for anticancer drug management: the renal insufficiency and anticancer medications (IRMA) study. *Cancer* 2007;110:1376-1384.

(10) Yancik R. Cancer burden in the aged: an epidemiologic and demographic overview. *Cancer* 1997;80:1273-1283.

(11) Yancik R, Ries LA. Aging and cancer in America. Demographic and epidemiologic perspectives. *Hematol Oncol Clin North Am* 2000;14:17-23.

(12) Ganz PA, Hussey MA, Moinpour CM et al. Late cardiac effects of adjuvant chemotherapy in breast cancer survivors treated on Southwest Oncology Group protocol s8897. *J Clin Oncol* 2008;26:1223-1230.

(13) Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol* 2007;25:3808-3815.

(14) Doyle JJ, Neugut AI, Jacobson JS, Grann VR, Hershman DL. Chemotherapy and cardiotoxicity in older breast cancer patients: a population-based study. *J Clin Oncol* 2005;23:8597-8605.

(15) Bonneterre J, Roche H, Kerbrat P et al. Long-term cardiac follow-up in relapse-free patients after six courses of fluorouracil, epirubicin, and cyclophosphamide, with either 50 or 100 mg of epirubicin, as adjuvant therapy for node-positive breast cancer: French adjuvant study group. *J Clin Oncol* 2004;22:3070-3079.

(16) Hequet O, Le QH, Moullet I et al. Subclinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults. *J Clin Oncol* 2004;22:1864-1871.

(17) Zambetti M, Moliterni A, Materazzo C et al. Long-term cardiac sequelae in operable breast cancer patients given adjuvant chemotherapy with or without doxorubicin and breast irradiation. *J Clin Oncol* 2001;19:37-43.

(18) Loehrer PJ, Sr., Johnson D, Elson P, Einhorn LH, Trump D. Importance of bleomycin in favorable-prognosis disseminated germ cell tumors: an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 1995;13:470-476.

(19) Nichols CR, Catalano PJ, Crawford ED, Vogelzang NJ, Einhorn LH, Loehrer PJ. Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. *J Clin Oncol* 1998;16:1287-1293.

(20) Duggan DB, Petroni GR, Johnson JL et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. *J Clin Oncol* 2003;21:607-614.

(21) Du XL, Xia R, Hardy D. Relationship between chemotherapy use and cognitive impairments in older women with breast cancer: findings from a large population-based cohort. *Am J Clin Oncol* 2010;33:533-543.

(22) Brezden CB, Phillips KA, Abdolell M, Bunston T, Tannock IF. Cognitive function in breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol* 2000;18:2695-2701.

(23) Meyers CA, Weitzner MA. Neurobehavioral functioning and quality of life in patients treated for cancer of the central nervous system. *Curr Opin Oncol* 1995;7:197-200.

(24) van Dam FS, Schagen SB, Muller MJ et al. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. *J Natl Cancer Inst* 1998;90:210-218.

(25) Ochs J, Mulhern R, Fairclough D et al. Comparison of neuropsychologic functioning and clinical indicators of neurotoxicity in long-term survivors of childhood leukemia given cranial radiation or parenteral methotrexate: a prospective study. *J Clin Oncol* 1991;9:145-151.

(26) Ganz PA, Greendale GA, Petersen L, Zibecchi L, Kahn B, Belin TR. Managing menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. *J Natl Cancer Inst* 2000;92:1054-1064.

(27) Greendale GA, Petersen L, Zibecchi L, Ganz PA. Factors related to sexual function in postmenopausal women with a history of breast cancer. *Menopause* 2001;8:111-119.

(28) Lamb MA. Effects of cancer on the sexuality and fertility of women. *Semin Oncol Nurs* 1995;11:120-127.

(29) Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N. Risk of menopause during the first year after breast cancer diagnosis. *J Clin Oncol* 1999;17:2365-2370.

(30) Andrykowski MA, Curran SL, Lightner R. Off-treatment fatigue in breast cancer survivors: a controlled comparison. *J Behav Med* 1998;21:1-18.

(31) Loge JH, Abrahamsen AF, Ekeberg O, Kaasa S. Hodgkin's disease survivors more fatigued than the general population. *J Clin Oncol* 1999;17:253-261.

(32) Beadle G, Baade P, Fritschi L. Acute myeloid leukemia after breast cancer: a population-based comparison with hematological malignancies and other cancers. *Ann Oncol* 2009;20:103-109.

(33) Schaapveld M, Visser O, Louwman MJ et al. Risk of new primary nonbreast cancers after breast cancer treatment: a Dutch population-based study. *J Clin Oncol* 2008;26:1239-1246.

(34) Praga C, Bergh J, Bliss J et al. Risk of acute myeloid leukemia and myelodysplastic syndrome in trials of adjuvant epirubicin for early breast cancer: correlation with doses of epirubicin and cyclophosphamide. *J Clin Oncol* 2005;23:4179-4191.

(35) Ganz PA, Desmond KA, Leedham B, Rowland JH, Meyerowitz BE, Belin TR. Quality of life in long-term, disease-free survivors of breast cancer: a follow-up study. *J Natl Cancer Inst* 2002;94:39-49.

(36) Gotay CC, Muraoka MY. Quality of life in long-term survivors of adult-onset cancers. *J Natl Cancer Inst* 1998;90:656-667.

(37) Skinner R, Parry A, Price L, Cole M, Craft AW, Pearson AD. Glomerular toxicity persists 10 years after ifosfamide treatment in childhood and is not predictable by age or dose. *Pediatr Blood Cancer* 2010;54:983-989.

(38) Diller L, Chow EJ, Gurney JG et al. Chronic disease in the Childhood Cancer Survivor Study cohort: a review of published findings. *J Clin Oncol* 2009;27:2339-2355.

(39) Oberlin O, Fawaz O, Rey A et al. Long-term evaluation of Ifosfamide-related nephrotoxicity in children. *J Clin Oncol* 2009;27:5350-5355.

(40) Lewis MA, Shaw J, Sinha M, Adalat S, Hussain F, Inward C. UK Renal Registry 11th Annual Report (December 2008): Chapter 13 Demography of the UK paediatric renal replacement therapy population. *Nephron Clin Pract* 2009;111 Suppl 1:c257-c267.

(41) Oeffinger KC, Mertens AC, Sklar CA et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006;355:1572-1582.

(42) Koch Nogueira PC, Hadj-Aissa A, Schell M, Dubourg L, Brunat-Mentigny M, Cochat P. Long-term nephrotoxicity of cisplatin, ifosfamide, and methotrexate in osteosarcoma. *Pediatr Nephrol* 1998;12:572-575.

(43) Douville P, Martel AR, Talbot J, Desmeules S, Langlois S, Agharazii M. Impact of age on glomerular filtration estimates. *Nephrol Dial Transplant* 2009;24:97-103.

(44) Ahmad S, Shen FH, Bleyer WA. Methotrexate-induced renal failure and ineffectiveness of peritoneal dialysis. *Arch Intern Med* 1978;138:1146-1147.

(45) Jaffe N. Toxicity of high-dose methotrexate (NSC-740) and citrovorum factor (NSC-3590) in osteogenic sarcoma. *Cancer Chemotherapy Reports* 1975;31-36.

(46) Widemann BC, Balis FM, Kempf-Bielack B et al. High-dose methotrexate-induced nephrotoxicity in patients with osteosarcoma. *Cancer* 2004;100:2222-2232.

(47) Ellison NM, Servi RJ. Acute renal failure and death following sequential intermediate-dose methotrexate and 5-FU: a possible adverse effect due to concomitant indomethacin administration. *Cancer Treat Rep* 1985;69:342-343.

(48) Stark AN, Jackson G, Carey PJ, Arfeen S, Proctor SJ. Severe renal toxicity due to intermediate-dose methotrexate. *Cancer Chemother Pharmacol* 1989;24:243-245.

(49) Seideman P, Muller-Suur R, Ekman E. Renal effects of low dose methotrexate in rheumatoid arthritis. *J Rheumatol* 1993;20:1126-1128.

(50) Condit PT, Chanes RE, Joel W. Renal toxicity of methotrexate. *Cancer* 1969;23:126-131.

(51) NCCN Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network. Available at: http://www.nccn.org/index.asp. 2011. Accessed April 4, 2013.

(52) American Cancer Society. Cancer Facts & Figures 2010. Available at: http://www.cancer.org. 2010. Accessed April 4, 2013.

(53) National Cancer Institute. Cancer Survivorship Research: Cancer Control and Population Sciences. Available at: http://www.nccn.org/professionals/physician_gls/default.asp 2010; Accessed April 4, 2013.

(54) Morimoto L, Coalson J, Mowat F, O'Malley C. Factors affecting receipt of chemotherapy in women with breast cancer. *Int J Womens Health* 2010;2:107-122.

(55) Aareleid T, Sant M, Hedelin G. Improved survival for patients with testicular cancer in Europe since 1978. EUROCARE Working Group. *Eur J Cancer* 1998;34:2236-2240.

(56) Wingo PA, Ries LA, Rosenberg HM, Miller DS, Edwards BK. Cancer incidence and mortality, 1973-1995: a report card for the U.S. *Cancer* 1998;82:1197-1207.

(57) Sant M, Capocaccia R, Coleman MP et al. Cancer survival increases in Europe, but international differences remain wide. *Eur J Cancer* 2001;37:1659-1667.

(58) Brenner H, Soderman B, Hakulinen T. Use of period analysis for providing more up-to-date estimates of long-term survival rates: empirical evaluation among 370,000 cancer patients in Finland. *Int J Epidemiol* 2002;31:456-462.

(59) Skinner R. Nephrotoxicity--what do we know and what don't we know? *J Pediatr Hematol Oncol* 2011;33:128-134.

(60) Greenburg A. *Primer on Kidney Disease*. 5 ed. Saunders Company, 2009.

(61) Mehta RL, Chertow GM. Acute renal failure definitions and classification: time for change? *J Am Soc Nephrol* 2003;14:2178-2187.

(62) Cohen E. *Cancer and the Kidney*. 2nd edition. Oxford University Press, 2010.

(63) Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004;8:R204-R212.

(64) Mehta RL, Kellum JA, Shah SV et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;11:R31.

(65) Thadhani R, Pascual M, Bonventre JV. Acute renal failure. *N Engl J Med* 1996;334:1448-1460.

(66) Ali T, Khan I, Simpson W et al. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. *J Am Soc Nephrol* 2007;18:1292-1298.

(67) Hsu CY, McCulloch CE, Fan D, Ordonez JD, Chertow GM, Go AS. Community-based incidence of acute renal failure. *Kidney Int* 2007;72:208-212.

(68) Bagshaw SM, George C, Bellomo R. Changes in the incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units. *Crit Care* 2007;11:R68.

(69) Liangos O, Wald R, O'Bell JW, Price L, Pereira BJ, Jaber BL. Epidemiology and outcomes of acute renal failure in hospitalized patients: a national survey. *Clin J Am Soc Nephrol* 2006;1:43-51.

(70) Darmon M, Ciroldi M, Thiery G, Schlemmer B, Azoulay E. Clinical review: specific aspects of acute renal failure in cancer patients. *Crit Care* 2006;10:211.

(71) Cheung CM, Ponnusamy A, Anderton JG. Management of acute renal failure in the elderly patient: a clinician's guide. *Drugs Aging* 2008;25:455-476.

(72) Anderson R. Clinical and Laboratory Diagnosis of Acute Renal Failure. In: *Acute Renal Failure: A Companion to Brenner & Rector's The Kidney, 6th Edition*, 1 ed., edited by Molitoris B, Finn W, W.B. Saunders Company; 2001;157-168.

(73) Brady HR, Singer GG. Acute renal failure. *Lancet* 1995;346:1533-1540.

(74) Shapiro SR, Bennett AH. Recovery of renal function after prolonged unilateral ureteral obstruction. *J Urol* 1976;115:136-140.

(75) Cooper K, Bennett WM. Nephrotoxicity of common drugs used in clinical practice. *Arch Intern Med* 1987;147:1213-1218.

(76) Pascual J, Liano F, Ortuno J. The elderly patient with acute renal failure. *J Am Soc Nephrol* 1995;6:144-153.

(77) Naughton CA. Drug-induced nephrotoxicity. *Am Fam Physician* 2008;78:743-750.

(78) Coca SG. Acute kidney injury in elderly persons. *Am J Kidney Dis* 2010;56:122-131.

(79) Kaufman J, Dhakal M, Patel B, Hamburger R. Community-acquired acute renal failure. *Am J Kidney Dis* 1991;17:191-198.

(80) Novis BK, Roizen MF, Aronson S, Thisted RA. Association of preoperative risk factors with postoperative acute renal failure. *Anesth Analg* 1994;78:143-149.

(81) Zanardo G, Michielon P, Paccagnella A et al. Acute renal failure in the patient undergoing cardiac operation. Prevalence, mortality rate, and main risk factors. *J Thorac Cardiovasc Surg* 1994;107:1489-1495.

(82) U.S. Renal Data System. *USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease & End-Stage Renal Disease in the United States.* 2009 ed. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2009.

(83) Wald R, Quinn RR, Luo J et al. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. *JAMA* 2009;302:1179-1185.

(84) Lo LJ, Go AS, Chertow GM et al. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. *Kidney Int* 2009;76:893-899.

(85) Newsome BB, Warnock DG, McClellan WM et al. Long-term risk of mortality and end-stage renal disease among the elderly after small increases in serum

creatinine level during hospitalization for acute myocardial infarction. *Arch Intern Med* 2008;168:609-616.

(86) Ishani A, Xue JL, Himmelfarb J et al. Acute kidney injury increases risk of ESRD among elderly. *J Am Soc Nephrol* 2009;20:223-228.

(87) Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.

(88) Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461-470.

(89) U.S. Renal Data System. *USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease & End-Stage Renal Disease in the United States.* 2010 ed. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2010.

(90) Jacobs SA, Stoller RG, Chabner BA, Johns DG. 7-Hydroxymethotrexate as a urinary metabolite in human subjects and rhesus monkeys receiving high dose methotrexate. *J Clin Invest* 1976;57:534-538.

(91) Lankelma J, van der Klein E, Ramaekers F. The role of 7-hydroxymethotrexate during methotrexate anti-cancer therapy. *Cancer Lett* 1980;9:133-142.

(92) Smeland E, Fuskevag OM, Nymann K et al. High-dose 7-hydromethotrexate: acute toxicity and lethality in a rat model. *Cancer Chemother Pharmacol* 1996;37:415-422.

(93) Messmann R, Allegra C. Antifolates. In: Chabner B LD, ed. *Cancer Chemotherapy and Biotherapy*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2001;139-184.

(94) Cetiner M, Sener G, Sehirli AO et al. Taurine protects against methotrexate-induced toxicity and inhibits leukocyte death. *Toxicol Appl Pharmacol* 2005;209:39-50.

(95) Kintzel PE, Dorr RT. Anticancer drug renal toxicity and elimination: dosing guidelines for altered renal function. *Cancer Treat Rev* 1995;21:33-64.

(96) Stillwell TJ, Benson RC, Jr. Cyclophosphamide-induced hemorrhagic cystitis. A review of 100 patients. *Cancer* 1988;61:451-457.

(97) Manda K, Bhatia AL. Prophylactic action of melatonin against cyclophosphamide-induced oxidative stress in mice. *Cell Biol Toxicol* 2003;19:367-372.

(98) Stankiewicz A, Skrzydlewska E. Protection against cyclophosphamide-induced renal oxidative stress by amifostine: the role of antioxidative mechanisms. *Toxicol Mech Methods* 2003;13:301-308.

(99) Senthilkumar S, Devaki T, Manohar BM, Babu MS. Effect of squalene on cyclophosphamide-induced toxicity. *Clin Chim Acta* 2006;364:335-342.

(100) Abraham P, Indirani K, Sugumar E. Effect of cyclophosphamide treatment on selected lysosomal enzymes in the kidney of rats. *Exp Toxicol Pathol* 2007;59:143-149.

(101) Sayed-Ahmed MM. Progression of cyclophosphamide-induced acute renal metabolic damage in carnitine-depleted rat model. *Clin Exp Nephrol* 2010;14:418-426.

(102) Ayhanci A, Gunes S, Sahinturk V et al. Seleno L-methionine acts on cyclophosphamide-induced kidney toxicity. *Biol Trace Elem Res* 2010;136:171-179.

(103) Ruggiero A, Ridola V, Puma N et al. Anthracycline cardiotoxicity in childhood. *Pediatr Hematol Oncol* 2008;25:261-281.

(104) Weening JJ, Rennke HG. Glomerular permeability and polyanion in adriamycin nephrosis in the rat. *Kidney Int* 1983;24:152-159.

(105) Saad SY, Najjar TA, Al-Rikabi AC. The preventive role of deferoxamine against acute doxorubicin-induced cardiac, renal and hepatic toxicity in rats. *Pharmacol Res* 2001;43:211-218.

(106) Injac R, Boskovic M, Perse M et al. Acute doxorubicin nephrotoxicity in rats with malignant neoplasm can be successfully treated with fullerenol C60(OH)24 via suppression of oxidative stress. *Pharmacol Rep* 2008;60:742-749.

(107) Liu LL, Li QX, Xia L, Li J, Shao L. Differential effects of dihydropyridine calcium antagonists on doxorubicin-induced nephrotoxicity in rats. *Toxicology* 2007;231:81-90.

(108) Pritsos CA, Ma J. Basal and drug-induced antioxidant enzyme activities correlate with age-dependent doxorubicin oxidative toxicity. *Chem Biol Interact* 2000;127:1-11.

(109) Mohan M, Kamble S, Gadhi P, Kasture S. Protective effect of Solanum torvum on doxorubicin-induced nephrotoxicity in rats. *Food Chem Toxicol* 2010;48:436-440.

(110) Badary OA, Abdel-Naim AB, Abdel-Wahab MH, Hamada FM. The influence of thymoquinone on doxorubicin-induced hyperlipidemic nephropathy in rats. *Toxicology* 2000;143:219-226.

(111) Burke JF, Jr., Laucius JF, Brodovsky HS, Soriano RZ. Doxorubicin hydrochloride-associated renal failure. *Arch Intern Med* 1977;137:385-388.

(112) Christiansen CF, Johansen MB, Langeberg WJ, Fryzek JP, Sorensen HT. Incidence of acute kidney injury in cancer patients: a Danish population-based cohort study. *Eur J Intern Med* 2011;22:399-406.

(113) Langeberg WJ, O'Malley CD, Critchlow CW, Fryzek JP. Risk of acute renal failure among breast cancer patients and chemotherapy treatment of breast cancer patients with a history of renal insufficiency in a commercially-insured population in the United States [abstract]Langeberg WJ, O'Malley CD, Critchlow CW, Fryzek JP. *J Clin Oncol* 2009.

(114) Children's Oncology Group. Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers. Available at: http://www.survivorshipguidelines.org. 2013. Accessed April 4, 2013.

(115) Khatcheressian JL, Wolff AC, Smith TJ et al. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. *J Clin Oncol* 2006;24:5091-5097.

(116) Carver JR, Shapiro CL, Ng A et al. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. *J Clin Oncol* 2007;25:3991-4008.

(117) Choudhury D, Ahmed Z. Drug-associated renal dysfunction and injury. *Nat Clin Pract Nephrol* 2006;2:80-91.

(118) American Cancer Society. Breast Cancer Facts & Figures 2009-2010. Available at: http://www.cancer.org/. 2010; Accessed April 4, 2013.

(119) National Cancer Institute. National Cancer Institute: Surveillance Epidemiology and End Results. Available at: *http://seer.cancer.gov/index.html*. 2012. Accessed April 4, 2013.

(120) Potosky AL, Riley GF, Lubitz JD, Mentnech RM, Kessler LG. Potential for cancer related health services research using a linked Medicare-tumor registry database. *Med Care* 1993;31:732-748.

(121) Glynn RJ, Schneeweiss S, Sturmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol* 2006;98:253-259.

(122) Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. *Stat Med* 2007;26:734-753.

(123) Giordano SH, Lin YL, Kuo YF, Hortobagyi GN, Goodwin JS. Decline in the use of anthracyclines for breast cancer. *J Clin Oncol* 2012;30:2232-2239.

(124) Arneson TJ, Li S, Gilbertson DT, Bridges KR, Acquavella JF, Collins AJ. Impact of Centers for Medicare & Medicaid Services national coverage determination on erythropoiesis-stimulating agent and transfusion use in chemotherapy-treated cancer patients. *Pharmacoepidemiol Drug Saf* 2012;21:857-864.

(125) Warren JL, Harlan LC, Fahey A et al. Utility of the SEER-Medicare data to identify chemotherapy use. *Med Care* 2002;40:IV-61.

(126) Du XL, Key CR, Dickie L, Darling R, Geraci JM, Zhang D. External validation of medicare claims for breast cancer chemotherapy compared with medical chart reviews. *Med Care* 2006;44:124-131.

(127) Waikar SS, Wald R, Chertow GM et al. Validity of International Classification of Diseases, Ninth Revision, Clinical Modification Codes for Acute Renal Failure. *J Am Soc Nephrol* 2006;17:1688-1694.

(128) Hebert PL, Geiss LS, Tierney EF, Engelgau MM, Yawn BP, McBean AM. Identifying persons with diabetes using Medicare claims data. *Am J Med Qual* 1999;14:270-277.

(129) Winkelmayer WC, Schneeweiss S, Mogun H, Patrick AR, Avorn J, Solomon DH. Identification of individuals with CKD from Medicare claims data: a validation study. *Am J Kidney Dis* 2005;46:225-232.

(130) Kern EF, Maney M, Miller DR et al. Failure of ICD-9-CM codes to identify patients with comorbid chronic kidney disease in diabetes. *Health Serv Res* 2006;41:564-580.

(131) Cooper GS, Virnig B, Klabunde CN, Schussler N, Freeman J, Warren JL. Use of SEER-Medicare data for measuring cancer surgery. *Med Care* 2002;40:IV-8.

(132) Lu B. Propensity score matching with time-dependent covariates. *Biometrics* 2005;61:721-728.

(133) Parsons LS. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. Proceedings of the Twenty-Sixth Annual SAS Users Group International Conference. 2001; Available at: http://www2.sas.com/proceedings/sugi26/p214-26.pdf. Accessed April 4, 2013.

(134) Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. *The American Statistician* 1985;39:33-38.

(135) Austin PC, Mamdani MM. A comparison of propensity score methods: a case-study estimating the effectiveness of post-AMI statin use. *Stat Med* 2006;25:2084-2106.

(136) Austin PC. Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: a systematic review and suggestions for improvement. *J Thorac Cardiovasc Surg* 2007;134:1128-1135.

(137) Normand ST, Landrum MB, Guadagnoli E et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *J Clin Epidemiol* 2001;54:387-398.

(138) Lin D, Wei L. The robust inference for the Cox proportional hazards model. *J Am Stat Assoc* 1989;84:1074-1078.

(139) Fine J, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of American Statistical Association* 1999;94:496-509.

(140) National Comprehensive Cancer Network Clinical Practice Guidelines. Myeloid Growth Factors Version 1: 2011. *JNCCN* 2011;9:914-932.

(141) U.S. Renal Data System. USRDS 2012 Annual Data Report: Atlas of Chronic Kidney Disease & End-Stage Renal Disease in the United States, Volume 1, Chapter 2, 2012 ed. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2012;56. Figure 2.5.

(142) Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. 3rd Edition ed. Lippincott Williams & Wilkins, 2008.

(143) Bowles EJ, Wellman R, Feigelson HS et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. *J Natl Cancer Inst* 2012;104:1293-1305.

(144) Martens EP, Pestman WR, de BA, Belitser SV, Klungel OH. Instrumental variables: application and limitations. *Epidemiology* 2006;17:260-267.

Appendices

Appendix A. Administrative Codes Used to Identify Cancer Treatment from Medicare Claims

Table A.1 Administrative Codes Used to Identify Receipt of Any Chemotherapy

Type of codes	Codes
ICD-9 procedure codes for administration	99.25
CPT codes for administration	96400-96549 excluding 96402
HCPCS codes for administration	C8953-C8955, G0355-G0362 excluding G0356, Q0083-Q0085
ICD-9 diagnosis code	V58.1, V66.2, V67.2
Revenue codes	0331; 0332; 0335
DRG codes	410, 492
HCPCS codes for chemo agents	A9523, A9534, A9542-A9545, C1081, C1083, C1166, C1178, C9017, C9110, C9117, C9118, C9120, C9414, C9415, C9417-C9427, C9429, C9431-C9433, C9437, C9440, G3001, J8510, J8520, J8521, J8530, J8560, J8600, J8610, J8700, J8999, J9000-J9999 (excluding J9217-J9219, J9202, J9225, J9395), S0087, S0108, S0178, S0179

Table A.2 HCPCS Codes Used to Identify Specific Agents Commonly used for Breast Cancer from Medicare Claims

Chemotherapeutic agent	HCPCS codes
5-FU	J9190
Doxorubicin	C9415; J9000; J9001
Epirubicin	J9178
Cyclophosphamide	C9420, C9421, J8530, J9070-J9097
Methotrexate	J8610, J9250, J9260
Paclitaxel	C9431, J9264, J9265
Docetaxel	J9170
Trastuzumab	J9355

Appendix B. ICD-9-CM Codes Used to Identify Specific Conditions

Table B.1 ICD-9-CM Codes Used to Identify Acute Kidney Injury

Codes	Description
ICD-9-CM Diagnosis Code	
584.5	Acute kidney injury with lesion of tubular necrosis
584.6	Acute kidney injury with lesion of cortical necrosis
584.7	Acute kidney injury with lesion of renal medullary necrosis
584.8	Acute kidney injury with other specified pathologic lesion
584.9	Acute kidney injury, unspecified
V45.1	Renal dialysis status
V56.0	Extracorporeal dialysis
V56.1	Fitting and adjustment of extracorporeal dialysis catheter
ICD-9-CM Procedure Code	
39.95	Hemodialysis
54.98	Peritoneal dialysis
CPT Code	
90935	Hemodialysis procedure with single physician evaluation
90937	Hemodialysis procedure requiring repeated evaluation(s) with or without substantial revision of dialysis prescription
90945	Dialysis procedure other than hemodialysis with single physician evaluation
90947	Procedure other than hemodialysis requiring repeated physician evaluations, with or without substantial revision of dialysis prescription
Revenue code	
0800	Inpatient renal dialysis, general classification
0801	Inpatient hemodialysis
0802	Inpatient peritoneal (Non-CAPD)
0803	Inpatient continuous ambulatory peritoneal dialysis (CAPD)
0804	Inpatient continuous cycling peritoneal dialysis (CCPD)
0809	Other inpatient dialysis

Table B.2 ICD-9-CM Diagnosis Codes Used to Identify Chronic Kidney Disease

Code	Description
016.0	Renal tuberculosis
095.4	Syphilis of kidney
189.0	Malignant neoplasm of kidney
189.9	Malignant neoplasm, urinary organ, site unspecified
223.0	Benign neoplasm of kidney
236.91	Neoplasm of uncertain behavior of kidney and ureter
250.4	Diabetes with renal manifestations
271.4	Renal glycosuria
274.1X	Gouty nephropathy
283.11	Hemolytic-uremic syndrome
403.X1	Hypertensive renal disease with renal failure
404.X2	Hypertensive heart and renal disease with renal failure
404.X3	Hypertensive heart and renal disease with CHF, renal failure
440.1	Atherosclerosis of renal artery
442.1	Other aneurysm of renal artery
447.3	Hyperplasia of renal artery
572.4	Hepatorenal syndrome
580	Acute glomerulonephritis
581	Nephrotic syndrome
582	Chronic glomerulonephritis
583	Nephritis & nephropathy, not specified as acute or chronic
584	Acute renal failure
585	Chronic renal failure
586	Renal failure, unspecified
587	Renal sclerosis
588	Disorders resulting from impaired renal function
591	Hydronephrosis
642.1	Hypertension secondary to renal disease, complicating pregnancy
646.2	Unspecified renal disease in pregnancy, without hypertension
753.12	Polycystic kidney, unspecified type
753.13	Polycystic kidney, autosomal dominant
753.14	Polycystic kidney, autosomal recessive
753.15	Renal dysplasia
753.16	Medullary cystic kidney
753.17	Medullary sponge kidney
753.19	Other specified cystic kidney disease
753.2X	Obstructive defects of renal pelvis and ureter
794.4	Abnormal renal function test

Table B.3 ICD-9-CM diagnosis codes used to identify comorbid conditions

Condition	ICD-9-CM Diagnosis Codes
Atherosclerotic Heart Disease (ASHD)	410-414; V45.18; V45.82
Cerebrovascular Accidents/Transient Ischemic Attacks (CVA/TIA)	430-438
Chronic Obstructive Pulmonary Disease (COPD)	491-494; 496; 510
Congestive Heart Failure (CHF)	398.91; 422; 425; 428; 402.x1; 404.x1; 404.x3; V42.1
Diabetes Mellitus (DM)	250; 357.2; 362.0x; 366.41
Cardiac dysrhythmia	426-427; V45.0; V53.3
Gastro-intestinal disease (GI)	456.0-456.2; 530.7; 531-534; 569.84; 569.85; 578
Liver disease	570; 571; 572.1; 572.4; 573.1-573.3; V42.7
Cardiac disease, other	420-421; 423-424; 429; 785.0-785.3; V42.2; V43.3
Peripheral Vascular Disease (PVD)	440-444; 447; 451-453; 557
Anemia	280-285
Hypertension	362.11; 401.x-405.x; 437.2

Table B.4 ICD-9-CM diagnosis codes used to identify cancer in situ, primary cancer, and metastatic cancer

Condition	ICD-9-CM Diagnosis Codes
Cancer in situ	
Digestive organs	230
Respiratory systems	231
Skin	232
Breast	2330
Genitourinary system	2331-2339
Other and unspecified sites	234
Primary cancer site	
Head and Neck	140-14999
Esophagus	150-15099
Stomach and Small Intestine	151-15299
Colon and Rectum	153-15489
Liver	155-15529
Gallbladder	156-15699
Pancreas	157-15799
Retroperitoneum and Peritoneum	158-15899
Spleen	159-15999
Lung	162-16399
Other Respiratory	160-16199, 164-16599
Bone	170-17099
Connective and Soft Tissue	171-17199
Melanoma	172-17299
Female Breast	174-17499
Male Breast	1750 or 1759
Sarcoma	176-17699
Gynecologic	179-18499
Prostate	185
Other Genitourinary	186-18999
Central Nervous System	190-19299
Endocrine	193-19499
Non-Hodgkins Lymphoma	200-20099; 202-20299
Hodgkins Lymphoma	201-20199
Multiple Myeloma	203-20380
Leukemia	204-20891
Ill Defined	195-19599; 199-19999
Metastasis sites	

Lymph nodes	196
Respiratory system	1970-1973
Digestive system	1974-1978
Urinary system	1980-1981
Skin	1982
Nervous system	1983-1984
Bone and bone marrow	1985
Ovary	1986
Adrenal Gland	1987
Other specified sites	1988

Table B.5 International Classification of Diseases, Ninth Revision, Clinical Modification Codes (ICD-9-CM) Procedure Codes and CPT Codes Used for Defining Surgery Type

Codes	Description
Mastectomy	
ICD-9 codes	
85.41	Unilateral simple mastectomy
85.42	Bilateral simple mastectomy
85.43	Unilateral extended simple mastectomy
85.44	Bilateral extended simple mastectomy
85.45	Unilateral radical mastectomy
85.46	Bilateral radical mastectomy
85.47	Unilateral extended radical mastectomy
85.48	Bilateral extended radical mastectomy
CPT codes	
19180, 19303	Mastectomy, simple, complete
19182, 19304	Mastectomy, subcutaneous
19200, 19305	Mastectomy, radical, including pectoral muscles, axillary lymph nodes
19220, 19306	Mastectomy, radical, including pectoral muscles, axillary and internal mammary lymph nodes (Urban type operation)
19240, 19307	Mastectomy, radical, including axillary lymph nodes, with or without pectoralis minor muscles, but excluding pectoralis major muscle
Breast Conserving Surgery	
ICD-9 codes	
85.21	Local excision of lesion of breast
85.22	Resection of quadrant of breast
85.23	Subtotal mastectomy
CPT codes	
19120	Local excision
19125	Excision of breast lesion identified by preoperative placement of radiological marker, open; signle lesion
19160, 19301	Mastectomy, partial (eg, lumpectomy, tylectomy, quadrantectomy, segmentectomy)
19162, 19302	Mastectomy, partial with axillary lymphadenectomy

Appendix C. Current Procedural Terminology Codes Used to Identify Assessment of Renal Function

Test	Codes
Blood test	
Serum Creatinine	80047-80050, 80053, 80054, 80069, and 82565
Urine test	
Urine albumin	82042, 82043, 82044, and 84156
ACR*	82042 and 82570, or 82043 and 82570 on the same claim

*ACR, urinary albumin to creatinine ratio.