THE CANCER BURDEN AND PATTERNS OF ERYTHROPOIESIS-STIMULATING AGENT USE AMONG END-STAGE RENAL DISEASE PATIENTS ON HEMODIALYSIS

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ABSTRACT

ANNE MOBLEY BUTLER: The cancer burden and patterns of erythropoiesis-stimulating agent use among end-stage renal disease patients on hemodialysis
(Under the direction of M. Alan Brookhart)

Patients with end-stage renal disease (ESRD) receiving dialysis have been reported to have increased risk of cancer. Yet, contemporary cancer burden estimates in this population are sparse, and estimates that account for the high competing risk of death in this population are non-existent. In addition, erythropoiesis-stimulating agents (ESAs) and blood transfusion are commonly used to treat anemia in both ESRD and cancer, however, anemia treatment patterns have not been described among ESRD patients undergoing hemodialysis with concurrent cancer, especially in the recent era of ESA-related safety concerns.

Using data from Medicare's ESRD program, we conducted a retrospective cohort study of hemodialysis patients to describe trends in overall and site-specific cancer incidence rates (1996-2009). We estimated the 5-year cumulative incidence of cancer since dialysis initiation, using competing risk methods. Among hemodialysis patients with incident cancer, we used multivariable generalized linear models to estimate temporal trends in ESA use, epoetin alfa (EPO) dose, transfusion use, and resulting hemoglobin levels (2000-2010).

We observed a constant rate of incident cancers for all sites combined, but identified increasing and decreasing rates for some common site-specific cancers. The 5-year cumulative incidence of any cancer was substantially lower in the analysis that did not censor deaths compared to the analysis that censored deaths (9.48% vs. 13.86%). Accounting for case-mix characteristics and the competing risk of death, the 5-year cumulative incidence of any cancer varied by demographic and clinical characteristics.

Among hemodialysis patients with incident cancer, ESA use was extremely high and constant whereas transfusion use became increasingly frequent. EPO dose and hemoglobin

values increased and then declined. Patients with hematological malignancies or patients who received chemotherapy had higher ESA use, EPO dose, and transfusion use as well as lower hemoglobin levels.

Our results suggest a high burden of cancer in the dialysis population, with varying patterns of cancer incidence across subgroups. Despite ESA-related safety concerns, ESA use remained extremely common and remarkably constant among hemodialysis patients with cancer between 2000 and 2010. Transfusions have increased in frequency. These results warrant additional research to examine the risk-benefit profile of ESA use in the dialysis population with cancer.

DEDICATION

To my family for their constant love and support. To my parents, Harry and Natalie, thank you for your lifelong encouragement and support, and for inspiring in me a love of learning. To my brother, Blake, thank you for keeping a fun perspective on life. To my husband extraordinaire, Andy, thank you for your endless encouragement, advice, and support.

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LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
APC	Annual percentage change
APPRISE	Assisting Providers and Cancer Patients with Risk Information for the Safe Use of ESAs
ASCO	American Society for Clinical Oncology
ASH	American Society for Hematology
AVF	Arteriovenous fistula
BEST	Breast Cancer Erythropoietin Survival Trial
CHOIR	Correction of Hemoglobin Outcomes in Renal Insufficiency
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMS	Centers for Medicare and Medicaid Services
CREATE	Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta
DAHANCA	Danish Head and Neck Cancer Group Study
EDB	Medicare Enrollment Database
eGFR	Estimates of glomerular filtration rate
ENHANCE	Erythropoietin in Head and Neck Cancer Study
ESA	Erythropoiesis-stimulating agent
ESRD	End-stage renal disease
EPO	Epoetin alfa
FDA	United States Food and Drug Administration
GFR	Glomerular filtration rate
HCPCS	Healthcare Common Procedure Coding System
HD	Hemodialysis
Hgb	Hemoglobin
HIFs	Hypoxia-inducible transcription factors

HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMO	Health maintenance organization
HPV	Human papillomavirus
ICD-9-CM	International Classification of Diseases, 9th revision, Clinical Modification
IP	Inverse probability
IQR	Interquartile range
KDIGO	Kidney Disease | Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHANES	National Health and Nutrition Examination Survey
NHL	Non-Hodgkin lymphoma
OPTN	Organ Procurement and Transplantation Network
PD	Peritoneal dialysis
pmp	Per million population
QoL	Quality of life
RBC	Red blood cell
REBUS	Renal Beneficiary and Utilization System
RRT	Renal replacement therapy
SEER	Surveillance, Epidemiology, and End Results
SIMS	Standard Information Management System
SIRs	Standardized incidence ratios
SMR	Standardized mortality ratio
Th	Helper T-cell
TSAT	Transferrin saturation

URR	Urea reduction ratio
USRDS	United States Renal Data System
VA	United States Department of Veterans Affairs Healthcare System

CHAPTER I. STATEMENT OF SPECIFIC AIMS

Patients with end-stage renal disease (ESRD) suffer almost universally from anemia because they produce insufficient amounts of endogenous erythropoietin to maintain hematocrit levels. Anemia is also a common complication in cancer patients undergoing chemotherapy. In the last two decades, erythropoiesis-stimulating agents (ESA) therapy has been widely used for anemia management in ESRD patients and cancer patients to reduce the need for red blood cell (RBC) transfusions and to alleviate anemia-related symptoms. In the last two decades, ESAs have had the highest sales worldwide of any biologic medication (1). Of $2.8 billion spent in 2010 on injectables for U.S. dialysis patients, ESAs accounted for 67%, or $1.9 billion (2). Beginning in 2003, eight randomized clinical trials in cancer patients reported increased risk of tumor progression and/or death among cancer patients treated with ESA therapy (3-11). Simultaneously, reports were published of increased risk of death and serious cardiovascular events in patients with chronic kidney disease (CKD). Over the next five years, subsequent United States Food and Drug Administration (FDA) black-box warnings, reimbursement changes, and revised anemia management guidelines were issued. Yet, it still remains unclear whether ESAs affect tumor progression or survival in cancer patients. The most recent meta-analysis of 60 experimental studies of more than 15,000 cancer patients failed to demonstrate any significant effect of ESAs on survival or disease progression (12). Current management of anemia in dialysis patients with cancer has become challenging due to the absence of formal guidelines for providers regarding appropriate usage of ESA therapy in this population. The United States recommendation for CKD patients on dialysis receiving ESAs is to initiate treatment when the Hgb level is less than 10 g/dL and to individualize dosing and use the lowest dose of ESA sufficient to reduce the need for RBC transfusions (13), whereas the ESA indication for cancer patients is for treatment of anemia due to concomitant myelosuppressive chemotherapy (14). While the FDA limits ESA treatment among cancer patients to those receiving chemotherapy for palliative intent, the short expected lifespan of the average patient on dialysis (2) is likely associated with major variability in utilization practices in this population.

Knowledge is limited about the cancer incidence in the dialysis population as well as patterns of ESA utilization in dialysis patients with cancer. Despite reports of increased risk of many cancers in the

dialysis population (15-17), the cancer burden has not been sufficiently characterized in ESRD patients on dialysis. Existing estimates of cancer incidence in the ESRD population are outdated, primarily focused on overall cancer or limited cancer types, determined from small, selective groups of dialysis patients, based on data (e.g., cancer diagnoses and cause of death) ascertained from sources of questionable reliability, and failed to account for competing risks of death (15, 16, 18-39). Competing risk methods are necessary to avoid the potentially large bias due to a large proportion of patients who experience the competing risk of death prior to receiving a cancer diagnosis (i.e., the event of interest) (40-43). In addition, the impact of recent safety reports, FDA black-box warnings, reimbursement changes, and revised anemia management guidelines on ESA utilization patterns in dialysis patients with cancer is unknown. ESA therapy use declined among CKD patients (44) and cancer patients (45, 46) after these events. However, information is limited about patterns of ESA therapy utilization in dialysis patients with cancer.

The objectives of this dissertation are to describe the cancer burden among ESRD patients on hemodialysis and to examine patterns of ESA utilization among ESRD patients on hemodialysis with cancer. The analyses utilized data from the USRDS, a national registry including all patients in Medicare's ESRD program with detailed demographic and clinical information at dialysis therapy initiation, as well as medication usage, diagnoses, and procedures from hospitalizations and outpatient visits after hemodialysis therapy initiation. The study population included almost half a million adults with ESRD who received dialysis between 1995 and 2010.

Aim 1. To characterize the overall and site-specific cancer burden among ESRD patients without cancer at hemodialysis initiation, across subgroups (e.g., by age, gender, race, ethnicity, primary cause of renal disease, kidney transplant evaluation, and era of dialysis initiation).

Aim 1a. To estimate the cumulative incidence of cancer, treating death as a censoring event.

Aim 1b. To estimate the cumulative incidence of cancer, treating death as a competing event.

Aim 1c. To describe trends in cancer incidence using annual incidence rates adjusted for case-mix characteristics.

Hypothesis – Specific Aim 1. The cumulative incidence of cancer will be lower after accounting for the competing risk of death. The cumulative incidence and incidence rates will vary across subgroups, with higher cancer incidence among patients with older age, white race, kidney transplant evaluation, and longer time since dialysis initiation.

Rationale – Specific Aim 1. Prior studies have demonstrated the increased risk of cancer in the dialysis population compared to the general population, under the hypothetical assumption of no competing risk of death. However, death is a common event in the dialysis population, and it precludes a cancer diagnosis. Competing risk methods are necessary to avoid the potentially large bias due to a large proportion of patients who experience the competing risk of death prior to receiving a cancer diagnosis (i.e., the event of interest). Estimation of the cumulative incidence of cancer, accounting for the competing risk of death, will quantify the real-world probability of a dialysis patient to develop cancer. The descriptive analysis of cancer incidence rates will vary by patient characteristics.

Aim 2. To examine temporal trends in anemia therapy (2000-2010) in ESRD patients diagnosed with cancer after hemodialysis initiation, for a time period before, during, and after negative safety reports, product labeling changes, black box advisories, revised anemia management guidelines, and reimbursement changes.

Aim 2a. To describe temporal trends in ESA therapy use among dialysis patients with cancer, by cancer site, receipt of chemotherapy, and other demographic and clinical characteristics relevant to the dialysis population.

Aim 2b. To describe temporal trends in mean epoetin alfa (EPO) therapy dose among dialysis patients with cancer, by cancer site, receipt of chemotherapy, and other demographic and clinical characteristics relevant to the dialysis population.

Aim 2c. To describe temporal trends in RBC transfusions among dialysis patients with cancer, by cancer site, receipt of ESA therapy, receipt of chemotherapy, and other demographic and clinical characteristics relevant to the dialysis population.

Aim 2d. To describe temporal trends in mean Hgb levels among dialysis patients with cancer, by cancer site, receipt of ESA therapy, receipt of chemotherapy, and other demographic and clinical characteristics relevant to the dialysis population.

Hypothesis – Specific Aim 2. The emergence of safety concerns and the subsequent changes in product labeling, reimbursement and clinical practice guidelines that occurred between 2003 and 2008 will influence health care provider practices for dialysis patients with cancer. Specifically, post-FDA-mandated labeling changes in dialysis patients with cancer will be characterized by a lower proportion of ESA therapy utilization, lower mean EPO dose, higher proportion of RBC transfusion, and lower mean Hgb values. Results will vary by cancer type and treatment, where patients with hematological malignancies and patients who undergo chemotherapy will be more likely to use ESA therapy, receive a higher EPO dose, receive RBC transfusions, and have lower Hgb values.

Rationale – Specific Aim 2. Anemia management patterns have been reported to have changed markedly in the years before and after the 2007 FDA black-box warning in the dialysis population and the cancer population. Anemia management patterns have not been described in the dialysis population with cancer. Recent reports about the dialysis population and the cancer population suggest declines in ESA therapy use, ESA dose, RBC transfusions, and hemoglobin levels. Changes in product labeling, reimbursement and clinical practice guidelines will likely have a similar but lesser impact on anemia management practices and Hgb levels in the ESRD population with cancer because of higher severity of illness.

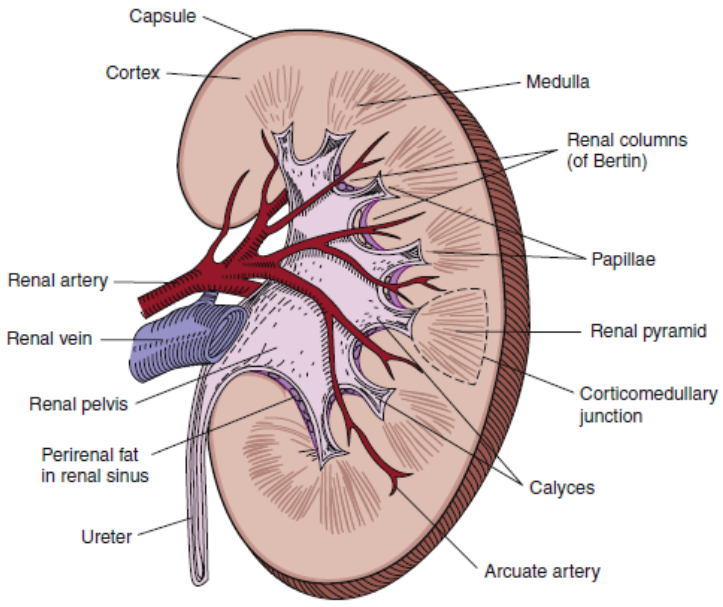
CHAPTER II. REVIEW OF LITERATURE

A. Overview of Chronic Kidney Disease (CKD) and End-stage Renal Disease (ESRD)

1. Anatomy of the kidney

The kidneys are a pair of small, bean-shaped organs located on each side of the vertebral column. Each kidney is approximately 11 to 12 cm long and weighs 115 to 170 g (47). The primary functions of the kidneys include filtering wastes from the blood, balancing the body's fluid content, and regulating blood pressure and RBC production. Healthy kidneys filter approximately 180 liters of largely protein-free plasma daily (48). A rich blood supply is delivered by the paired renal arteries, travels through the microvasculature, and drains into the paired renal veins. As the kidney filters blood it subsequently produces urine, a fluid containing toxic substances and waste products. Urine collects in the renal pelvis, exits the kidney through ureters, and flows to the urinary bladder (Figure 1).

Figure 1. Diagram of the cut surface of a bisected kidney, depicting important anatomic structures



Adapted from Nielsen et al. (2012) (47)

Nephrons are the basic functional unit of the kidney. Each human kidney contains approximately one million nephrons which are established during prenatal development. After birth, new nephrons cannot be developed and lost nephrons cannot be replaced. The essential components of the nephron include a) the renal corpuscle, comprised of the glomerulus and Bowman's capsule, and b) the renal tubule, comprised of the proximal tubule (i.e., convoluted part and straight part), the intermediate tubule (i.e., descending and ascending thin limbs of Henle's loop) and the distal tubule (i.e., thick ascending limb of Henle's loop and convoluted part). The glomeruli, proximal tubules and distal tubules are situated in the cortex, whereas the loops of Henle and the collecting ducts extend down through the medulla. Nephrons have either short or long loops of Henle, where the length of the loop of Henle is generally related to the position of the parent renal corpuscle in the cortex. Cortical nephrons have short loops that turn back in the outer medulla or even in the cortex. Juxtamedullary nephrons have long loops that turn back at successive levels of the inner medulla. Cortical nephrons and juxtamedullary nephrons represent approximately 85% and 15%, respectively, of the nephrons in the kidney.

2. Physiology of the kidney

The kidneys filter blood through three main processes: a) glomerular filtration filters blood to produce an ultrafiltrate of plasma; b) tubular secretion removes substances from the blood and secretes them into the filtrate; and c) tubular reabsorption returns substances to the blood.

Glomerular filtration. The first fundamental step in urine formation is glomerular filtration which is the separation of blood into two components: filtered blood and an ultrafiltrate of plasma. As blood flows from the afferent arteriole into the glomerulus under high pressure, the glomerular capillary walls function as a filter that allows the passage of small molecules into the encircling glomerular capsule (i.e., Bowman's capsule) while molecules the size of albumin or larger remain in the blood. The filtered fluid is called ultrafiltrate and includes water, small proteins, salts (Na^+, Cl^-, K^+, H^+), glucose, nitrogenous waste products such as urea and other metabolic waste products and drug metabolites. Filtration is determined principally by the molecular size and shape of the solute and, to a much lesser extent, by its charge (48). The remaining

blood exits the glomerulus through the efferent arteriole and the ultrafiltrate exits the glomerular capsule into the proximal convoluted tubule.

Tubular secretion. The second fundamental step in urine formation is tubular secretion which is the process that removes substances from the blood and secretes them into the filtrate. Secreted substances include H^+, K^+, $NH4^+$ (i.e., ammonium ion), creatinine, urea, and various other substances. Secretion occurs in portions of the proximal convoluted tubule, the distal convoluted tubule and the collecting duct.

Tubular reabsorption. The third fundamental step in urine formation is tubular reabsorption which increases the concentration of the glomerular filtrate by reabsorbing the glomerular filtrate back into the blood. As the glomerular filtrate flows through the proximal tubule, nearly all of the filtered water and solutes (Na^+, Cl^-, K^+, $Ca2^+$, $Mg2^+$, $HCO3^+$, glucose, amino acids, retinol-binding protein, α- and β-microglobulins, calcium, phosphate, urea) are reabsorbed and transferred back into the peritubular capillaries that surround the tubule. The proximal tubule is conducive to reabsorption because of the large absorptive area of epithelial cells with microvilli on their apical surface; the basolateral membrane with folds that similarly enhance surface area; and the relatively leaky tight junctions between adjacent cells. The amounts of water and ions that are reabsorbed into the blood are regulated so that blood volume, pressure and ion concentration are maintained within required levels for homeostasis. Solute transport across cell membranes occurs via passive or active mechanisms. Passive transport is simple diffusion that occurs down an electrochemical gradient and does not require a direct energy source. Active transport occurs when an ion is moved directly against an electrochemical gradient and requires a source of energy.

3. Measures of renal function

The glomerular filtration rate (GFR) is the best overall index of renal function in health and disease, and provides an excellent measure of the filtering capacity of the kidneys. The total kidney GFR is equal to the sum of the filtration rates in each of the functioning nephrons. Thus, the total GFR can be used as an index of functioning renal mass (49). The definition and staging of CKD depends, in part, on

the assessment of GFR. A low or decreasing GFR is a hallmark of CKD. As GFR declines, patient complications are manifested first by high blood pressure and abnormalities in laboratory tests and then by symptoms and abnormalities in physical examination. In general, the severity of complications worsens as levels of GFR declines. The most significant complications are high blood pressure, anemia, malnutrition, bone disease, neuropathy, and decreased overall functioning and well-being. At very low levels of GFR, these complications are common and collectively known as “uremia” or the “uremic syndrome (50).”

Direct measure of GFR is an impracticality for clinical practice, therefore kidney function is routinely assessed using estimates of GFR (eGFR). Prediction equations such as the Modification of Diet in Renal Disease (MDRD) estimating equation (51), the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (52) and the Cockcroft-Gault equation (53) commonly used to estimate GFR in adults factor in the serum creatinine concentration as well as age, gender and race. The most common method used to estimate renal function is the simplified four-variable Modification of Diet in Renal Disease (MDRD) equation, where GFR (mL/min/1.73 m^2) = 186 * [serum creatinine level]$^{-1.154}$ * [age]$^{-0.203}$ * [0.742 if patient is female] * [1.212 if patient is black]. This equation was derived using data from 1,628 patients enrolled in the baseline period of the MDRD study, in whom GFR was measured directly with the use of urinary clearance of injected iodine-125-iothalamate (51). The more recently developed CKD-EPI equation performs better than the MDRD equation, especially at higher GFR, with less bias, improved precision, and greater accuracy. This equation was developed using an equation development data set of 8,254 participants from 10 studies, a validation data set of 3,896 participants from 16 studies and prevalence estimates based on 16,032 National Health and Nutrition Examination Survey (NHANES) participants. The CKD-EPI equation is expressed as GFR (mL/min/1.73 m^2) = 141 * min[serum creatinine level/κ, 1]$^{\alpha}$ * max[serum creatinine level/κ, 1]$^{-1.209}$ * [0.993]^{age} * [1.018 if patient is female] * [1.159 if patient is black], where κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males (52).

4. Definitions of CKD and ESRD

CKD is defined as the presence for three or more months of impaired renal function across a continuum of renal injury from isolated anatomic, radiographic, biomarker, and urinary abnormalities to

decreased GFR, irrespective of the primary cause of the renal injury (50). The National Kidney Foundation classification defines five stages of CKD by increasing degree of impaired kidney function, as measured by GFR (Table 1) (50). CKD is a nonspecific diagnosis that describes the presence and degree of structural and functional abnormalities of the kidney, thus the complete clinical diagnosis should include both the stage and primary cause of kidney disease (54). The abnormalities used to define CKD are 1) proteinuria (i.e., increased urinary excretion of albumin, other specific proteins, or total protein); 2) an abnormal urinary sediment as evidenced by the presence of RBCs, RBC casts, white blood cells, white blood cell casts, tubular cells, cellular casts, granular casts, oval fat bodies, fatty casts, or free fat; and 3) abnormal findings on imaging tests, including ultrasound, intravenous pyelogram, computer tomography, magnetic resonance imaging, and nuclear scans (54). The specific types of protein, such as albumin or low molecular weight globulins, that are excreted through urine depend on the type of kidney disease. For example, albuminuria (i.e., increased excretion of albumin) is a sensitive marker for CKD due to diabetes, glomerular disease, and hypertension. Increased excretion of low molecular weight globulins is a sensitive marker for some types of tubulointerstitial disease (50).

Table 1. Stages of chronic kidney disease (age ≥20 years)

Stage	Description	GFR mL/min/1.73 m^2
1	Kidney damage with normal or increased GFR*	≥ 90
2	Kidney damage with mild decreased GFR*	60-89
3	Moderate decreased GFR	30-59
4	Severe decreased GFR	15-29
5	Kidney failure/ESRD	< 15

Adapted from KDOQI clinical practice guidelines for chronic kidney disease (2002) (50). An estimated GFR above 60 mL/min/1.73 m^2, in the absence of other anatomic, radiographic, or urinary abnormalities is not classified as CKD.

End-stage renal disease (ESRD) is the final stage of CKD that occurs when renal function is insufficient to sustain life and renal replacement therapy (RRT), such as hemodialysis, peritoneal dialysis, or renal transplantation, is necessary for survival. ESRD is a syndrome characterized by hypertension, anemia, renal/metabolic bone disease, nutritional impairment, neuropathy, impaired quality of life, and reduced life expectancy (55).

5. Pathogenesis of ESRD

The progressive nature of renal disease has been characterized as a final *common pathway* of mechanisms, independent of the primary cause of nephropathy (56). Thus, CKD is a generic term for all of the clinical conditions with differing pathogenesis and widely varying pathologic characteristics that lead to the same pattern of chemical and functional derangements in the kidney which can eventually lead to renal failure (57).

The central tenets of the common pathway theory state that CKD progression occurs through focal nephron loss and that the adaptive responses of surviving nephrons, although initially serving to increase single-nephron GFR and offset the overall loss in clearance, ultimately prove detrimental to the kidney. As the number of functional nephrons decreases, each residual nephron must perform a greater fraction of total renal function. In order to maintain balance of any specific solute and avoid retention of body fluid, the quantity excreted by each nephron must increase as the total population of functioning nephrons decreases. As kidney damage progresses, the remaining nephrons compensate for the reduction in nephron mass by increasing the single nephron filtration rate, and this hyperfiltration promotes further kidney injury. Raised glomerular hydraulic pressure (glomerular hypertension) appears to be the major effector of glomerular injury following renal mass reduction. Over time, glomerulosclerosis and tubular atrophy further reduce nephron number, fueling a self-perpetuating cycle of nephron destruction culminating in uremia (56, 57).

After GFR falls to a critical threshold (i.e., approximately less than 50% of normal renal function), a progressive further loss of function ensues which leads to proteinuria, systemic hypertension, glomerulosclerosis, and eventual renal failure. This phenomenon has been observed in rats after partial ablation of renal mass as well as humans with diverse renal diseases, including individuals born with greatly reduced nephron number (i.e., congenital oligomeganephronia). In rats, a maximal increase of approximately 50% of GFR of a single kidney was reported at 8 days after uninephrectomy and a 300% increase in GFR of the remnant kidney was observed at 16 days after 5/6 nephrectomy (58). In humans, the effects of nephron loss on the physiology of the remnant kidney have been studied mainly in healthy individuals undergoing donor nephrectomy for kidney transplantation. A meta-analysis of data from 48

studies that included 2,988 living human kidney donors estimated that single-kidney GFR (and therefore also the average single-nephron GFR) increased by 30% to 40% after uninephrectomy (59, 60).

6. Risk factors for progression to ESRD

Risk factors for CKD can be separated into susceptibility, initiation, and progression factors. Susceptibility factors predispose to CKD, initiation factors trigger kidney damage, and progression factors contribute to progression of kidney damage after CKD has developed. This section focuses on progression to ESRD. Briefly, kidney function progressively declines in most patients with CKD after sufficient damage has occurred to lower the GFR, regardless of the cause of the initial renal injury. While the rate of GFR decline is often relatively constant over time in an individual patient, the rate of GFR decline is highly variable among patients, ranging from slowly progressive over decades to rapidly progressive over months. The high variability in the rate of progression of CKD between individuals suggests that risk factors exist that may influence the course of the renal disease. The major risk factors for progression to ESRD include age, race/ethnicity, diabetes, hypertension, glomerulonephritis, elevated serum creatinine, obesity, smoking, and use of nonsteroidal anti-inflammatory drugs (61-63).

7. Treatment modalities: hemodialysis, peritoneal dialysis, kidney transplantation

RRT options for ESRD patients include hemodialysis, peritoneal dialysis and renal transplantation. Renal transplantation is the preferred method for treatment because it is associated with longer survival, less hospitalizations, better quality of life, and lower costs compared with dialysis (2, 64). Preemptive transplantation, which is transplantation performed before dialysis is ever initiated, is associated with better outcomes than transplantation following dialysis (65). Change in modality is much more common for peritoneal dialysis to hemodialysis than from hemodialysis to peritoneal dialysis, and that change in treatment from peritoneal dialysis to hemodialysis is associated with an increased risk of hospitalization and mortality (66). The optimal time for initiation of RRT varies by modality, clinical characteristics and sociodemographic characteristics. Patients who receive a preemptive transplant or initiate peritoneal dialysis begin RRT therapy at higher mean levels of GFR than patients who initiate

hemodialysis. Dialysis is initiated at higher mean levels of GFR among patients who are older, or who have diabetes, cardiovascular disease, or other comorbid conditions (2, 50). A detailed description of all RRT modalities is presented below.

Hemodialysis. The purpose of hemodialysis is to deliver blood reliably from the patient to the dialyzer, to enable an efficient removal of uremic toxins and fluid, and to deliver the cleared blood back to the patient. Vascular access is a necessary step prior to dialysis. The main components of the dialysis system are the extracorporeal blood circuit, the dialyzer, the dialysis machine, and the water purification system. The dialysis machine delivers dialysis fluid with the intended flow rate, temperature, and chemical composition. The dialysis machine has monitoring and safety systems for air, blood, conductivity, and pressure; blood and dialysate pumps; a heating system; a dialysate mixing and degassing unit; and an ultrafiltrate balancing system. The role of the water purification system is to produce water for dialysis that complies with set chemical and microbiologic standards (67). Thus, hemodialysis replaces the work of the damaged kidneys by using an artificial kidney machine to filter blood. Hemodialysis is conventionally delivered in three treatment sessions per week, except for occasional patients with substantial residual renal function that opt for two treatment sessions per week. Typical treatment lengths are 3 to 4 hours per session (67). Hemodialysis is almost always performed in dialysis facilities and rarely performed at home. Sixty percent of dialysis patients are treated in units owned by Fresenius or DaVita, and the remainder are treated in units owned by Dialysis Clinic, Inc., other small dialysis organizations, or hospital-based facilities (2).

Peritoneal dialysis. The purpose of peritoneal dialysis is to provide a continuous mode of removal of small solutes and excess body water, thus maintaining relatively stable blood chemistry and body hydration status. The peritoneal cavity, which is the largest serosal space in the body, is used as a container for 2 to 2.5 liters of sterile, usually glucose-containing dialysis fluid. The peritoneal membrane acts as an endogenous dialyzing membrane through which waste products diffuse to the dialysate and excess body fluid is removed by osmosis. Ultrafiltration is induced in the dialysis fluid using glucose or another osmotic agent. The dialysis fluid is provided in plastic bags and is exchanged four or five times daily through a permanent peritoneal indwelling catheter. A catheter is necessary to provide obstruction-free access to the peritoneum and can be inserted surgically at the patient's bedside by an experienced nephrologist or

a surgeon or through a laparoscopic insertion (68). Peritoneal dialysis is a home-based therapy, and most patients are trained to do the bag exchanges themselves. Peritoneal dialysis is usually provided 24 hours a day and 7 days a week in the form of continuous ambulatory peritoneal dialysis (69).

Renal transplant. Transplantation is performed to replace the damaged kidneys with a functional kidney. Only one donated kidney is necessary to resume renal function. In preparation for transplantation, patients undergo a comprehensive evaluation of medical, surgical, and psychosocial histories (70-72). The availability of more potent immunosuppression and improvements in human leukocyte antigen (HLA) typing and crossmatching have made it feasible for immunologically high-risk patients to be considered candidates for transplantation (73). Three sources of kidneys for transplantation in order of most to least frequent are: donation before cardiac death donors, donation after cardiac death cadaveric donors, and live donors. Preservation of deceased donor organs is crucial to allow time for matching, sharing of organs, and preparation of the recipient. Organs are preserved by cold storage (kept in crushed ice after flushing with preservation solution) or by machine-driven pulsatile perfusion (74). The renal transplantation procedure involves general anesthesia before surgery. The kidney is placed into the iliac fossa. The external iliac artery and vein are mobilized. Surrounding lymphatic vessels are ligated and divided. End-to-side anastomoses are performed between the renal vein and the external iliac vein, followed by the renal artery and the external iliac artery. The ureter is implanted into the bladder (74, 75). Blood is then able to flow through the transplanted kidney, and the kidney should begin to filter and remove wastes and to produce urine. Kidney transplant surgery takes about three hours. After transplant, immunosuppressive medications are administered to prevent organ rejection (73). Major postoperative complications are rare. Surveillance of laboratory testing in the kidney transplant recipient is a routine and critical part of post-transplant management because early detection and treatment of graft dysfunction is crucial for preservation of allograft function.

8. Clinical and preventive care of ESRD patients

Given the risks and associated complications of infections in ESRD patients on dialysis, strategies to effectively improve overall care and prevent complications are of paramount importance.

Although the majority of national guidelines emphasize the importance of timely preparation for dialysis and clinical management of dialysis recipients, several measures fall far short of recommended guidelines. A number of clinical indicators and preventive care measures are discussed below, including early referral to a nephrologist, vascular access, dialysis adequacy, diabetic management, and vaccinations. Anemia management is summarized later in the chapter.

Early referral to a nephrologist. Adequate preparation for initiation of dialysis is important for patients with progressive CKD approaching renal failure. The Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for CKD recommend that CKD patients with GFR less than 30 mL/min/1.73 m^2 should be referred to a nephrologist (50) as patients referred earlier to nephrology services have reduced mortality, hospitalization and vascular access infections (2, 76, 77). Improved prognosis among patients with early referral appears to be independent of differences in traditional cardiovascular risk factors and instead related to careful management during the transition to ESRD. Specific explanations include informed selection of RRT, placement and maturation of vascular access, workup for kidney transplantation, counseling for coping with the psychosocial effects of starting RRT, and arrangement of family and work commitments (77, 78). Effective preparation for RRT requires input from multiple staff disciplines (e.g., medical, nursing, pharmacy, dietetics, psychology and social work) and is best delivered in a multidisciplinary clinic (78). In 2010, 25.4% of ESRD patients in the United States had seen a nephrologist for at least 12 months prior to RRT initiation (2).

Vascular access. Functional vascular access is necessary for hemodialysis. Certain types of vascular access are associated with substantially higher risks of infectious morbidity and mortality. Several types of vascular access used in hemodialysis, listed in order of increasing risk of infection, are as follows: arteriovenous fistulas (AVFs) created from the patient's own blood vessels; arteriovenous grafts constructed from synthetic materials; tunneled central venous catheters; and nontunneled central venous catheters (79, 80). Compared with AVFs, dialysis catheters are associated with a nearly two-fold increased risk for bacteremia or sepsis (81) and a more than two-fold increased risk for infection-related mortality (82). Guidelines from the KDOQI Clinical Practice Guidelines for Vascular Access (83) and the

Fistula First initiative (84) recommend that catheter use be reduced and that more patients use an AVF. Despite this consensus, AVF utilization has historically been very low. In 2010, only 36% of incident hemodialysis patients in the United States had an AVF access either in use or maturing at the first outpatient dialysis treatment (2).

Dialysis adequacy. Patients with renal failure require dialysis to remove uremic toxins from the blood because their damaged kidneys can no longer metabolize and secrete these toxins into the urine. Urea is only mildly toxic, but a high urea level indicates simultaneous retention of many other waste products that are more harmful and not as easily measured. Dialysis adequacy refers to the delivery of a dialysis dose that is sufficient to remove waste products such as urea from the blood and to ultimately promote an optimal long-term outcome (85). Poor dialysis adequacy has been associated with morbidity in hemodialysis patients at dialysis doses well below the current standard (86), however, the current standard seems appropriate (79, 87). The KDOQI Clinical Practice Guidelines for Vascular Access recommend that dialysis adequacy be assessed by monthly measurement of the delivered dose of dialysis (79). The delivered dose of dialysis is assessed by the removal of urea and expressed either by the urea reduction ratio (URR) or by the treatment index *Kt/V*. URR refers to the treatment-related reduction of serum urea concentration and is computed as follows: URR (%) = $(1 - C_t/C_0) \times 100\%$ where C_t is post-dialysis and C_0 is predialysis serum urea concentration. URR correlates well with dialysis outcome and is an accepted method for assessment of dialysis adequacy (85). A minimum URR of 65% to 70% is recommended for adequate hemodialysis (79). Alternatively, the treatment index *Kt/V* is the most widely used parameter to assess dialysis dose. *Kt/V* is a dimensionless number representing urea volume cleared (*K* x *t*, in liters) divided by urea volume of distribution (*V*, in liters), where *K* is the dialyzer blood water urea clearance (liters per hour), *t* is dialysis session length (hours), and *V* is the distribution volume of urea (liters), which equates closely to total body water (85). A minimum *Kt/V* of 1.2 and 1.7 is recommended for adequate hemodialysis and peritoneal dialysis, respectively (79). A patient's URR or *Kt/V* can be increased either by increasing time on dialysis or increasing blood flow through the dialyzer. In 2010, 94.0% of hemodialysis patients achieved URR greater than or equal to 65% and 87.1% of peritoneal dialysis patients achieved a minimum *Kt/V* of 1.7 (2).

Diabetic management. Diabetes is the most common cause of ESRD in the United States (2, 88). Among ESRD patients, diabetes is a strong risk factor for infections, cardiovascular disease, hospitalizations and mortality (2, 82). Glycemic control can be achieved with insulin or oral hypoglycemic agents, however, ESRD patients face therapeutic challenges such as prolongation of insulin half-life and accumulation of oral hypoglycemic agents that make self-monitoring of blood glucose concentration imperative (89). Additional therapeutic challenges in this population include hypertension, hypervolemia, malnutrition and bacterial infections (90). Microvascular (e.g., retinopathy and polyneuropathy), macrovascular (e.g., coronary heart disease, left ventricular hypertrophy, congestive heart failure, stroke and periperal artery occlusive disease) and mixed (e.g., diabetic foot) complications are common, thus patients should be monitored at regular intervals for timely detection (90). Comprehensive diabetic monitoring includes at least four glycosylated Hgb (A1c) tests, two fasting lipid profile tests, and one eye examination yearly. Although the rate of comprehensive monitoring among ESRD patients with diabetes has been increasing over time, between 2009-2010 only 17.2% of prevalent diabetic ESRD patients in the United States received all three types of recommended preventive care (2).

Vaccinations. Viral infections are a common cause of morbidity and mortality in ESRD patients, therefore the Centers for Disease Control and Prevention recommends that dialysis patients receive regular influenza, pneumococcal and hepatitis vaccinations. Although dialysis patients have lower response rates to vaccination compared with the general population, immunogenicity studies report development of protective antibody levels for the majority of influenza, pneumococcal and hepatitis B strains (91-94). Vaccine administration to dialysis patients has been reported to be a cost-effective approach for prevention of infections (95-97), however, recent reports of limited vaccine effectiveness raise concerns about vaccination policies in the ESRD population (98, 99). To date vaccination remains an underutilized prevention strategy in the ESRD population, with rates of vaccination far below the *Healthy People 2020* target of 90%. In 2009, rates of vaccinations in prevalent ESRD patients receiving hemodialysis were as follows: influenza (69%), pneumococcal pneumonia (30%), hepatitis B (28%). Rates should be interpreted with caution, as patients may be vaccinated through non-Medicare programs (2).

B. Epidemiology of ESRD in the United States

1. Incidence and prevalence of ESRD

More than 114,000 new ESRD cases initiated RRT in 2010, for an adjusted ESRD incidence rate of 348 per million population. The rate of incident ESRD cases per million population has been relatively stable since 2000, and rose just 1.1% in 2009, to 355 cases per million population (adjusted for age, gender and race). The prevalence of ESRD has been steadily increasing. Nearly ten times more patients in the United States were treated for ESRD in 2009 compared to 1980. Since 2000, the adjusted rate of prevalent ESRD has increased nearly 23%. The annual rate of increase has remained between 1.9% and 2.4% since 2003. Of more than 593,000 prevalent ESRD cases receiving RRT at the end of 2010, the distribution of treatment modalities were as follows: hemodialysis, 64.7%; renal transplantation, 30.2%; and peritoneal dialysis 5.0%. A total of 87,932 were on the renal transplant waiting list, which has a median wait time of 2.6 years (2).

The incidence of ESRD varies considerably across patient subgroups (Table 2). ESRD incidence increases with age and is more common among men than women. In 2010, the incidence rate of ESRD was 3.4 times higher in blacks and 1.7 times higher in Native Americans compared to whites. Compared to the non-Hispanic population, the Hispanic population had an incidence rate 1.5 times higher. Similarly, the ESRD prevalence in 2010 was higher among minority groups: blacks, 5234 per million population (pmp); Hispanics, 2602 pmp; Native Americans, 2563 pmp; Asians, 2098 pmp; and whites, 1309 pmp. Rates of ESRD vary substantially by geography. The highest adjusted rates occur in the Ohio Valley, portions of Texas and California, and the southwestern states.

Table 2. Incident and prevalent counts and adjusted rates of ESRD by age, gender, race and ethnicity, U.S., 2010*

	Incidence		Prevalence	
	Number of patients	Rate per million**	Number of patients	Rate per million**
Age				
20-44	13,404	127	98,008	937
45-64	43,663	579	261,445	3,395
65-74	27,029	1,365	119,751	6,062
75+	28,640	1,771	93,202	5,862
Gender				
Male	64,905	440	328,529	2,166
Female	49,127	275	251,226	1,423
Race				
White	75,514	275	353,849	1,309
Black	31,686	923	186,482	5,234
Native American	1,389	465	7,958	2,563
Asian	5,443	387	31,466	2,098
Ethnicity				
Hispanic	15,273	501	85,062	2,602
Non-Hispanic	98,759	337	494,693	1,714

*These data exclude patients with missing demographic information.
**Adjusted for age, gender, race and ethnicity, as appropriate.

In the United States, the three most common primary diagnoses for ESRD are diabetes, hypertension and glomerulonephritis (Table 3). Since 2000, the rate of incident ESRD caused by diabetes has remained quite stable (with the exception of an increase in 2006), the rate of incident ESRD due to hypertension has increased 9%, and the rate of incident ESRD due to glomerulonephritis has decreased 23%. In 2010, the primary diagnoses of diabetes and hypertension were associated with 44% and 29% of incident ESRD patients, respectively (2).

Table 3. Incident and prevalent counts and adjusted rates of ESRD by most common primary diagnoses, U.S., 2010

	Incident ESRD		Prevalent ESRD	
Primary Diagnosis	Number of patients	Rate per million*	Number of patients	Rate per million*
Diabetes	50,305	151.7	219,568	655.1
Hypertension	32,510	99.0	145,011	436.9
Glomerulonephritis	7,290	22.7	84,318	262.2

*Adjusted for age, gender, race and ethnicity.

2. Kidney transplantation in the ESRD population

In 2010, 16,843 kidney transplants were performed in patients ≥20 years in the United States. Among incident ESRD patients in 2009, 22% were added to the waiting list or received a transplant within one year of ESRD certification, a proportion remaining fairly stable over the past two decades. The median wait time for patients transplanted in 2010 was 2.6 years. The number of adult candidates on the kidney transplantation waiting list with certified kidney failure continues to increase, with a 6% increase in 2010 to reach 75,807 patients on December 31 (2). Of patients listed on the transplant wait list in 2006, substantially more whites (21%) than blacks (9%) received a living donor transplant within three years. After three years, 47% of blacks and 31% of whites were still waiting for a transplant (100).

3. Mortality in the ESRD population

Mortality is exceptionally high in the ESRD population. The most common causes of death in United States prevalent dialysis patients between 2008 and 2010 were cardiovascular events (41.5%), infections (10.9%), withdrawal of dialysis (10.5%) and malignancy (3.7%). Survival probabilities for the 2004 USRDS cohort of incident ESRD patients was 75% at one year, 50% at three years, and 34% at five years following dialysis initiation (100). Mortality is highest during the first year of dialysis. Specifically, mortality rates are lowest within the first month, peak in the second and third month, and slowly decline in months four through twelve to return to a similar rate as the first month (2, 101). For incident hemodialysis patients in 2009, all-cause mortality reached 435 deaths per 1,000 patient-years at risk in month two, then fell to 206 by month 12. Cardiovascular mortality peaked at 169 in month two, and decreased to 78.

Infection-related mortality peaked in months two and three, at 40-43 deaths per 1,000 patient-years at risk. Hemodialysis and peritoneal dialysis patients have similar survival probabilities during the first year of treatment, although the risk of death appears to be higher for peritoneal dialysis in the second year (102). Prevalent death rates have been falling for a number of years, and mortality in the first year of dialysis has, since 2004, continued to decline, reaching rates which are the lowest in 30 years (2).

It is well-established that black ESRD patients on dialysis experience better survival compared to whites, despite the higher mortality rates in blacks versus whites in the general population and in earlier stages of CKD. Among 20 cohort studies from North America and Canada that examined black-white differences in all-cause mortality among ESRD patients on dialysis therapy, adjusted hazard ratio estimates comparing blacks to whites or non-blacks ranged between 0.4 and 1.0 (103-122). The wide variability in estimates of the black-white disparity in all-cause mortality is likely attributable to differences in the following study characteristics: time origin for analysis (range, 0 days to 1 year after dialysis initiation among incident ESRD patients), variable follow-up period (range, 90 days to 14.8 years), inclusion of prevalent dialysis users (n=4 studies), inclusion of peritoneal dialysis users (n=16 studies), small sample of black patients (minimum = 45 blacks), population-specific prevalence of comorbidities including diabetes mellitus and hypertension, methods to account for competing events (e.g., transplantation, change in dialysis modality, dialysis withdrawal), and availability of data on vascular access status, laboratory assessments, and provider characteristics. No meta-analyses have been conducted to date. However, the adjusted hazard ratio of 0.84 (95% CI, 0.83-0.84) reported by Kucirka et al. (106) likely represents the best estimate due to the large USRDS population (N=1,330,007), the large sample size of blacks (n=407,140), the time origin of ESRD onset, the long follow-up period (14.8 years), and exploration of subgroups (e.g., age is an effect modifier).

4. Economic burden of ESRD

The direct financial cost of care for the ESRD population is substantial. In 2009, national expenditure reached $42.5 billion, including $29 billion for Medicare spending and $13.5 billion for non-Medicare spending. Although ESRD patients only account for 1.3% of Medicare patients, ESRD patients account for 8.1% of Medicare spending. Annual Medicare costs per patient were $82,285 for

hemodialysis recipients, $61,588 for peritoneal dialysis recipients and $29,983 for transplant patients (100). These costs only partially capture the full economic burden of ESRD, which includes the costs of chronic disability, premature mortality, and diminished quality of life (55).

C. Cancer in the ESRD population

1. Cancer burden in the ESRD population

Prevalence. In the USRDS data, information on history of cancer before dialysis initiation is ascertained on the Medical Evidence Report by a question about "malignant neoplasm/cancer in the last 10 years." Studies commonly report cancer prevalence estimates from this data as baseline characteristics of the study population. For example, a recent study of incident hemodialysis patients reported a steady increase over the study period in cancer prevalence from 3.9% in 2002 to 4.7% in 2008 (123). In another study of ESRD patients who initiated hemodialysis between 1995 and 2009, estimates of cancer prevalence varied substantially by age and race: white patients 18-30 years (1.0%); white patients 31-50 years (2.6%); white patients >50 years (8.4%); black patients 18-30 years (0.5%); black patients 31-50 years (1.5%); and black patients >50 years (5.8%) (106).

Incidence. The incidence of cancer is not well characterized in the dialysis population (17). Annual estimates of cancer incidence rates do not exist. Two studies that report standardized incidence ratios (SIRs) for overall and site-specific cancers in ESRD patients compared to the general population (Table 4) do not directly report site-specific cancer incidence estimates, however, the data necessary for calculation of cancer incidence over the study periods (i.e., 1980-1994 (15) and 1982-2003 (16)) are presented in the publication tables.

Mortality. According to the 2012 USRDS Annual Data Report, mortality was attributable to malignancy in 5.0% of incident dialysis patients (i.e., first 180 days of dialysis) and 3.7% of prevalent dialysis patients in the period between 2008-2010 (2). Otherwise, mortality studies in dialysis patients primarily report on all-

cause or cardiovascular mortality, with very little focus on cancer mortality. One recent exception is the 2010 study of U.S. hemodialysis patients that reported stable cancer-specific mortality rates between 1995 and 2005. Crude first-year cancer-specific mortality rates for 1995 and 2005 were 13.8 and 15.2 deaths per 1,000 patient-years, respectively (18). These rate estimates are limited by lack of covariate adjustment and highly inaccurate cause of death data from the Death Notification form (CMS-2726) (124, 125).

2. Epidemiologic studies of cancer risk in the ESRD population

ESRD patients on dialysis have a modestly increased risk for many cancers compared to the general population (Table 4) (15-17, 23). A large, international, collaborative study (n=831,804) from three registry populations from the United States, Europe, and Australia/New Zealand with data from 1980-1994 reported that ESRD patients on dialysis had an elevated risk of many cancer sites, including kidney (SIR=3.60 (95% CI, 3.45-3.76)), bladder (SIR=1.50 (95% CI, 1.42-1.57)), and thyroid and endocrine organs (SIR=2.28 (95% CI, 2.03-2.54)) compared to the background population (accounting for age, sex, race, country, and calendar time). Other sites with excess cancer risk included Kaposi's sarcoma and tumors of the oral cavity, stomach, liver, lung and cervix (15). A more recent analysis of the Australia/New Zealand registry (n=24,926) included extended follow-up (1982-2003) and reported similar cancer site-specific risk estimates as reported by Maisonneuve et al (16). A 2012 population-based case-control study among U.S. elderly adults (1,029,695 cancer cases and 99,610 controls) reported similar elevated risks for cancers of the stomach, small intestine, colon, liver, biliary tract, lung, cervix, and kidney, as well as multiple myeloma and chronic myeloid leukemia. No increase in risk was identified for cancers previously reported to have increased risk such as thyroid cancer, non-Hodgkin lymphoma (modest inverse association), Hodgkin lymphoma, and Kaposi sarcoma (23). These studies reported excess cancers in several organs for which viruses have been suspected as causative agents (e.g., hepatitis B and C/liver cancer; Epstein-Barr/lymphoma; HPV/ tongue, cervix, vagina, vulva, penis cancers) (15, 16, 23).

Table 4. Published studies of cancer incidence in the dialysis population

Data source & study population	Years	N	Cancer (N or %)	Overall cancer relative risk (95% CI)	Site-specific cancer (N)	Site-specific cancer relative risk (95% CI)
Maisonneuve et al (1999)						
Three national dialysis registries with cancer information	1980-1994	831,804 dialysis patients	Pooled 25,044	Pooled 1.18 (1.17-1.20)	Kidney (2,053) Bladder (1,646) Thyroid & other endocrine organs (314)	3.60 (3.45-3.76) 1.50 (1.42-1.57) 2.28 (2.03-2.54)
Australia & NZ Europe U.S.			By region 500 6,849 17,695	By region 1.8 (1.7-2.0) 1.1 (1.0-1.1) 1.2 (1.2-1.2)		
Vajdic et al. (2006)						
Population-based cohort of ANZDATA & Australian National Cancer Statistics Clearing House	1982-2003	28,855 dialysis patients	1,136 870, excluding cancers known to frequently cause ESRD (i.e., kidney, renal pelvis, myeloma, bladder, ureter, and other urinary organs)	1.98 (1.88-2.09) 1.35 (1.27-1.45)	Lip (29) Tongue (12) Stomach (28) S. intestine (6) Liver (14) Lung (135) Cervix (13) Thyroid (38) Anal (2) Prostate (74)	↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↓ ↓

Shebl et al. (2012)						
Population-based case-control study among US elderly using SEER-Medicare data	1992-2005	1,029,695 cancer cases & 99,610 controls	ESRD in: - 0.35% cancer cases - 0.36% controls	1.02 (0.91-1.14)	Stomach (118) S. intestine (24) Colon (390) Liver (63) Biliary tract (27) Lung (661) Cervix (28) Multiple myeloma (92) Chronic myeloid leukemia (18)	1.45 (1.16-1.81) 1.92 (1.27-2.92) 1.17 (1.00-1.36) 1.53 (1.16-2.01) 1.78 (1.20-2.65) 1.17 (1.02-1.34) 2.12 (1.39-3.23) 1.77 (1.40-2.24) 1.74 (1.08-2.80)

↑ denotes increased incidence, where SIRs unavailable; ↓ denotes decreased incidence, where SIRs unavailable.

Information on cancer incidence in dialysis patients by subgroups is sparse. Despite the recognized racial disparity in cancer incidence and the increased risk of many cancers among dialysis patients, no studies of dialysis patients have comprehensively investigated whether cancer risk differs between blacks and whites. Effect modification of cancer risk by race has been reported in a number of large studies of kidney transplant recipients, with a demonstrated decrease in risk for blacks relative to whites (126-129). Future studies are necessary to estimate black-white differences in risk of cancer (all sites and site-specific) among dialysis patients, accounting for differential rates of death.

These studies have several limitations. Authors of the large, international study (15) note two major limitations that may have affected the cancer risk estimates. First, there was variable data quality across the three registry populations, in terms of completeness of the dialysis population and complete ascertainment of cancer diagnoses. Secondly, it is possible that some patients with prevalent cancers may not have been excluded from the analysis, despite the exclusion of patients with a cancer diagnosis that preceded dialysis or in whom cancer treatment was the cause of renal failure. Third, the Australia/New Zealand study of registry data (16) likely had the most complete ascertainment of dialysis patients and cancer outcomes, however, many of the cancer site-specific estimates are limited due to the relatively small study population (N = 28,855). Fourth, subgroup analyses have been limited. Lastly, none of these studies used competing risk methodology to account for the high annual mortality in the dialysis population.

3. Cancer as a cause of CKD/ESRD

Of 558,639 incident ESRD patients in the United States between 2005-2009, a small proportion of these patients had a malignancy-related primary cause of ESRD including multiple myeloma (n=5,700, 1.0%), malignant renal tumor (n=2,191, 0.4%), malignant urinary tract tumor (n=727, 0.1%), lymphoma of kidneys (n=190, 0.0%), other immunoproliferative neoplasms (n=710, 0.1%) ((100)). Accordingly, Vajdic et al. separately examined the risk of cancers known to frequently cause ESRD (i.e., myeloma, kidney and urinary tract cancers), and did not include these cancers in the overall cancer rate (16).

4. Pathogenesis and progression of cancer in the ESRD population

The increased risks reported for several infection-related cancers (i.e., liver, stomach, and cervical cancers) could reflect immunodeficiency associated with ESRD. Chronic uremia leads to metabolic abnormalities that alter the immune response such that antigen-presenting cell function is impaired, lymphocyte survival is shortened, proliferation of T-cells is impaired, together with an increased suppressor T-cell activity, decreased helper T-cell (Th) activity, and increased Th1/Th2 ratio (130, 131). Nutritional abnormalities that are prevalent among ESRD patients, such as selenium deficiency, reduced glutathione peroxidase activity, and vitamin D deficiency (132-135) could also play a role in development of cancer, particularly for colon cancer (136-138). Erythropoietin, which is commonly used among ESRD patients for the treatment of anemia, may contribute to carcinogenesis via two proposed mechanisms: activation of EPO receptors that exist on the surface of the cancer cells, and EPO-induced angiogenesis that allows the tumor to grow and spread (1, 139). Excess cancer risk may also be due to an interaction of uremic and dialysis-induced immune dysfunction with established risk factors such as UV radiation (lip cancer), tobacco (lip, lung, and cervical cancer), or alcohol (liver cancer) (16).

5. Cancer screening in the ESRD population

Although evidence suggests that dialysis patients have increased risk for cancer, screening for cancer in ESRD patients remains controversial due to the exceptionally high mortality in this population (2, 140, 141). Population-based estimates suggest that cancer screening occurs less frequently in dialysis patients compared to the general population (142). Possible causes for lower screening rates include physician inattentiveness, physician fatalism about patient outcomes, poor patient adherence to testing procedures, and inadequate financial coverage for screening (142). The cost-effectiveness of cancer screening depends, in part, on the survival benefit and the cost of the screening test and treatment. Cost-effectiveness analyses suggest that a general screening program in this population would be a relatively inefficient allocation of financial resources, and would add minimal days of life saved per person under the most optimistic assumptions (143-145). Despite lower rates of screening in the ESRD population, these patients are not more likely to present with later stage malignancies, with the exception of prostate cancer (146). This may be attributable to the higher frequency of healthcare visits or more intensive

medical workups in patients who are on dialysis (146). ESRD patients undergo comprehensive evaluation of medical, surgical, and psychosocial histories to become a kidney transplant candidate (70-72). Patients with active or recent history of malignancy are generally contraindicated for immunosuppression, therefore they are advised to postpone or cancel further transplant evaluation (70). An individualized approach to cancer screening in dialysis patients is required and should be based on the patient's cancer risk factors, expected survival, and transplant status (141).

6. Cancer treatment in the ESRD population

Cancer in a dialysis patient is generally treated as in the nondialysis patient with appropriate consideration of the renal clearance, dosing, and dialyzability of chemotherapeutic agents. Dialysis must often be precisely timed in conjunction with chemotherapy administration to avoid toxicity. The lack of clinical trials in this population precludes definitive recommendations. Therefore recommendations for treating dialysis patients with cancer can be made only when data on prognosis become available. Individualized treatment through collaboration of surgeons, oncologists, nephrologists, and dialysis units is vital. (141).

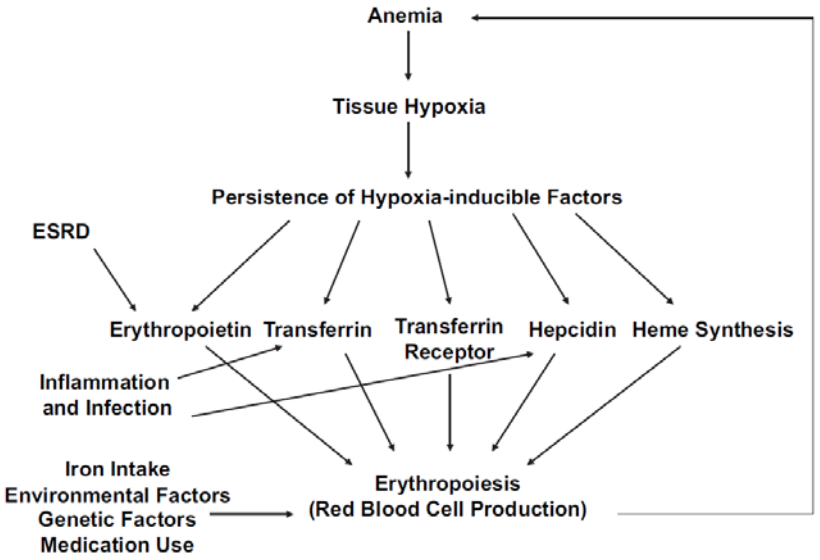
D. Erythropoiesis-stimulating agent (ESA) therapy for anemia management

1. Pathogenesis of anemia in ESRD patients

Patients with ESRD suffer universally from anemia because they produce insufficient amounts of endogenous erythropoietin to maintain hematocrit levels. Figure 2 illustrates how the feedback system that regulates Hgb levels is disrupted in ESRD patients. In a patient with a healthy kidney, hypoxia-inducible transcription factors (HIFs) are activated when the oxygen-carrying capacity of the blood decreases below a certain threshold (147-149). Activation of HIFs leads to expression of endogenous erythropoietin and subsequent stimulation of erythropoiesis (i.e., the process of RBC production), provided that iron is available (150). In ESRD patients, system equilibrium is disturbed when the sustained presence of HIFs do not lead to expression of endogenous erythropoietin and subsequent stimulation of erythropoiesis. System equilibrium is also disturbed by inflammation, which limits iron

availability for erythropoiesis by down-regulating transferrin (concerned with iron transport) and up-regulating hepcidin (a hormone that regulates iron availability and absorption) (151, 152).

Figure 2. Physiologic model of the feedback system that regulates hemoglobin levels



Adapted from Brookhart et al. (2011) (153).

2. Diagnosis of anemia in ESRD patients

Routine screening for anemia includes laboratory evaluation of a complete blood count including RBC indices, reticulocyte count, serum ferritin concentration, and transferrin saturation (TSAT) or reticulate Hgb content. Routine testing for EPO levels in anemic patients is not recommended because the test is expensive and patients who respond to exogenous ESAs may have a normal or even elevated EPO concentration, which may nevertheless be inappropriately low for the severity of their anemia. Recommendations specify that EPO deficiency be a diagnosis of exclusion in the anemic CKD patient. The anemia of EPO deficiency is normocytic (normal mean corpuscular volume, or MCV) and normochromic (normal mean corpuscular Hgb concentration). A low MCV is suggestive of iron deficiency but may be seen in hemoglobinopathies such as thalassemia. A high MCV (macrocytosis) is suggestive of vitamin B_{12} or folate deficiency. Elevated MCV suggest assessment of B_{12} and folate levels. The serum

ferritin level, which correlates with iron bound to tissue ferritin in the reticuloendothelial system, increases in the setting of acute or chronic inflammation independent of tissue iron stores. A TSAT of <16% in an anemic patient with CKD is consistent with absolute or functional iron deficiency, both of which are characterized by decreased delivery of iron to the eyrthroid marrow. An elevated reticulocyte count is inconsistent with EPO deficiency (154).

3. Overview of ESA therapy

ESA therapy has revolutionized the management of patients with anemia, including ESRD patients receiving dialysis. Prior to the approval of ESAs, anemia management was based on RBC transfusions. However, RBC transfusions have a number of limitations such as blood supply limitations, risk of infection, risk of RBC transfusion reaction, and immune sensitization. Appropriate use of ESA therapy and intravenous iron supplementation can effectively manage anemia by raising Hgb levels, reducing the need for RBC transfusions, and ultimately improving clinical outcomes (155, 156). Drugs in the ESA class are structurally and biologically similar to the naturally occurring protein erythropoietin. ESAs stimulate erythropoiesis via the same mechanism as the endogenous glycoprotein hormone erythropoietin, through binding of the erythropoietin receptor leading to antiapoptosis of RBC progenitor cells and the subsequent production and maturation of RBCs (157, 158). Below, a summary is provided for ESAs regarding timeframe for introduction to the U.S. market, indications, contraindications, and administration. Since the third-generation ESA methoxy polyethylene glycol-epoetin beta (Mircera) is not yet available in the United States, nor is it approved for cancer patients, the discussion focuses on epoetin alfa and darbepoetin alfa.

Introduction to the U.S. market. In 1989, the FDA approved epoetin alfa (Epogen/Procrit) (159), the first member of the family of ESAs. In 2001, the FDA approved the second-generation ESA darbepoetin alfa (Aranesp) (160). These drugs were initially indicated for treatment of anemia, including ESRD patients. The FDA approved epoetin alfa and darbepoetin alfa for use in cancer patients in 1993 and 2003, respectively.

Indications and contraindications. ESA therapy is indicated for the: a) treatment of anemia due to CKD, including patients on dialysis and not on dialysis to decrease the need for RBC transfusion; b) treatment of anemia due to zidovudine administered at ≤ 4200 mg/week in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL; c) treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy; and d) reduction of allogeneic RBC transfusions among patients with perioperative Hgb > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery. ESA therapy is not indicated for use: a) in patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy; b) in patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure; c) in patients scheduled for surgery who are willing to donate autologous blood; d) in patients undergoing cardiac or vascular surgery; or e) as a substitute for RBC transfusions in patients who require immediate correction of anemia. ESA therapy is contraindicated in patients with: a) uncontrolled hypertension; b) pure red cell aplasia that begins after treatment with ESA therapy; and c) serious allergic reactions to ESA therapy (159, 160).

ESA administration. Among U.S. hemodialysis patients, epoetin alfa is the most commonly used ESA while darbepoetin alfa is administered infrequently (155). Administration frequency is more burdensome for epoetin alfa compared to longer acting darbepoetin alfa. The elimination half-life in humans after a single intravenous injection of darbepoetin alfa is three-fold that of epoetin alfa (i.e., 25.3 vs. 8.5 hours). Epoetin alfa requires two or three injections per week due to the fairly short circulating half-life of plasma EPO (161), whereas darbepoetin alfa requires injections once weekly or once every other week (162). Route of administration for ESA therapy is available both intravenously and subcutaneously. In the United States, ESA therapy is most commonly administered intravenously for hemodialysis patients per FDA recommendations because of the risk of pure red cell aplasia that is associated with the subcutaneous route. Internationally, ESA therapy is typically administered subcutaneously to hemodialysis patients because of a 20% to 30% dose reduction compared with the intravenous route.

Economic impact. During the last two decades, ESA drugs have had the highest sales worldwide of any biologic medication (1). Of $2.8 billion spent in 2010 on injectables for U.S. dialysis patients, ESAs accounted for 67%, or $1.87 billion (2).

4. ESA therapy and cancer outcomes

Beginning in 2003, several reports from randomized clinical trials raised questions regarding the safety of ESA therapy in patients with cancer. Of 60 randomized controlled trials in patients with cancer at various sites, the majority reported no difference in tumor progression or survival between ESA-treated and placebo groups (1). However, eight trials report increased risk of tumor progression and/or death in cancer patients treated with ESAs (3-11). Details on these eight trials are presented in Table 5.

Table 5. Eight randomized, controlled trials reporting decreased survival and/or decreased locoregional control in ESA-treated patients

Trial	Cancer type (n)	Target Hgb (g/dL)	Actual Hgb (g/dL)	ESA	Primary efficacy outcome	Adverse outcome for ESA-containing arm
Chemotherapy alone						
BEST (3, 4)	Metastatic breast (n = 939)	12-14	Md=12.9 Q1=12.2 Q3=13.3	EPO-α	12-month overall survival	Decreased 12-month survival (OS at 1 year: 70% (E) vs. 76% (NE), HR 1.37, p = 0.01)
AMG 2000-0161 (6)	Lymphoid malignancy (n = 344)	13-15 (M) 13-14 (F)	Md=11.0 Q1=9.8 Q3=12.1	DPO-α	Proportion of patients achieving a Hgb response	Decreased overall survival (30-day survival: 94% (E) vs. 98% (NE) 11-month survival: 47% (E) vs. 45% (NE))
PREPARE (9)	Early breast cancer (n = 733)	12.5-13	Md=13.1 Q1=12.5 Q3=13.7	DPO-α	Relapse-free and overall survival	Decreased 3-year relapse-free and overall survival (DFS at 3 years: 74.3% (E) vs. 80.0% (NE) HR 1.31, p = 0.061 OS: 88% (E) vs. 91.8% (NE), HR 1.33, p = 0.139)
GOG-0191 (10)	Cervical (n = 109)	12-14	Md=12.7 Q1=12.1 Q3=13.3	EPO-α	Progression-free and overall survival and locoregional control	Decreased 3-year progression-free and overall survival and locoregional control (PFS at 3 years: 58% (E) vs. 66% (NE) OS: 60% (E) vs. 74% (NE))
Radiotherapy alone						
ENHANCE (5)	Head and neck (n = 351)	≥ 15 (M) ≥ 14 (F)	Not available	EPO-β	Locoregional progression-free survival	Decreased 5-year locoregional progression-free and overall survival (LR-PFS: RR 1.62, p = 0.0008. OS: RR 1.39, p = 0.02)
DAHANCA-10 (11)	Head and neck (n = 522)	14-15.5	Not available	DPO-α	Locoregional disease control	Decreased locoregional disease control (LR control: 56% (E) vs. 69% (NE), RR 1.44, p = 0.02 DFS: 48% (E) vs. 63% (NE), RR 1.49, p = 0.004 OS: 38% (E) vs. 51% (NE), RR 1.28, p = 0.08)

Chemotherapy and radiotherapy						
EPO-CAN-20 (7)	Non-small cell lung (n = 70)	12-14	Not available	EPO-α	Quality of life	Decreased overall survival (MS: 63 (E) vs. 129 (NE) days, HR 1.84, p = 0.04)
AMG-2001-103 (8)	Non-myeloid malignancy (n = 989)	12-13	Md=10.6 Q1=9.4 Q3=11.8	DPO-α	RBC transfusions	Decreased overall survival (OS: 45.7% (E) vs. 48.8% (NE), HR 1.22, p = 0.022 Adjusted: HR 1.15, p = 0.121)

DFS, disease-free survival; DPO-α, darbepoietin alfa; E, ESA treatment arm; EPO-α, erythropoietin alfa; EPO-β, erythropoietin beta; F, female; Hemoglobin, Hgb; M, male; Md, median; MS, median survival; HR, hazard ratio; LR, loco-regional; NE, no ESA treatment arm; OS, overall survival; PFS, progression-free survival; Q1=25th percentile, Q3=75th percentile.

The majority of meta-analyses performed report no significant difference between cancer patients treated with ESAs compared to placebo (12, 163-165). A 2005 meta-analysis by the Cochrane group reported a survival benefit for the ESA group (HR = 0.81; 95% CI, 0.67-0.99). A 2009 meta-analysis by the Cochrane group reported higher rates of mortality in the ESA group (HR = 1.06; 95% CI, 1.00-1.12). The most recent meta-analysis of 60 experimental studies of more than 15,000 cancer patients failed to demonstrate any significant effect of ESAs on survival or disease progression (OR = 1.06; 95% CI, 0.97-1.15) (12). Contradictory results from these eight trials compared to the majority of trials and the most recent meta-analysis may be attributable to a number of study design issues, including: discrepancies between the comparison groups, lack of longitudinal tumor assessments, excessively elevated Hgb levels, differences in ESA administration, and/or early termination of the trials (1).

5. Timeline of events related to anemia management with ESAs, 2003-2009

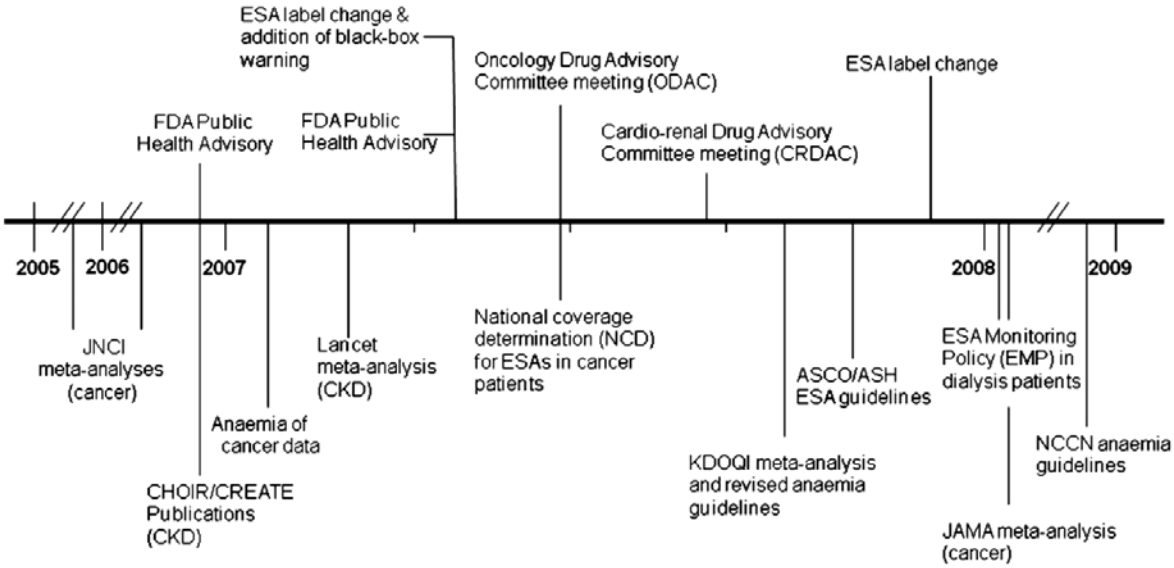
Between 2003 and 2009, a series of events occurred relating to anemia management with ESA therapy. These events included safety reports, FDA black-box warnings, reimbursement changes, and revised anemia management guidelines.

The following is a chronological summary of the relevant studies that preceded and followed the March 2007 U.S. FDA advisory on ESAs. August 2003: BEST breast cancer study stopped early due to observed higher mortality in ESA group (3); October 2003: ENHANCE head and neck cancer study reported poorer locoregional progression-free survival (5); (May 2004): FDA mandates change in ESA product labeling to include results of BEST and ENHANCE studies; (April 2005): Meta-analysis among cancer patients using ESAs is published and reported 58% increased risk of thromboembolic events (non-significant), and suggestive but inconclusive evidence for improved overall survival (166); (May 2006): Updated meta-analysis among cancer patients using ESAs is published and reported significant increase in thromboembolic events, and no association between ESA use and survival and possibly even decreased survival for ESA users (165); (November 2006): Publication of results from randomized clinical trials in CKD patients (167, 168) that identified risks when targeting patients to Hgb levels above the labeled target range of 10–12 g/dL; (February 2007): Publication of two meta-analyses examining the effects of treatment with ESAs to higher versus lower Hgb targets in CKD patients (169, 170); (March

2007): FDA black box warning (171) and publication of results from clinical trial in cancer patients identifying thromboembolic and mortality risks when treating with ESAs (7); (January 2008): Publication of results from clinical trial in cancer patients identifying thromboembolic and mortality risks when treating with ESAs (8); (February 2008): Publication of meta-analysis showing elevated risks for thromboembolic events and mortality when comparing treatment with ESAs to placebo in patients with cancer (172); (May 2009): Publication of meta-analysis showing elevated risks for mortality when comparing treatment with ESAs to placebo in patients with cancer (173).

Figure 3 presents a timeline of the major regulatory actions, reimbursement changes, peer-reviewed publications and revisions to clinical practice guideline recommendations that occurred between 2005 and 2009. Regidor et al (44) summarized these events as follows: (1) Convening of separate FDA drug advisory committee meetings (Oncology Drug Advisory Committee and Cardio-renal Drug Advisory Committee and Drug Safety and Risk Management) to evaluate the risk: benefit profile of anemia management with ESAs in cancer and kidney disease patients, respectively; (2) Revisions to the ESA labels that first removed the target range of 10–12 g/dL: replacement with 'use the lowest dose to avoid the need for RBC transfusions'; addition of a black-box warning highlighting the risks identified when targeting Hgb levels of 13.5 and 14 g/dL; subsequently, the Hgb range of 10–12 g/dL was reinstated; however, many of the quality of life (QoL) claims were identified as not being adequately supported given current standards and were removed, and in the cancer setting, a 'not indicated' statement was added for patients receiving chemotherapy when the anticipated outcome is cure; (3) FDA and ESA manufacturer communications to healthcare professionals regarding changes to the ESA label and the insertion of a black-box warning; (4) Revisions to the anemia management guidelines issued by the KDOQI (170), the American Society for Clinical Oncology/American Society for Hematology (ASCO/ASH) (174) and the National Comprehensive Cancer Network (NCCN) (175); (5) Implementation of a national coverage determination in the cancer setting by the Centers for Medicare and Medicaid Services (CMS) restricting reimbursement for ESA treatment to an Hgb level <10 g/dL; and (6) Revisions to the erythropoietin monitoring policy in dialysis patients reducing payment by 50% if Hgb levels remained >13 g/dL for three consecutive months.

Figure 3. A timeline of the major regulatory actions, reimbursement changes, peer-reviewed publications and revisions to clinical practice guideline recommendations that occurred between 2005 and 2009

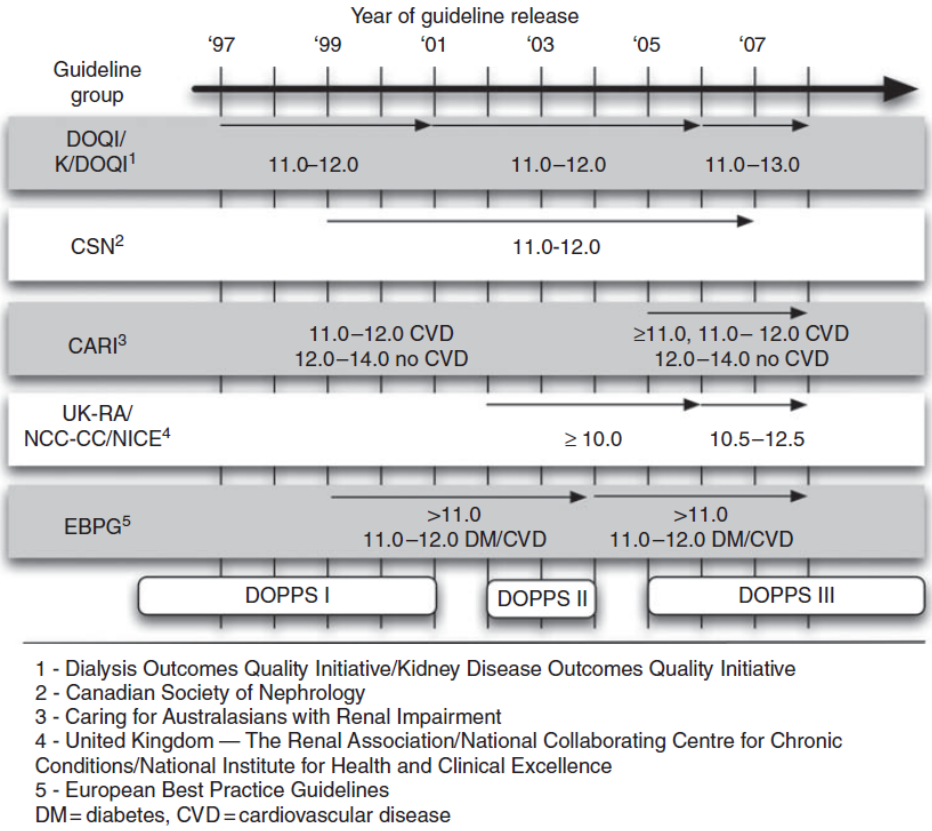


Adapted from Regidor et al. 2011 (44). Regulatory events are presented above the line and all other events are described below the line.

6. Clinical guidelines & recommendations for ESA therapy

Over the last decade, the Hgb target range has changed repeatedly as new studies were published. Figure 4 lists the recommended Hgb target levels for adult hemodialysis patients on an ESA by year and by international group (176).

Figure 4. Hemoglobin target range for adult hemodialysis patients receiving ESA therapy, by year and international guideline group



Adapted from McFarlane et al. 2010 (176). Hemoglobin range in g/dL.

Management of anemia in dialysis patients with cancer has been challenging due to the absence of formal guidelines for providers regarding appropriate usage of ESA therapy in this population. The U.S. recommendation for CKD patients on dialysis receiving ESAs is to initiate treatment when the Hgb level is less than 10 g/dL and to individualize dosing and use the lowest dose of ESA sufficient to reduce the need for RBC transfusions (13), whereas the ESA indication for cancer patients is for treatment of anemia due to concomitant myelosuppressive chemotherapy (14). In 2012, KDIGO published clinical practice guidelines for anemia in CKD that recommends “using ESA therapy with great caution, if at all, in CKD patients with active malignancy—in particular when cure is the anticipated outcome—(1B), a history of stroke (1B), or a history of malignancy (2C).” The strength and quality of the KDIGO recommendations

are 1B (i.e., level 1 recommendations with moderate quality of evidence) and 2C (i.e., level 2 suggestions with low quality of evidence). As of February 2010, the FDA requires prescribers and hospitals to enroll in and comply with the ESA APPRISE Oncology Program requirements in order to prescribe and/or dispense ESA therapy to patients with cancer and anemia due to myelosuppressive chemotherapy. Prior to each new course of ESA therapy in patients with cancer, prescribers and patients must provide written acknowledgment of a discussion of the risks of ESA therapy (159, 160).

7. Anemia management in the ESRD population and the cancer population

Anemia management, including % ESA use, ESA dosage, % RBC transfusions, and Hgb levels, has not been described in ESRD patients with cancer. However, a dramatic shift in anemia management has been documented over the last decade in both ESRD patients and cancer patients (Table 6).

Table 6. Published studies of ESRD populations or cancer populations that report patterns of ESA utilization and dose in the time period before and/or after the March 1, 2007 FDA black-box warning

Study author	Study period	Study population (data source)	Sample size (N)	% ESA use
ESRD population				
Freburger (123)	2002-2008	ESRD patients receiving hemodialysis therapy (USRDS)	233,547-280,400	The percentage of patients receiving EPO decreased from 95% in 2002 to 90% in 2008
Cancer population				
Stroupe (46)	2002-2009	Adults diagnosed with cancer between 2002-2009 (VA)	257,498	The percentage of patients prescribed an ESA within 12 months after diagnosis was 8.5%*
Tarlov (45)	2002-2008	Lung and colon cancer patients receiving chemotherapy (VA)	21,239	Any ESA use decreased after the March 2007 FDA black-box warning from 36% to 21% for lung cancer patients and from 20% to 12% for colon cancer patients
Wright (177)	1995-2005	Breast, lung, or colon cancer patients (excluding ESRD patients) diagnosed between 1995-2005 and receiving chemotherapy (SEER-Medicare)	24,112	The percentage of patients receiving ESAs increased from 71% in 1995 to 86% in 2005

SEER, Surveillance, Epidemiology, and End Results; VA, United States Department of Veterans Affairs Healthcare System
*23% of patients received chemotherapy after the FDA black-box warning.

% ESA use. ESA utilization is very high in the ESRD population on hemodialysis, according to a recent study by Freburger et al. Between 2002 and 2008, the percentage of hemodialysis patients receiving ESA therapy decreased from 95% to 90% (123). ESA utilization in the cancer population is more variable, with reports of between 9% (46) and 86% (177) of cancer patients receiving ESA therapy. In a SEER-Medicare study of 24,112 breast, lung, and colon cancer patients receiving chemotherapy, the percentage of patients receiving ESAs increased from 71% in 1995 to 86% in 2005 (177). In contrast, two studies in the VA population reported much lower ESA utilization. Among cancer patients receiving chemotherapy, any ESA use decreased after the March 2007 FDA black-box warning from 36% to 21% for lung cancer patients and from 20% to 12% for colon cancer patients (45). In a more heterogeneous population of cancer patients diagnosed between 2002 and 2009, only 8.5% of cancer patients were prescribed an ESA within 12 months after diagnosis (46).

ESA dose. In a study of ESRD patients on hemodialysis, mean monthly EPO dose increased from ~65,000 units/month in quarter 1 of 2002, to a high of 77,000 units/month by the end of 2006, and then decreased to 71,000 units/month by the end of 2008 (123). The mean EPO dose among ESRD patients in September 2010 was 72,139 units/month (2).

% RBC transfusions. In the dialysis population, the RBC transfusion rate declined with the introduction and routine use of ESA therapy. In prevalent dialysis patients with Medicare parts A and B, RBC transfusion rates decreased in both outpatient and inpatient settings from 535 per 1,000 patient-years in 1992 to 264 per 1,000 patient-years in 2005 (178).

Hgb levels. In a study of ESRD patients between 2002 and 2008, the mean Hgb level was 11.7 g/dL in 2002 and increased to its peak of 12.1 g/dL in the first quarter of 2007 and then began to decline, and reached 11.6 g/dL by the end of 2008 (123). According to the 2012 USRDS Annual Data Report, 69% had a Hgb between 10-12 g/dl by the end of 2010, the highest proportion since 1998. The percentage of patients with a Hgb >12 g/dl decreased from a peak of 51% to 21% between February 2007 and December 2010. The percentage of patients with a Hgb <10 g/dl increased from 6% in the middle of the

decade to 10% by the end of 2010 (2). Among cancer patients diagnosed at the VA between 2002 and 2009, the average Hgb level that prompted first use of ESA therapy in a patient was lower after the black-box warning (10.2 vs. 9.6 g/dl) (46).

E. Public health relevance

This dissertation will contribute to the existing ESRD literature by characterizing the overall and site-specific cancer incidence in U.S. hemodialysis patients. The innovative application of competing risks methodology to account for the high annual mortality characteristic of the dialysis population will provide real-world estimates of cancer incidence, rather than hypothetical estimates that assume no competing risks. The results can be used to inform health policy decisions. In addition, this will be the first study to document temporal trends in ESA utilization among ESRD patients with cancer. Given the unclear association between ESA use and tumor progression and/or decreased survival, the impact of negative safety reports in cancer trials, black box advisories, revised anemia management guidelines, and reimbursement changes related to ESA therapy is of particular interest. The large and representative USRDS dataset will allow identification of important differences by various patient and facility-level characteristics in cancer incidence among ESRD patients and ESA utilization in ESRD patients with cancer.

CHAPTER III. METHODS

A. Study design and population

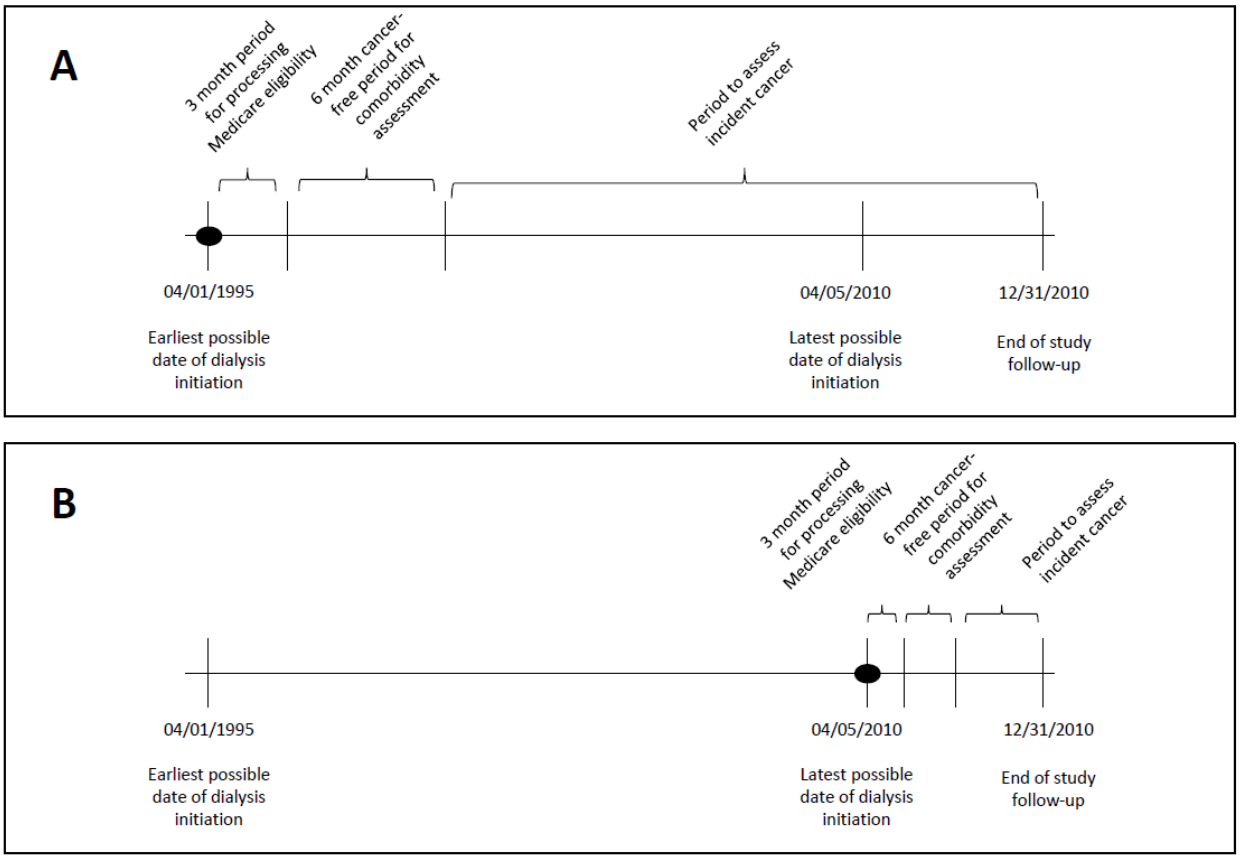
Data was utilized from the USRDS, which is a national registry that includes all patients in the Medicare ESRD program. For this dissertation work, the study population was restricted to ESRD patients ≥ 18 years of age who received in-center hemodialysis between April 1, 1995 and December 31, 2010 and had Medicare as their primary payer with both part A and B coverage in order to insure collection of complete claims data on patients. Patients with a history of kidney transplantation or HIV/AIDS were excluded to insure that cancer was not due to another cause of immunosuppression. The study

population was limited to patients who remained alive without a cancer diagnosis for at least 9 months after dialysis initiation. Three months after the first service date is the amount of time required to process Medicare eligibility/enrollment forms and to insure stability in dialysis treatment modality. A subsequent six month period (i.e., the baseline period) was required for assessment of comorbidities and functional status. The proposed study aims incorporated a retrospective cohort study design with three distinct study populations:

1. Study design and population for aims 1a and 1b

The analyses for aims 1a and 1b utilized a retrospective cohort of all ESRD patients who initiated in-center hemodialysis between April 1, 1995 and April 5, 2010 (Figure 5). Patients were observed from 9 months post-dialysis initiation to the first of the following: the event of interest (i.e., cancer diagnosis); or censoring event (i.e., renal replacement therapy modality change to peritoneal dialysis or kidney transplantation; end of Medicare as primary payer status; lost-to-follow-up; 5 years since dialysis initiation; end of study on December 31, 2010; or death, as appropriate). For aim 1b, death was treated as a competing event.

Figure 5. Study design for aims 1a and 1b



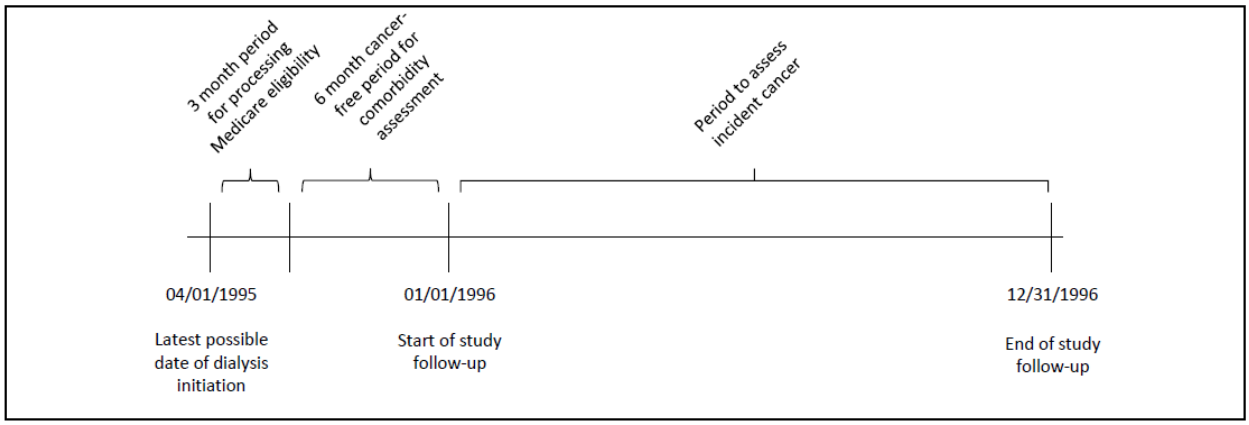
Study participants are depicted with A) the earliest possible date of dialysis initiation (i.e., April 1, 1995); and B) the latest possible date of dialysis initiation (i.e., April 5, 2010). The solid circle denotes dialysis initiation.

2. Study design and population for Aim 1c

The analysis for aim 1c utilized 14 annual cohorts (i.e., 1996-2009) of incident and prevalent hemodialysis patients that met eligibility criteria by January 1. All ESRD patients who initiated in-center hemodialysis on or before April 1 of the previous year and remained alive until January 1 of the current year were eligible for that yearly cohort. Patients with cancer during the 6 month baseline period (i.e., July 4 to December 31 of prior year) were excluded from that yearly cohort. Patients were observed from 9 months post-dialysis initiation to the first cancer diagnosis. Patients were censored due to the loss of Medicare as primary payer status, change of modality, lost-to-follow-up, kidney transplantation, death or

end of study (December 31). As an example, Figure 6 depicts the time periods used to construct the 1996 annual cohort.

Figure 6. Study design for aim 1c, 1996 annual cohort



Study participants consist of prevalent ESRD patients on hemodialysis where April 1, 1995 was the latest possible date of dialysis initiation. The solid circle denotes dialysis initiation.

3. Study design and population for Aim 2

The analyses for aim 2 utilized the same retrospective cohort as aim1a, further restricted to patients who received their first cancer diagnosis at least 9 months after dialysis initiation, and with post-cancer diagnosis follow-up time between 2000 and 2010 to ensure a similar distribution of incident and prevalent hemodialysis patients over time.

B. Data source

The USRDS is uniquely situated for this research because it is a large, longitudinal population-based registry with detailed patient-level data capture on all patients in the Medicare ESRD program. The USRDS has also helped to inform other cancer studies in ESRD patients (15, 18, 29). All ESRD patients in the United States are eligible for Medicare coverage regardless of age, however, some patients remain on private or HMO insurance, or have a combination of insurance coverage. All patients diagnosed with

ESRD and initiated on dialysis therapy are entered into the USRDS via the ESRD Medical Evidence Report (form CMS-2728) which establishes eligibility for individuals previously not Medicare beneficiaries and reclassifies previously eligible beneficiaries as ESRD patients. The dialysis provider is required to complete the Medical Evidence Report within 45 days of initiation (2).

The major source of data for the USRDS is the Renal Beneficiary and Utilization System (REBUS), which receives regular updates from the Centers for Medicare and Medicaid Services (CMS) based on the Medicare Enrollment Database (EDB), Medicare inpatient and outpatient claims, the Organ Procurement and Transplantation Network (OPTN) transplant database, ESRD Medical Evidence Report forms (2728) provided by the ESRD networks, ESRD Death Notification forms (2746) obtained from renal providers, and the Standard Information Management System (SIMS) database of the ESRD networks. A unique patient identifier is common to both the SIMS and CMS databases (2).

The USRDS comprises data from the patient file, the Medical Evidence Report and Medicare Parts A and B claims. The patient file includes information on demographics. The Medical Evidence Report collects information on demographics, primary cause of renal failure, and clinical conditions at dialysis therapy initiation. Medicare Parts A and B claims include information on diagnoses and procedures recorded for all hospitalizations and outpatient visits since dialysis therapy initiation. Medicare Part A claims include all hospital inpatient, hospital-based outpatient, skilled nursing facility, home health agency, and hospice claims. Medicare Part B physician/supplier claims include durable medical equipment charges, physician and other outpatient healthcare provider services (e.g., office-based outpatient visits). Medicare Part B institutional claims include monthly data on dialysis care such as total EPO dose, number of EPO administrations, and hematocrit values. Medicare requires that the final hematocrit value of the month must be submitted with each claim for ESA reimbursement. The facility file, which has data from the CMS ESRD Annual Facility Survey and can be linked to dialysis claims by the provider ID, contains information on facility characteristics (2).

C. Dependent variable definitions

1. Cancer outcomes (aim 1)

Overall and site-specific cancers were ascertained from inpatient and outpatient Medicare claims using *International Classification of Diseases, 9th revision, Clinical Modification* (ICD-9-CM) diagnosis codes. Cancer cases were identified using three claims-based algorithms (Table 7), adapted from algorithms defined by Setoguchi et al. (179). Definitions 2 and 3 have been reported to have high specificity (>98.5%) and relatively high sensitivity (range, 76% to 89%) for identification of incident cancers including lung, colorectal, stomach, breast and lymphoma in Medicare data (179). The sensitivity for identification of leukemia (definition 2, 52%; definition 3, 74%) is substantially lower than for other sites (179). Definition 1 was used for primary analyses because the extended time period of 6 months between cancer diagnosis codes allows for delays in health care encounters that may occur due to the high severity of illness characteristic of the ESRD population. Definitions 2 and 3 were used in sensitivity analyses to assess the impact of different cancer definitions. Dissertation work expanded on these definitions to create several more site-specific cancer definitions including lip, tongue, mouth, salivary gland, esophagus, stomach, small intestine, anus, liver, gallbladder, pancreas, nasopharynx, larynx, trachea, bronchus, mesothelioma, melanoma, connective and other soft tissue, Kaposi sarcoma, ovary, testis, vulva, cervix uteri, corpus uteri, penis, kidney, renal pelvis, ureter, bladder, eye, brain, thyroid, Hodgkin disease, Non-Hodgkin lymphoma and multiple myeloma.

Table 7. Sensitivity and specificity of claims-based definitions for incident cancers

	Sensitivity (%)	Specificity (%)
Definition 1 ≥ 2 cancer diagnoses of cancer within 6 months		
Lung	N/A	N/A
Colorectal	N/A	N/A
Stomach	N/A	N/A
Breast	N/A	N/A
Lymphoma	N/A	N/A
Leukemia	N/A	N/A
Definition 2 ≥ 2 cancer diagnoses of cancer within 2 months		
Lung	76.19	99.54
Colorectal	80.36	99.51
Stomach	81.36	99.90
Breast	78.89	99.62
Lymphoma	79.81	99.81
Leukemia	52.20	99.92
Definition 3 ≥ 1 cancer diagnosis		
Lung	86.69	98.78
Colorectal	88.02	98.51
Stomach	89.41	99.75
Breast	87.23	98.65
Lymphoma	88.71	99.33
Leukemia	73.63	99.63

*Adapted from Setoguchi et al. (2007) (179)

A 6-month cancer-free period after dialysis initiation (i.e., the baseline period) was required to prevent misclassification of prevalent cases as incident cases (179). Patients with a malignancy-related primary cause of ESRD were identified as a prevalent cancer case. Date of cancer onset was defined as the first date of a cancer-related diagnosis code in the claims data. *In situ* carcinomas were included for two sites (i.e., breast and bladder) (180). Secondary tumors, benign tumors, and non-melanoma skin cancers were excluded. Only the first cancer diagnosis after dialysis initiation was included as an event.

2. Anemia management outcomes (aim 2)

Information on ESAs and hematocrit was identified from dialysis claims from the Medicare Part A institutional claims files and Medicare Part A and B claims. Information on transfusions was identified from Medicare Part A and B claims. The codes used to identify ESAs and transfusions are presented in

Appendix A (Supplemental Table 19). Monthly outlier values were set to missing if outside the specified ranges (EPO dose, 500-700,000 units; hematocrit, 20-60 g/dL) (123). Data were summarized by calendar quarter. We calculated the quarterly proportion of the study population treated with ESAs (epoetin alfa (EPO), darbepoetin alfa). Mean EPO dose (units/month) was calculated as the quarterly sum of EPO doses divided by 3. Darbepoetin alfa dose was excluded from the analysis due to extreme missingness. Mean quarterly hemoglobin levels were calculated by dividing hematocrit levels by 3. We calculated the quarterly proportion of the study population that received transfusions, as well as the mean number of days per year that each patient received a transfusion.

D. Independent variable definitions

The analyses utilized several covariates from the USRDS and Medicare claims data (Table 8). The following information was obtained from the USRDS patient file: first service date, sex, race, primary cause of ESRD. Information on ethnicity was obtained from the Medical Evidence file. The earliest date for each of the following competing risks and censoring events were identified from the USRDS: change in Medicare payer status, change in modality, kidney transplantation, and death. Age at dialysis initiation and dialysis vintage (i.e., number of years on dialysis) were calculated by subtracting the first service date. History of kidney transplant evaluation was defined as a claim assigned a V-code of V72.83 (other specified preoperative examination) during the 6-month baseline period. The sensitivity and specificity of code V72.83 has not been reported. Chemotherapy administration was identified using ICD-9-CM diagnosis and procedure codes, Healthcare Common Procedure Coding System (HCPCS) codes, and revenue codes (Appendix B, Supplemental Table 20) (181, 182). All other variables were used as given in the data source.

Table 8. Covariates necessary for statistical analyses of specific aims

Variable	Coding
Demographics	
Age at ESRD onset	Continuous, categorical
Gender	Male, female
Race	White, African American, Other
Ethnicity	Hispanic, non-Hispanic
Primary cause of ESRD	Diabetes, hypertension, glomerulonephritis, polycystic kidney disease, other
Clinical	
Years on dialysis (dialysis vintage)	Continuous, categorical
Kidney transplant evaluation	Yes, no
Chemotherapy use	Yes, no
Dates	
Date of first service (i.e., dialysis initiation)	Month/day/year
Date of change in Medicare payer status	Month/day/year
Date of change in dialysis modality	Month/day/year
Date of first kidney transplantation	Month/day/year
Date of death	Month/day/year

E. Statistical analysis for aim 1

1. Estimation of the cumulative incidence of cancer (aims 1a and 1b)

For the study cohort of incident dialysis patients, the number and percentage of patients were calculated by patient characteristics. Total and average person-years were calculated by patient characteristics. For each cancer site, the total number of observed cases was calculated.

First, we estimated the cumulative incidence of cancer ignoring the competing risk of death (i.e., censoring death). Here, the cumulative incidence of cancer at time t is simply the complement of the survival function of time until cancer (183). Next, we estimated the cumulative incidence of cancer accounting for the competing risk of death. Here, the cumulative incidence is defined as the probability of cancer given that an individual has survived up to time t without cancer or has had a competing event of death prior to time t. In contrast to the survival function that eliminates individuals who experience the competing event from the risk set, the competing risks model specifies that individuals who experience the competing event remain in the risk set for the event of interest. Thus, the risk set includes two distinct groups: those who have not failed from any cause and those who have previously failed from a competing event (184, 185). The cumulative incidence analysis that ignored competing risks was conducted with

standard software (SAS *proc lifetest* and *phreg* functions), whereas the analysis that accounted for competing risks required a customized SAS program (186).

In the analysis accounting for the competing risk of death, crude and standardized cumulative incidence estimates were stratified by several patient characteristics. We used inverse probability (IP) of exposure weights to standardize each stratum to the total study sample at baseline with respect to age, sex, race, Hispanic ethnicity, primary cause of ESRD, and calendar year of dialysis initiation, as appropriate. IP exposure weights were calculated as the marginal proportion of patients receiving the level of exposure they received (i.e., the stabilizing factor) divided by the predicted probability of receiving that exposure from the linear-logistic model. For each patient characteristic, we fit both a null linear-logistic model to calculate the marginal proportion of exposure and a full linear-logistic model to calculate the predicted probability of a particular exposure level for each combination of covariates.(186) Age was modeled using restricted quadratic splines with 4 knots placed at the 5th, 35th, 65th, and 95th percentiles of the age distribution in the study sample (187). Supplemental Table 17 (Appendix A) presents descriptive characteristics of the IP exposure weights.

We also estimated IP of censoring weights to account for informative censoring. First, we partitioned the 5-year follow-up period into quintiles defined by the distribution of when patients became lost to follow-up (i.e., 1.12, 1.66, 2.31, 3.30 years from dialysis initiation). Then we fit both a null pooled linear-logistic model to calculate the marginal probability of remaining uncensored and a full pooled linear-logistic model to calculate the adjusted predicted probability of remaining uncensored during the quintile of follow-up time. IP censoring weights were constructed as defined above, with adjustment for the same covariates (186). We obtained 95% CIs as a measure of uncertainty due to sampling error using a nonparametric bootstrap. Specifically, we resampled 482,510 patients at random with replacement with equal probability 200 times. The standard deviation of the 200 bootstrap resamples was used as an estimate of the standard error. SAS software, version 9.3 (Cary, NC) was used for all analyses.

2. Annual incidence rates of cancer (aim 1c)

For incident and prevalent dialysis patients at risk for cancer in the 1996, 2000, 2004 and 2009 cohorts, the number and percentage of patients were calculated by patient characteristics.
The crude annual incidence rates of overall and site-specific cancer were calculated by dividing the total number of observed cancer diagnoses during the year by the total patient time at risk. Rates, expressed as cancer diagnoses per 100,000 patients per year, were calculated overall and within strata of patient characteristics. To derive cancer rates adjusted for temporal trends, standardized mortality ratio (SMR)-weighted models were created with a weight of 1 for patients diagnosed with cancer in 2000 (the comparator group) and a weight of (p/[1- p]) for patients diagnosed with cancer in all other years (1996-1999 and 2001-2009).

A multivariable logistic regression model was fit to estimate the propensity score, p, where p represents the probability that the patient was diagnosed with cancer in 2000 given a combination of covariates used for adjustment. All incidence rates were adjusted for age at dialysis initiation, sex, race, ethnicity, primary cause of ESRD, comorbid conditions, functional status and years on dialysis. The Joinpoint Regression Program (version 4.0.4, NCI) was used to model trends of adjusted annual incidence rates over the entire study period (1996-2009). The Joinpoint Program uses permutation tests to find a best fit of regression model with the smallest number of "joinpoints" which are distinct linear segments that differ statistically in their slopes. We calculated annual percentage change (APC) and 95% CIs, from a log-linear model in the joinpoint analysis using the logarithm of observed rates (188).

Age-standardized incidence rates were calculated for the U.S. general population (SEER data) using the age distribution of our study population of hemodialysis patients with cancer (USRDS data). Rates were adjusted to the 2000 U.S. population.

3. Sensitivity analysis (aims 1a-c)

A sensitivity analysis was conducted to assess the influence of various incident and prevalent cancer definitions. Incident and prevalent cancer were redefined using the claims-based cancer definitions 2 and 3 (Table 7), as described by Setoguchi et al (179). Information from the Medical

Evidence Form Report will not be used in the analysis because of missing data (~10%) and the inability to distinguish benign tumors and non-melanoma skin cancer.

F. Statistical analysis for aim 2

We calculated descriptive statistics on the demographic and clinical characteristics of the population by year. We also described the annual distribution of cancer diagnoses by cancer site. To describe trends in anemia treatment by calendar quarter, we used generalized linear models to generate unadjusted and adjusted estimates. Specifically, we used logistic regression models to calculate quarterly estimates of the proportion of patients that used ESAs or transfusion, linear regression models to calculate mean quarterly estimates of EPO dose (units/month) and hemoglobin levels, and Poisson regression models to calculate estimates of the mean number of transfusion days per year. Since EPO dose and hematocrit levels were only reported with the administration of ESAs, these analyses were restricted to patients who received ESAs at least once during the quarter. Calendar quarter was treated as a categorical variable in the models to relax the assumption of linearity. The results section presents plots of the adjusted estimates for ESA use, EPO dose, transfusion use, number of transfusion days per year, and hemoglobin levels, which are population marginal means that account for changes over time in demographic (age, sex, race, ethnicity) and clinical characteristics (primary cause of ESRD, dialysis vintage) (189). We stratified estimates by cancer site and chemotherapy use (primary analysis), as well as several additional demographic and clinical characteristics (secondary analysis). We further stratified the analyses by using three categories of cancer site: a) all cancer sites; b) the most common solid tumors in our study population (i.e., cancers of the prostate, female breast, colon/rectum, lung/bronchus, kidney/renal pelvis, bladder, and pancreas); and c) hematologic malignancies (i.e., Hodgkin lymphoma, non-Hodgkin lymphoma (NHL), leukemia, and myeloma). We performed complete case analyses since covariate missingness was less than 1% (i.e., ethnicity (n=134) and race (n=28)).

CHAPTER IV. RESULTS

A. Cancer incidence among U.S. Medicare end-stage renal disease patients on hemodialysis, 1996-2009.

1. Introduction

Despite reports of increased risk of many cancers in the dialysis population (15-17, 22), the contemporary cancer burden has not been adequately characterized among patients with end-stage renal disease (ESRD) receiving dialysis. Existing estimates of cancer incidence in the ESRD population are outdated, primarily focused on all cancer sites combined or a limited number of cancer sites, determined from small, select groups of dialysis patients, and failed to account for competing risks of death (15, 16, 18-39). Furthermore, information is sparse on cancer incidence in dialysis patients by subgroups such as age, sex, race, ethnicity, primary cause of ESRD, and years on dialysis.

The objective of this study was to describe the cancer burden among ESRD patients receiving hemodialysis, overall and among relevant patient subgroups. Using data from the United States Renal Data System (USRDS), a national registry including all patients in Medicare's ESRD program, we described temporal trends in cancer incidence rates (1996-2009). In addition, we estimated the cumulative incidence of all cancers combined as well as site-specific cancers since dialysis initiation. We used competing risk methods to avoid inflating the estimated risk of cancer by censoring the deaths that occurred prior to cancer diagnosis (i.e., the event of interest) (40-43).

2. Methods

Data and population

We used data from the USRDS, a national registry that includes all patients in Medicare's ESRD program. The study population included ESRD patients ≥ 18 years of age who received in-center hemodialysis between April 1, 1995 and December 31, 2010. The study population was restricted to individuals with Medicare as their primary payer and both parts A and B coverage in order to ensure

collection of complete claims data on patients. Patients were excluded for a history of kidney transplantation, HIV/AIDS, or a malignancy-related primary cause of ESRD.

The study population was limited to patients who remained alive without a cancer diagnosis for at least 9 months after dialysis initiation. This time period was selected because three months after the first service date is the amount of time required to process Medicare eligibility/enrollment forms and to ensure stability in dialysis treatment modality (190). A subsequent six month period (i.e., the baseline period) was required for assessment of comorbidities and functional status, as done previously (191-193). History of kidney transplant evaluation was defined as a claim assigned a V-code of V72.83 (other specified preoperative examination) during the 6-month baseline period. The sensitivity and specificity of code V72.83 has not been reported.

Assessment of Incident Cancers

We identified incident site-specific cancers using *International Classification of Diseases, 9th revision, Clinical Modification* (ICD-9-CM) diagnosis codes from inpatient and outpatient Medicare claims. Supplementary Table 16 (Appendix A) presents the ICD-9-CM codes used in the site-specific cancer definitions. The claims-based algorithm used to define site-specific cancers required ≥ 2 ICD-9-CM diagnosis codes within 6 months (179). Date of cancer onset was defined as the first date of a cancer-related diagnosis code in the claims data. *In situ* carcinomas were included for two sites (i.e., breast and bladder), in accordance with the Surveillance Epidemiology and End Results (SEER) Program (180). Secondary tumors, benign tumors, and non-melanoma skin cancers were excluded from the analysis. Only the first cancer diagnosis after dialysis initiation was included as an event. Patients diagnosed with multiple cancer sites on the same date were included in each site-specific analysis.

Annual Incidence Rates of Cancer

We used 14 annual cohorts (i.e., 1996-2009) of prevalent hemodialysis patients that met eligibility criteria by January 1 to calculate incidence rates of cancer. All ESRD patients who initiated in-center hemodialysis on or before April 1 of the previous year and remained alive until January 1 of the current year were eligible for that yearly cohort. Patients were eligible for multiple cohorts. Patients with cancer

during the 6 month baseline period (i.e., July 4 to December 31 of prior year) were excluded from that yearly cohort. Patients were observed from 9 months post-dialysis initiation to the first cancer diagnosis. Patients were censored due to the loss of Medicare as primary payer status, change of modality, lost-to-follow-up, kidney transplantation, death or end of study (December 31).

The crude annual incidence rates of overall and site-specific cancer were calculated by dividing the total number of observed cancer diagnoses during the year by the total patient time at risk. Rates, expressed as cancer diagnoses per 100,000 patients per year, were calculated overall and within strata of patient characteristics. To derive cancer rates adjusted for secular trends, standardized mortality ratio (SMR)-weighted models were created with a weight of 1 for patients diagnosed with cancer in 2000 (the comparator group) and a weight of (p/[1-p]) for patients diagnosed with cancer in all other years (1996-1999 and 2001-2009).

A multivariable logistic regression model was fit to estimate the propensity score, p, where p represents the probability that the patient was diagnosed with cancer in 2000 given a combination of covariates used for adjustment. All incidence rates were adjusted for age at dialysis initiation, sex, race, ethnicity, primary cause of ESRD, comorbid conditions, functional status and years on dialysis. The Joinpoint Regression Program (version 4.0.4, NCI) was used to model trends of adjusted annual incidence rates over the entire study period (1996-2009). The Joinpoint Program uses permutation tests to find a best fit of regression model with the smallest number of "joinpoints" which are distinct linear segments that differ statistically in their slopes. We calculated annual percentage change (APC) and 95% CIs, from a log-linear model in the joinpoint analysis using the logarithm of observed rates (188).

Age-standardized incidence rates were calculated for the U.S. general population (SEER data) using the age distribution of our study population of hemodialysis patients with cancer (USRDS data). Rates were adjusted to the 2000 U.S. population.

Cumulative Incidence Estimates of Cancer

We used a retrospective cohort of incident patients who initiated in-center hemodialysis between April 1, 1995 and April 5, 2010 to estimate the cumulative incidence of cancer. The retrospective cohort design spanned the 5 years after dialysis initiation, including a 3-month eligibility period (to process

Medicare eligibility/enrollment forms and to ensure stability in dialysis treatment modality), a subsequent 6-month baseline period (to assess comorbidities and functional status), and a follow up period for up to 5 years after dialysis initiation. Time at risk was measured from 9 months post-dialysis initiation to the first of the following: the event of interest (i.e., cancer diagnosis); or censoring (i.e., cancer diagnosis at another site; renal replacement therapy modality change to peritoneal dialysis or kidney transplantation; end of Medicare as primary payer status; lost-to-follow-up; 5 years since dialysis initiation; end of study on December 31, 2010; or death, as appropriate).

First, we estimated the cumulative incidence of cancer ignoring the competing risk of death (i.e., censoring death). Here, the cumulative incidence of cancer at time *t* is simply the complement of the survival function of time until cancer (183). Next, we estimated the cumulative incidence of cancer accounting for the competing risk of death. Here, the cumulative incidence is defined as the probability of cancer given that an individual has survived up to time *t* without cancer or has had a competing event of death prior to time *t*. In contrast to the survival function that eliminates individuals who experience the competing event from the risk set, the competing risks model specifies that individuals who experience the competing event remain in the risk set for the event of interest. Thus, the risk set includes two distinct groups: those who have not failed from any cause and those who have previously failed from a competing event (184, 185). The cumulative incidence analysis that ignored competing risks was conducted with standard software (SAS *proc lifetest* and *phreg* functions), whereas the analysis that accounted for competing risks required a customized SAS program (186).

In the analysis accounting for the competing risk of death, crude and standardized cumulative incidence estimates were stratified by several patient characteristics. We used inverse probability (IP) of exposure weights to standardize each stratum to the total study sample at baseline with respect to age, sex, race, Hispanic ethnicity, primary cause of ESRD, and calendar year of dialysis initiation, as appropriate. IP exposure weights were calculated as the marginal proportion of patients receiving the level of exposure they received (i.e., the stabilizing factor) divided by the predicted probability of receiving that exposure from the linear-logistic model. For each patient characteristic, we fit both a null linear-logistic model to calculate the marginal proportion of exposure and a full linear-logistic model to calculate the predicted probability of a particular exposure level for each combination of covariates (186). Age was

modeled using restricted quadratic splines with 4 knots placed at the 5th, 35th, 65th, and 95th percentiles of the age distribution in the study sample (187). Supplemental Table 17 (Appendix A) presents descriptive characteristics of the IP exposure weights.

We also estimated IP of censoring weights to account for informative censoring. First, we partitioned the 5-year follow-up period into quintiles defined by the distribution of when patients became lost to follow-up (i.e., 1.12, 1.66, 2.31, 3.30 years from dialysis initiation). Then we fit both a null pooled linear-logistic model to calculate the marginal probability of remaining uncensored and a full pooled linear-logistic model to calculate the adjusted predicted probability of remaining uncensored during the quintile of follow-up time. IP censoring weights were constructed as defined above, with adjustment for the same covariates (186). We obtained 95% CIs as a measure of uncertainty due to sampling error using a nonparametric bootstrap. Specifically, we resampled 482,510 patients at random with replacement with equal probability 200 times. The standard deviation of the 200 bootstrap resamples was used as an estimate of the standard error. SAS software, version 9.3 (Cary, NC) was used for all analyses.

3. Results

Annual Incidence Rates of Cancer

Table 9 describes characteristics of the study population of incident and prevalent dialysis patients for selected years of the study period. Over time, the number of patients per cohort increased. Patients were more likely to be male, white, or have diabetes as the primary cause of ESRD in recent cohorts. In addition, mean age and mean duration of dialysis increased over the study period.

Adjusted annual incidence rates of cancer are presented in Figure 7. We observed a constant rate of incident cancer diagnoses for all sites from 1996-2009, from 3923 to 3860 cases per 100,000 person years [annual percentage change (APC), 0.1; 95% confidence interval (CI), -0.4, 0.6]. Between 1996-2009, incidence rates increased for cancers of the kidney/renal pelvis, decreased for cancers of the colon/rectum, lung/bronchus, pancreas, and other sites (1996-2003 only), and remained constant for cancers of the prostate, female breast, bladder, NHL, and other sites (2003-2009 only). Across all calendar years, cancers of the prostate and female breast were the most commonly diagnosed,

representing 1195 and 718 cases per 100,000 person years in 2009, respectively. Crude rates are presented in Supplemental Figure 17 (Appendix A).

Figure 8 presents adjusted incidence rates for the four most frequently diagnosed cancer sites stratified by subgroups. Adjusted incidence rates were much higher among older patients, males, or whites and less common among patients with diabetes as the primary cause of ESRD. Prostate cancer had the highest incidence rate across all but four strata (i.e., <65 years, female, non-white, or diabetes as primary cause of ESRD).

Between 1996-2009, the unadjusted incidence rate estimate for all cancer sites was almost three times higher in the dialysis population compared to the age-standardized rate in the U.S. general population (3788 vs. 1348 cases/100,000 person-years). Similarly, incidence rate estimates were higher in the dialysis population for all eight of the most common incident site-specific cancers diagnosed in the study population. Rates were most elevated for cancers of the kidney/renal pelvis (417 vs. 51 cases/100,000 person-years) and pancreas (168 vs. 43 cases/100,000 person-years) compared to the U.S. general population (Appendix A, Supplemental Table 13).

Cumulative Incidence Estimates of Cancer

Of 482,510 patients who met study eligibility requirements (Appendix A, Supplemental Figure 18), 48.4% were female, 62.7% were white, 32.0% were African American, and 13.1% were Hispanic. The most common reported causes of ESRD were diabetes (50.4%) and hypertension (30.5%). Median age at dialysis initiation was 67 years (Appendix A, Supplemental Table 14). Median length of follow-up after dialysis initiation was 2.5 years.

During 988,395 person-years of follow-up between 9 months and 5 years after dialysis initiation, 37,128 patients were diagnosed with cancer. A total of 217,773 (45.1%) patients died prior to receipt of a cancer diagnosis. Twelve percent (n=57,345) of the 482,510 patients were censored alive and cancer-free before 5-years of follow-up or December 31, 2010.

The 5-year crude cumulative incidence of any cancer was substantially lower in the analysis that did not censor deaths (9.48%; 95% CI, 9.39% to 9.57%) compared to the analysis that censored deaths

(13.86%; 95% CI, 13.71% to 14.01%) (Table 10). Figure 9 illustrates the divergence of these cumulative incidence estimates with increasing time since dialysis initiation.

Table 11 presents crude and standardized 5-year cumulative incidence estimates of any cancer accounting for death as a competing risk, stratified by patient characteristics. Figure 10 and supplemental figure 19 (Appendix A) present standardized and crude cumulative incidence estimates accounting for death as a competing risk, by time from dialysis initiation, respectively. Results were not meaningfully altered when drop-out was not accounted for in the analysis (~1% change) (results not shown). After accounting for case-mix characteristics measured at baseline and the competing risk of death, the 5-year cumulative incidence of any cancer was higher among the following patient subgroups: ≥ 65 years at dialysis initiation (11.28%); males (10.93%); non-whites (9.79%); non-Hispanics (9.65%); primary ESRD cause other than diabetes (hypertension, 10.39%; other, 11.54%; glomerulonephritis, 12.01%); dialysis initiation between 2003-2010 (9.75%); and history of kidney transplant evaluation (11.67%). Supplemental figure 4 presents crude cumulative incidence estimates that censored deaths, stratified by patient characteristics.

Table 10 and Supplemental Table 15 (Appendix A) present results from more and less common site-specific cancer analyses (i.e., ≥150 and <150 site-specific cancer cases over the study period). The most frequently diagnosed cancer sites were prostate (n=5,396), lung/bronchus (n=4,969), colon/rectum (n=4,360), female breast (n=3,688), kidney/renal pelvis (n=2,805), bladder (n=2,216), non-Hodgkin lymphoma (n=1,284), leukemia (n=1,077), myeloma (n=1,024), and pancreas (n=928). For all site-specific cancers, the 5-year cumulative incidence estimate was lower in the competing risks analysis compared to the analysis that censored deaths.

4. Discussion

We conducted a large national study of ESRD patients undergoing hemodialysis to describe the incidence of cancer in this population. After accounting for the substantial competing risk of death in the ESRD population undergoing dialysis, we observed a high cumulative incidence of cancer, with over 9% of the ESRD population being diagnosed with cancer over a 5-year period after initiating dialysis. Between 1996-2009, we observed constant rates of incident cancer diagnoses for all sites combined, but

identified trends of increasing and decreasing incidence rates for some site-specific cancers. There are no previous population-based estimates of cumulative incidence or annual incidence rates of cancer in the dialysis population, therefore these estimates provide important new information on the cancer burden in this unique population. In addition, our results demonstrate varying patterns of cancer incidence in subgroups, after accounting for measured patient characteristics.

Our 5-year cumulative incidence estimate of 9.48% depends on the risk of both cancer and the competing event of death that precludes development of cancer. In contrast, the analysis that censored deaths yielded a much higher 5-year cumulative incidence estimate of 13.86%, representing the risk of cancer in the dialysis population assuming that all deaths could be prevented. This estimate of cancer risk was higher than the estimate that accounted for the competing risk of death because standard survival analysis techniques implicitly allow for some censored deaths to later become cancer cases after death. The competing risk approach provides an estimate of the total amount of cancer diagnoses that will occur in the population, which is valuable for health care policy and planning in the dialysis population characterized by very high mortality (194).

We observed higher incidence rates of cancer in the dialysis population compared to the U.S. general population, suggesting that ESRD patients are uniquely at risk for developing cancer while receiving hemodialysis treatment. Our findings are consistent with previous population-based studies of cancer in the dialysis population which have reported increased risk for any cancer (SIR range, 1.2-2.0) and several site-specific cancers compared to the general population (15, 16, 22). One exception is a recent SEER-Medicare study restricted to patients >65 years that reported no increased overall risk of cancer in ESRD patients compared to the general population (23). This discrepancy may be due to inadvertent inclusion of non-ESRD patients with less severe kidney disease, with reportedly lower risk of cancer than ESRD patients on dialysis (16).

Several explanations have been proposed for increased cancer incidence in the dialysis population, including ESRD-associated immunodeficiency and nutritional abnormalities (130-138). Excess cancer risk may also be due to an interaction of uremic and dialysis-induced immune dysfunction with established risk factors such as UV radiation, tobacco, or alcohol (16). Recently, there has been a focus on the potential role of erythropoietin stimulating agents (ESAs), commonly used to manage anemia, in

carcinogenesis. ESAs are known to activate erythropoietin receptors on the surface of cancer cells. Additionally, erythropoietin-induced angiogenesis may promote tumor growth (1, 139). Yet, we did not observe temporal trends in overall cancer incidence that correlate with the documented rise and fall of ESA use and dose (123). Instead, we observed constant incidence rates over the study period, which suggests that ESA therapy is not related to increased cancer incidence.

One explanation for subgroup differences in 5-year cumulative incidence estimates of cancer could be differences in mortality. In our analysis that censored deaths, we observed that 5-year cumulative incidence was similar by era of dialysis initiation. In contrast, the competing risks approach (which allowed patients who died to remain in the denominator of patients at risk) yielded a higher 5-year cumulative incidence estimate among patients who initiated dialysis in 2003-2010 versus 1995-2002. This suggests that higher cancer incidence in the most recent era is due to improved survival in the dialysis population. We observed a similar pattern in the comparison between patients with and without kidney transplant evaluation, in which patients with evaluation had higher cancer incidence due to longer survival.

Another explanation for higher 5-year cumulative incidence of cancer among patients who received kidney transplant evaluation, despite a healthier profile than patients who did not receive evaluation, are unexpected cancer diagnoses yielded by intensive medical workup involving comprehensive cancer screening (70). Our finding should be interpreted cautiously due to unknown validity of the code used to define kidney transplant evaluation. In addition, the diffusion curve was a monotonic linear increase in annual use over the study period (i.e., 0% to 10%), raising concern about reliability of the kidney transplant evaluation code over time.

Our findings are subject to several limitations. First, claims-based cancer definitions have not been validated in the ESRD population. Second, the possibility of overestimating cancer incidence due to misclassification of prevalent cases as incident cases cannot be excluded. However, identification of prevalent cases of cancer during the 6-month baseline period minimized the possibility of misclassification. Third, use of claims-based definitions of cancer made it impossible to determine whether cancers identified as incident cases were truly new primaries, metastases, or histories of cancer miscoded as new primaries. Lastly, information on cancer risk factors was absent from the USRDS data.

Strengths of our study include more than a decade of data on the large and representative population of U.S. ESRD patients on hemodialysis. The large sample size allowed characterization of cancer incidence within subgroups. Additionally, competing risks methodology is an innovative approach appropriate for the inherent competing risks problem in the dialysis population due to high annual mortality.

There are currently no standard recommendations for cancer screening (i.e., KDIGO, KDOQI) in the dialysis population. Our study demonstrates that overall risk of cancer among dialysis patients is higher than among the general population. Yet, the life-expectancy of individuals receiving dialysis is lower than the general population, and previous cost-effectiveness analyses have suggested general cancer screening would add minimal days of life saved per person (2, 140, 141). In practice, cancer screening in dialysis patients has been provided on an individualized patient-focused manner based on the patient's cancer risk factors, expected survival, and transplant status (141). Our findings highlight the need to potentially reevaluate cancer screening practices among certain subgroups. Furthermore, targeted screening for certain cancer types should be considered.

In conclusion, we reported a high and constant overall burden of cancer among ESRD patients receiving hemodialysis, with certain subgroups of the population exhibiting a particularly elevated cancer risk.

Table 9. Demographic and clinical characteristics of annual study cohorts at risk for cancer in 1996, 2000, 2004, and 2009

	Year[a]			
Characteristics	1996	2000	2004	2009
Patients (n)	88,676	110,897	142,142	164,214
Age at dialysis initiation (years), mean (sd)	61.3 (14.8)	62.1 (14.7)	62.7 (14.6)	62.5 (14.5)
Age at dialysis initiation (years)				
18-44	15.0	13.7	12.2	11.8
45-64	35.8	36.0	37.6	40.4
65-74	30.3	28.6	26.7	25.1
≥75	18.9	21.7	23.5	22.7
Male sex	49.5	50.3	51.5	52.6
White race	51.4	51.4	52.4	53.0
Reported cause of ESRD				
Diabetes	35.4	42.3	46.2	48.4
Hypertension	32.3	30.5	30.0	29.6
Glomerulonephritis	13.1	13.0	11.6	10.3
Other	19.2	14.2	12.3	11.7
Duration of dialysis (years), mean (sd)	3.5 (3.4)	3.6 (3.3)	3.6 (3.3)	3.9 (3.5)
Duration of dialysis (years)				
0-1	30.7	30.2	28.3	25.1
2-5	51.3	50.3	51.5	51.3
>5	18.0	19.5	20.3	23.6
History of kidney transplant evaluation				
No	100.0	95.7	93.8	90.0
Yes	0.0	4.3	6.7	10.0

[a]January 1 of respective years.

Table 10. The crude 5-year cumulative incidence of site-specific cancers among U.S. hemodialysis patients

Cancer site	No. of patients	5-year cumulative incidence % (95% CI) Death treated as censoring event	Death treated as competing event
Lip, oral cavity, and pharynx			
Tongue	156	0.07 (0.06, 0.08)	0.04 (0.04, 0.05)
Mouth	191	0.08 (0.07, 0.09)	0.05 (0.04, 0.06)
Pharynx	183	0.08 (0.07, 0.09)	0.05 (0.05, 0.06)
Digestive system			
Esophagus	369	0.16 (0.14, 0.17)	0.10 (0.09, 0.11)
Stomach	590	0.25 (0.23, 0.27)	0.16 (0.15, 0.18)
Colon/rectum	4,360	1.76 (1.70, 1.82)	1.18 (1.15, 1.22)
Liver	865	0.36 (0.33, 0.39)	0.24 (0.22, 0.26)
Gallbladder	202	0.08 (0.07, 0.10)	0.06 (0.05, 0.06)
Pancreas	928	0.39 (0.36, 0.42)	0.26 (0.24, 0.28)
Respiratory system			
Larynx	318	0.13 (0.11, 0.14)	0.09 (0.08, 0.10)
Lung/bronchus	4,969	2.03 (1.97, 2.09)	1.36 (1.32, 1.39)
Bone and cartilage	206	0.09 (0.07, 0.10)	0.06 (0.05, 0.07)
Skin/connective tissue[a]			
Melanoma	872	0.36 (0.33, 0.39)	0.24 (0.22, 0.26)
Connective & other soft tissue	285	0.12 (0.10, 0.13)	0.08 (0.07, 0.09)
Reproductive and genitourinary			
Breast (female) [b]	3,688	1.48 (1.43, 1.53)	1.00 (0.97, 1.03)
Cervix uteri	345	0.14 (0.12, 0.15)	0.09 (0.08, 0.10)
Corpus and uterus	551	0.23 (0.21, 0.25)	0.15 (0.14, 0.16)
Ovary	341	0.14 (0.12, 0.16)	0.09 (0.08, 0.10)
Prostate	5,396	1.98 (1.93, 2.04)	1.41 (1.37, 1.44)
Bladder [b]	2,216	0.84 (0.80, 0.88)	0.59 (0.56, 0.61)
Kidney/renal pelvis	2,805	1.14 (1.09, 1.19)	0.76 (0.73, 0.79)
Neurological			
Brain and other nervous system	560	0.23 (0.21, 0.25)	0.15 (0.14, 0.17)
Endocrine			
Thyroid	337	0.14 (0.12, 0.16)	0.09 (0.08, 0.10)
Hematological			
Non-Hodgkin lymphoma	1,284	0.51 (0.48, 0.55)	0.35 (0.33, 0.37)
Myeloma	1,024	0.40 (0.37, 0.43)	0.27 (0.26, 0.29)
Leukemia	1,077	0.43 (0.40, 0.46)	0.29 (0.27, 0.31)
Ill-defined and unspecified	1,941	0.81 (0.77, 0.85)	0.53 (0.51, 0.56)
All sites	37,128[c]	13.86 (13.71, 14.01)	9.48 (9.39, 9.57)

Data presented for cancer sites with ≥150 cases over the study period. Supplemental Table 15 (Appendix A) presents results for cancer sites with <150 cases.

[a]Excludes non-melanoma skin cancer

[b]Malignant and carcinoma *in situ*

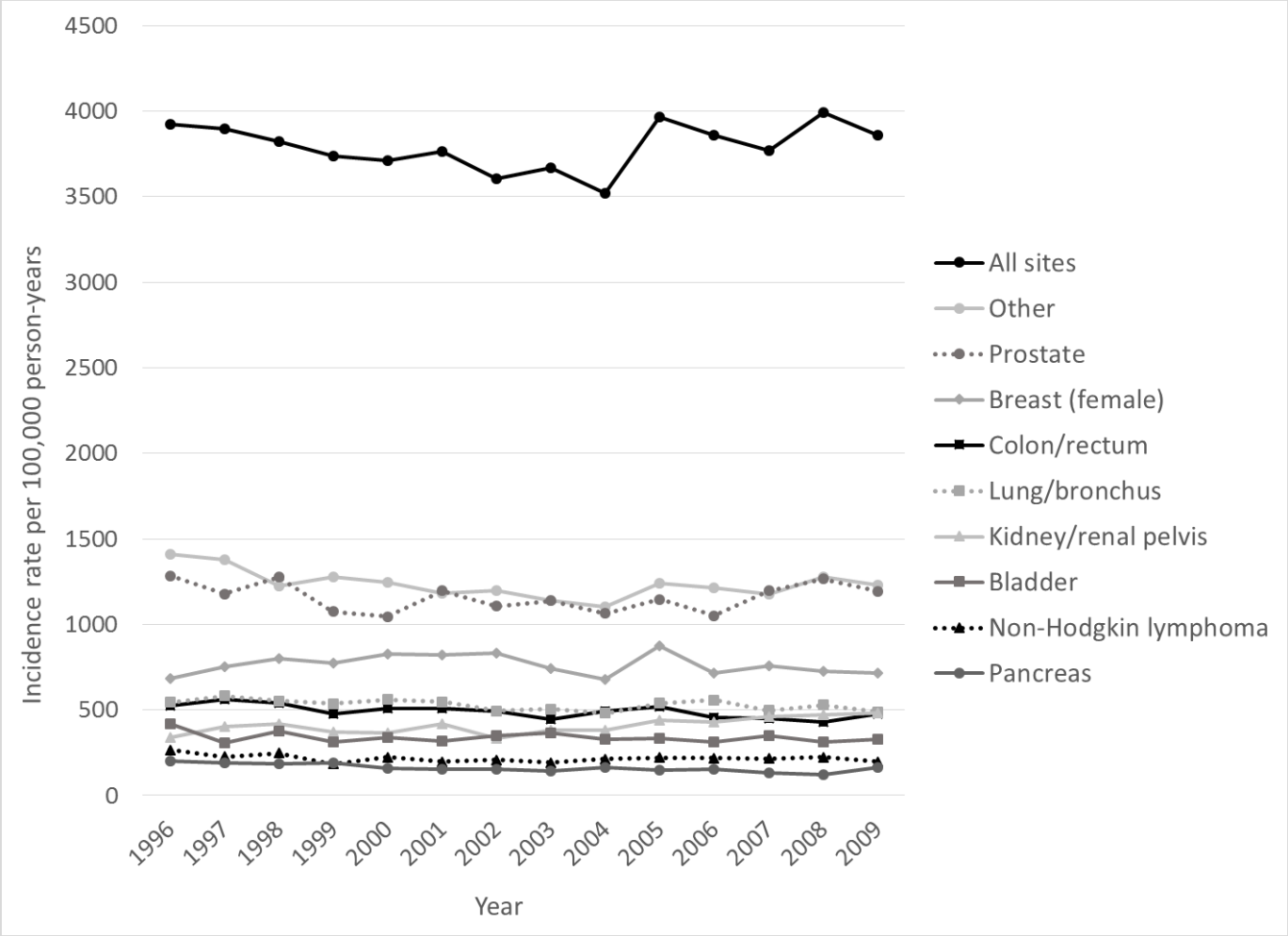
[c]The total number of patients with site-specific cancer diagnoses exceeds the total number of patients with any cancer because 667 patients were diagnosed with multiple cancer sites on the same date.

Table 11. Crude and standardized 5-year cumulative incidence estimates of any cancer, accounting for the competing risk of death, by demographic and clinical characteristics

	5-year cumulative incidence % (95% CI)	
	Crude	Standardized[a]
Age at dialysis initiation		
18-44 years	3.91 (3.70, 4.11)	3.81 (3.55, 4.06)
45-64 years	7.83 (7.65, 8.00)	8.07 (7.89, 8.25)
≥ 65 years	11.17 (11.05, 11.29)	11.28 (11.15, 11.42)
Sex		
Male	10.59 (10.46, 10.71)	10.85 (10.73, 10.99)
Female	8.23 (8.10, 8.36)	8.15 (8.01, 8.28)
Race		
White	9.75 (9.62, 9.87)	9.36 (9.23, 9.48)
Non-white	9.05 (8.91, 9.19)	9.79 (9.57, 10.00)
Ethnicity		
Hispanic	7.17 (6.92, 7.41)	8.57 (7.84, 9.30)
Non-Hispanic	9.83 (9.73, 9.93)	9.65 (9.54, 9.75)
Reported cause of ESRD		
Diabetes	8.14 (8.02, 8.26)	8.30 (8.18, 8.42)
Hypertension	10.78 (10.60, 10.97)	10.39 (10.19, 10.59)
Glomerulonephritis	10.52 (10.18, 10.87)	12.01 (11.59, 12.43)
Other	11.36 (11.05, 11.67)	11.54 (11.20, 11.89)
Calendar period of dialysis initiation		
1995-2002	9.26 (9.15, 9.37)	9.14 (9.02, 9.25)
2003-2010	9.65 (9.51, 9.79)	9.75 (9.60, 9.89)
History of kidney transplant evaluation		
No	8.90 (8.79, 9.00)	8.70 (8.59, 8.80)
Yes	10.93 (10.74, 11.12)	11.65 (11.44, 11.86)

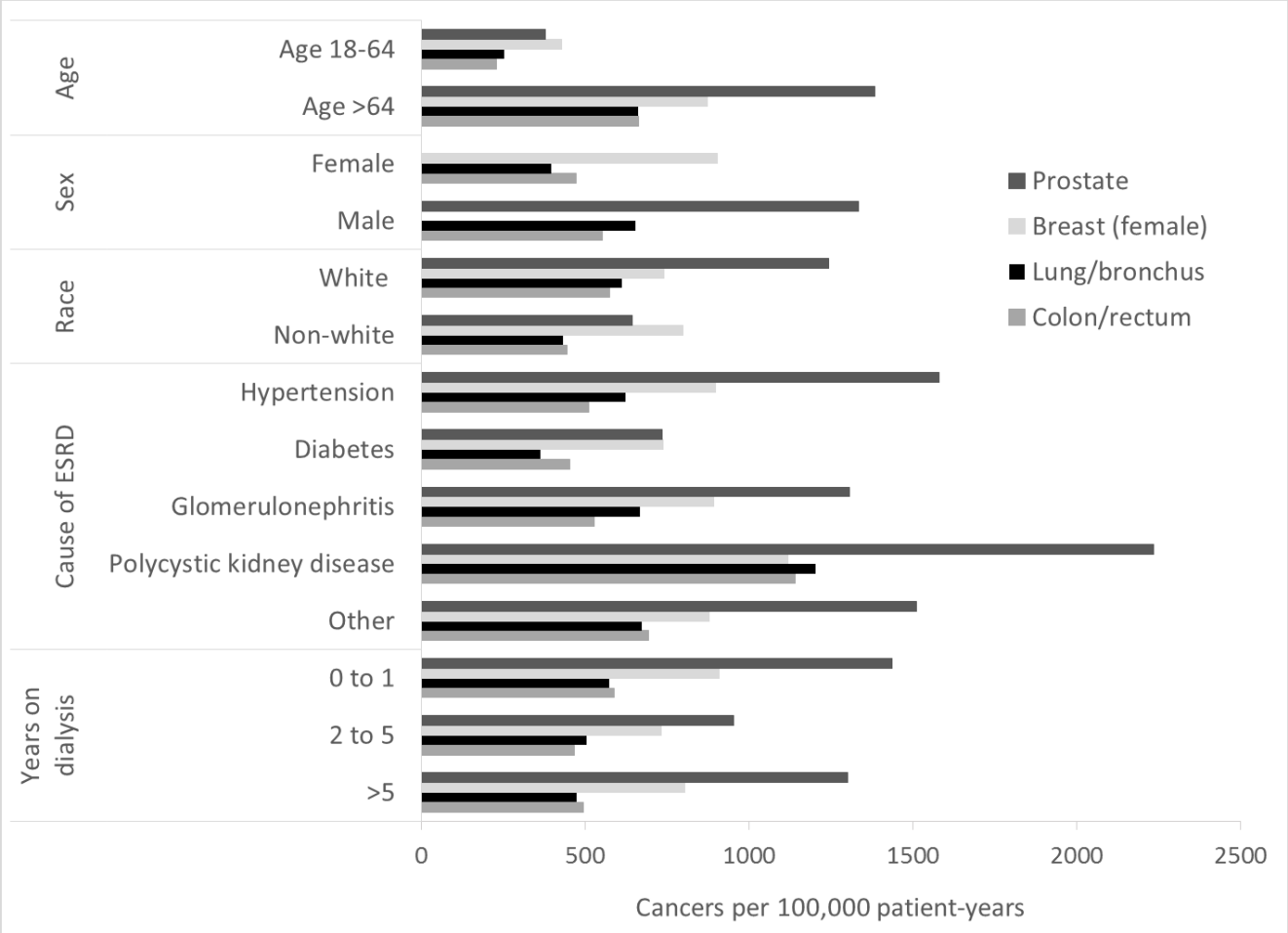
[a]Standardized cumulative incidence estimates account for case-mix characteristics (age at dialysis initiation, sex, race, ethnicity, primary cause of ESRD, year of dialysis initiation) measured at baseline using inverse-probability weights.

Figure 7. Adjusted annual incidence rates of cancer diagnoses among U.S. hemodialysis patients by cancer site, 1996-2009



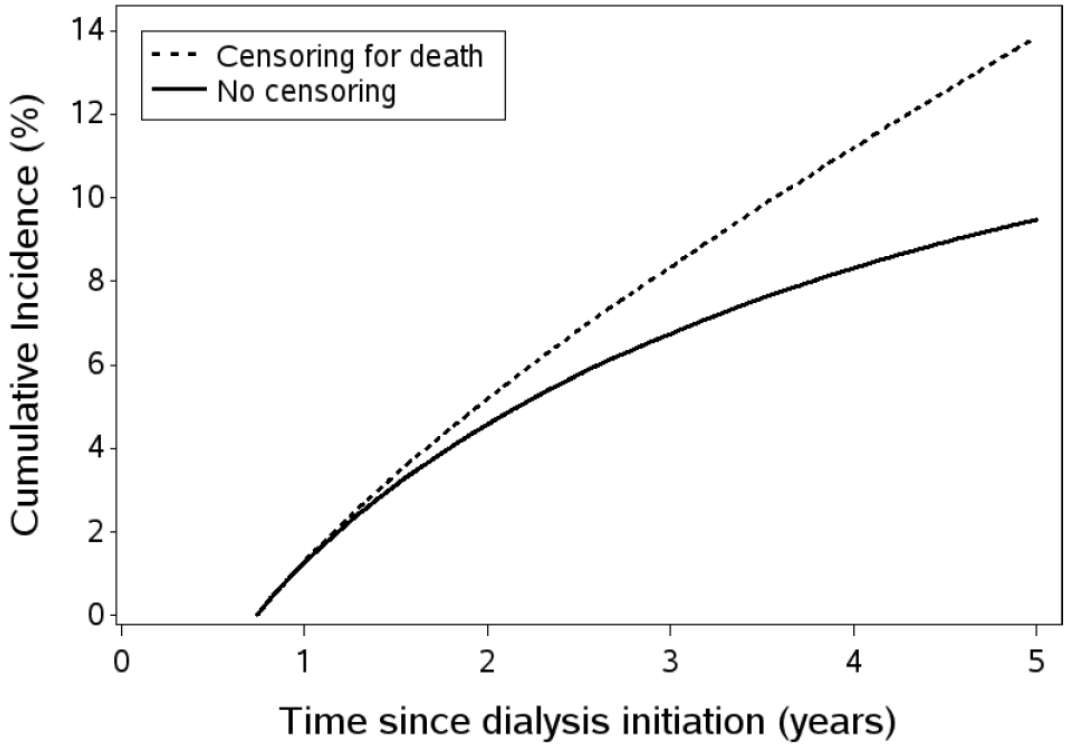
Adjusted annual incidence rates of cancer diagnoses for all sites remained constant [annual percentage change (APC), 0.1; 95% confidence interval (CI), -0.4, 0.6]. Incidence rates increased for cancers of the kidney/renal pelvis [APC, 2.0; 95% CI, 0.9, 3.2], decreased for cancers of the colon/rectum [APC, -1.4; 95% CI, -2.0, -0.8], lung/bronchus [APC, -0.8; 95% CI, -1.5, -0.1], pancreas [APC, -2.5; 95% CI, -3.8, -1.3], and other sites (1996-2003 only) [APC, -2.8; 95% CI, -4.3, -1.3], and remained constant for cancers of the prostate [APC, -0.2; 95% CI, -1.2, 0.8], female breast [APC, -0.3; 95% CI, -1.5, 0.9], bladder [APC, -1.1; 95% CI, -2.3, 0.1], NHL [APC, -1.1; 95% CI, -2.4, 0.2], and other sites (2003-2009 only) [APC, 1.7; 95% CI, -0.5, 3.9]. Rates were adjusted for age, sex, race, cause of ESRD, and years on dialysis. Incident cases were defined as the first cancer diagnosis of the year among patients without a history of cancer in the last 6 months of the previous calendar year. Other cancers were defined as all other site-specific cancers (e.g., cancers of the esophagus, stomach, liver, etc.). The sum of the site-specific cancer rates exceeds the rate for any cancer, due to patients diagnosed with multiple cancer sites on the same date.

Figure 8. Adjusted cancer incidence rates for cancers of the prostate, breast (female), lung/bronchus, and colon/rectum among U.S. hemodialysis patients, by demographic and clinical characteristics, 1996-2009



Incident cases were defined as the first cancer diagnosis of the year among patients without a history of cancer in the last 6 months of the previous calendar year. Rates were adjusted for age, sex, race, cause of ESRD, and years on dialysis. Age adjustment was performed for four strata (18-44, 45-64, 65-74, ≥75 years), although only two categories are presented due to limited case numbers in the 18-44 age group. The subgroup of interest was omitted from the adjustment for each respective subgroup category.

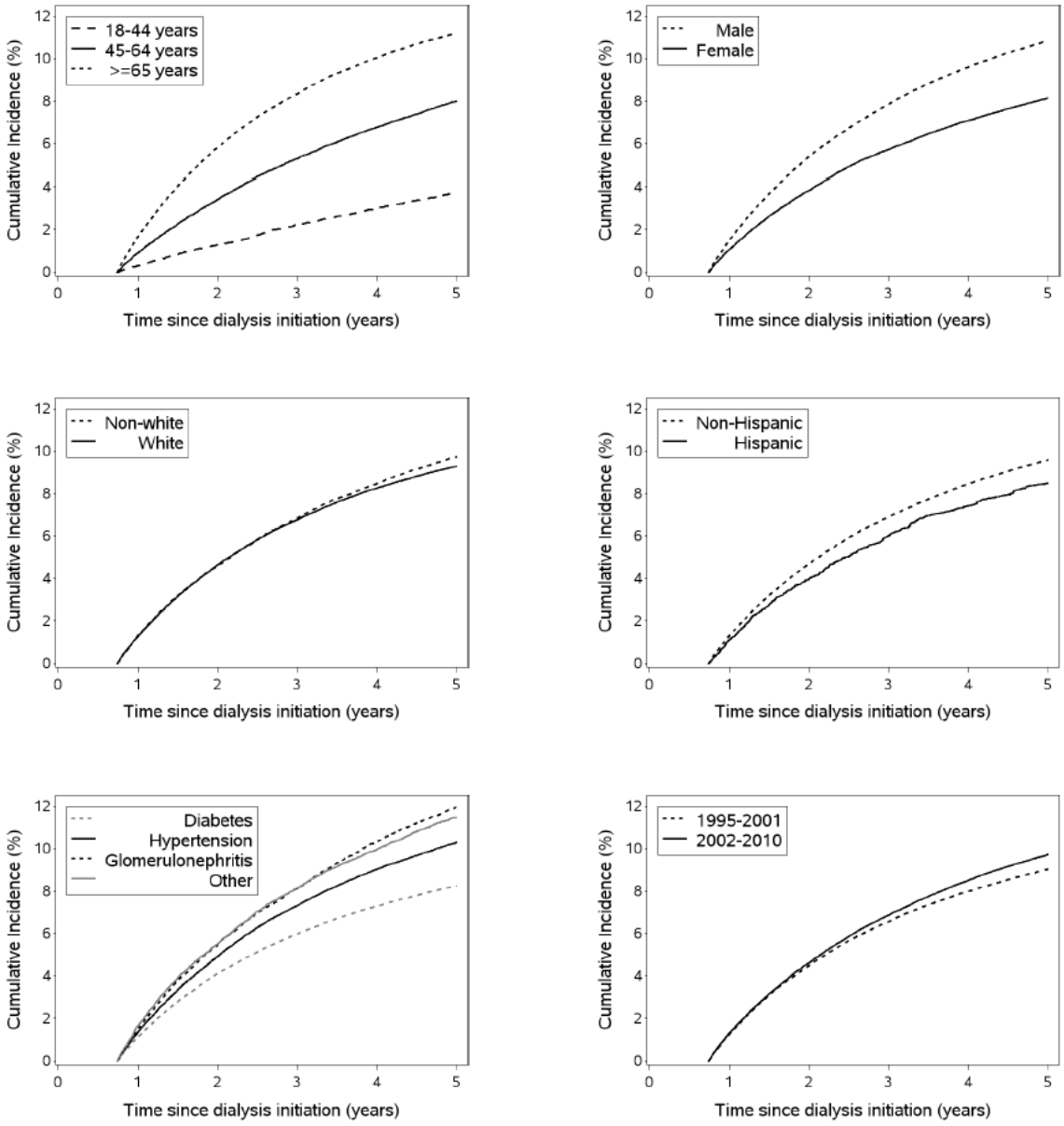
Figure 9. The crude cumulative incidence of any cancer by time since dialysis initiation among U.S. hemodialysis patients

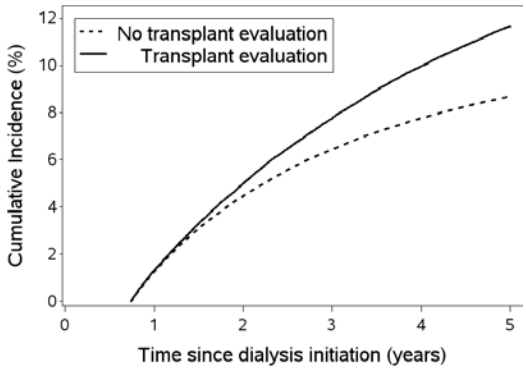


No. at risk	482,510	431,525	291,956	197,524	131,318	84,890
No. of cancer cases	0	6,061	20,477	28,656	33,854	37,128
No. of deaths	0	27,313	103,527	155,709	192,605	217,773

Cumulative incidence estimates were substantially lower in the analysis that treated death as a competing event versus a censoring event.

Figure 10. The standardized cumulative incidence of any cancer by time since dialysis initiation, accounting for the competing risk of death, by demographic and clinical characteristics





Figures were stratified by patient characteristics including (A) age at dialysis initiation; (B) sex; (C) race; (D) ethnicity; (E) primary cause of ESRD; (F) year of dialysis initiation; and (G) history of kidney transplant evaluation. Cumulative incidence functions were standardized to the total study population by combining the cumulative incidence function with inverse probability of exposure weights that account for case-mix characteristics (age at dialysis initiation, sex, race, ethnicity, primary cause of ESRD, year of dialysis initiation) measured at baseline.

B. Trends in use of erythropoiesis-stimulating agents and blood transfusions in U.S. hemodialysis patients with cancer

1. Introduction

Erythropoiesis-stimulating agents (ESAs) have been widely used for anemia management in both end-stage renal disease (ESRD) patients undergoing dialysis and cancer patients to increase hemoglobin levels, reduce the need for red blood cell transfusions, and alleviate anemia-related symptoms. In May 2004, the United States Food and Drug Administration (FDA) mandated the first of an increasingly restrictive series of product labeling changes for the ESA class of drugs in response to reports of increased mortality in patients with cancer (195). In March 2007, the FDA mandated the addition of a black-box warning for ESA drugs due to reports of increased risk of death and serious cardiovascular events in patients with chronic kidney disease and increased risk of tumor progression and/or death in patients with cancer when hemoglobin levels were greater than 12.0 g/dL (196). This advisory was quickly followed by revisions of clinical guidelines for ESA use (170, 174, 197). Also in 2007, the Centers for Medicare and Medicaid Services published a National Coverage Decision to limit reimbursement for ESA administration and tie reimbursement to specific hemoglobin levels and time schedules (198). Clinical guidelines have been regularly updated as emerging safety data has become available.

After several years of escalating ESA use in both the dialysis population and the cancer populations, anemia management patterns changed markedly during and after the period of negative safety reports, product labeling changes, black box advisories, revised anemia management guidelines, and reimbursement changes. Recent declines in ESA use, ESA dose, and hemoglobin levels have been reported in several national studies of cancer populations or dialysis populations (45, 123, 199-203). However, no information exists regarding trends in anemia treatment among dialysis patients also diagnosed with cancer.

A cancer diagnosis complicates anemia management in dialysis patients for many reasons. First, there are additional safety concerns associated with ESA treatment in the cancer population including tumor progression, thromboembolic complications, and mortality (204, 205). Beginning in 2003, eight randomized clinical trials in cancer patients reported increased risk of tumor progression and/or death among cancer patients treated with ESAs (3-11). The most recent meta-analyses of cancer patients

demonstrated significant effects of ESAs on increased thromboembolic events and mortality but not on disease progression (206). Second, there are currently no formal guidelines for providers regarding appropriate usage of ESAs in ESRD patients with cancer (205). For patients undergoing dialysis, the United States recommendation is to initiate treatment when the hemoglobin level is less than 10 g/dL and to individualize dosing and use the lowest dose of ESA sufficient to reduce the need for transfusions (13). For cancer patients, the recommendations are similar except the ESA indication for treatment of anemia is restricted to patients undergoing myelosuppressive chemotherapy (14). Third, little is known regarding patterns of ESA use in dialysis patients with cancer. In this population, it remains unclear how anemia treatment has been affected by recent clinical and policy events.

The objectives of this study were to examine trends in anemia management in the U.S. hemodialysis population after the diagnosis of cancer. Using population-based data from the United States Renal Data System (USRDS), a national registry including all patients in Medicare's ESRD program, we described patterns of use of ESAs and transfusions as well as resulting hemoglobin levels. We also examined anemia management patterns within subgroups, including cancer site and chemotherapy use. We report trends from 2000 to 2010, a time period that includes data before and after negative safety reports, product labeling changes, black box advisories, revised anemia management guidelines, and reimbursement changes.

2. Methods

Study Population

Using data from the USRDS, a national registry of patients in Medicare's ESRD program, we identified all ESRD patients ≥ 18 years who received in-center hemodialysis between April 1, 1995 and December 31, 2010 with Medicare as their primary payer and both parts A and B coverage. We restricted the cohort to patients who received their first cancer diagnosis at least 9 months after dialysis initiation. This time period was to ensure stability in dialysis treatment modality (months 0-3 post-dialysis initiation) (190), and to exclude prevalent cancer cases identified using Medicare claims (months 3-8 post-dialysis initiation), as previously described (191-193). Patients with a malignancy-related primary cause of ESRD or a history of kidney transplantation or HIV/AIDS were also excluded. We further restricted the cohort to

patients with post-cancer diagnosis follow-up time between 2000 and 2010, to ensure a similar distribution of incident and prevalent hemodialysis patients over time.

Incident Cancer Definitions

We identified incident site-specific cancers using *International Classification of Diseases, 9th revision, Clinical Modification* (ICD-9-CM) diagnosis codes from inpatient and outpatient Medicare claims (Appendix B, Supplemental Table 18). Site-specific cancers were defined by ≥ 2 ICD-9-CM diagnosis codes within 6 months (179). Date of cancer onset was defined as the first date of a cancer-related diagnosis code in the claims data. *In situ* carcinomas were included for two sites (i.e., breast and bladder) (180). Secondary tumors, benign tumors, and non-melanoma skin cancers were excluded. Only the first cancer diagnosis after dialysis initiation was included as an event.

Anemia Therapy Outcomes

Information on ESAs and hematocrit was identified from dialysis claims from the Medicare Part A institutional claims files and Medicare Part A and B claims. Information on transfusions was identified from Medicare Part A and B claims. The codes used to identify ESAs and transfusions are presented in Supplemental Table 19 (Appendix B). Monthly outlier values were set to missing if outside the specified ranges (EPO dose, 500-700,000 units; hematocrit, 20-60 g/dL) (123). Data were summarized by calendar quarter. We calculated the quarterly proportion of the study population treated with ESAs (epoetin alfa (EPO), darbepoetin alfa). Mean EPO dose (units/month) was calculated as the quarterly sum of EPO doses divided by 3. Darbepoetin alfa dose was excluded from the analysis due to extreme missingness. Patients treated at a hospital-based facility were excluded from the EPO dose calculation to remove the possibility of simultaneous treatment with EPO and darbepoetin alfa. Mean quarterly hemoglobin levels were calculated by dividing hematocrit levels by 3. We calculated the quarterly proportion of the study population that received transfusions, as well as the mean number of days per year that each patient received a transfusion.

Covariates

We obtained the following information from the USRDS patient file: first service date, sex, race, primary cause of ESRD. Information on ethnicity was obtained from the Medical Evidence file. For each calendar quarter, age at dialysis initiation and duration of dialysis (i.e., vintage) were calculated on the first date of the quarter by subtracting the first service date. We identified chemotherapy administration during each quarter using ICD-9-CM diagnosis and procedure codes, Healthcare Common Procedure Coding System (HCPCS) codes, and revenue codes (Appendix B, Supplemental Table 20) (181, 182).

Statistical Analysis

We calculated descriptive statistics on the demographic and clinical characteristics of the population by year. We also described the annual distribution of cancer diagnoses by cancer site. To describe trends in anemia treatment by calendar quarter, we used generalized linear models to generate unadjusted and adjusted estimates. Specifically, we used logistic regression models to calculate quarterly estimates of the proportion of patients that used ESAs or transfusion, linear regression models to calculate mean quarterly estimates of EPO dose (units/month) and hemoglobin levels, and Poisson regression models to calculate estimates of the mean number of transfusion days per year. Since EPO dose and hematocrit levels were only reported with the administration of ESAs, these analyses were restricted to patients who received ESAs at least once during the quarter. Calendar quarter or year was treated as a categorical variable in the models to relax the assumption of linearity. The results section presents plots of the adjusted estimates for ESA use, EPO dose, transfusion use, number of transfusion days, and hemoglobin levels, which are population marginal means that account for changes over time in demographic (age, sex, race, ethnicity) and clinical characteristics (primary cause of ESRD, dialysis vintage) (189). The trend lines and corresponding 95% confidence intervals were calculated as a smoothed conditional mean of the quarterly or yearly adjusted estimates. We stratified estimates by cancer site and chemotherapy use, as well as several additional demographic and clinical characteristics. We further stratified the analyses by using three categories of cancer site: a) all cancer sites; b) the most common solid tumors in our study population (i.e., cancers of the prostate, female breast, colon/rectum, lung/bronchus, kidney/renal pelvis, bladder, and pancreas); and c) hematologic malignancies (i.e.,

Hodgkin lymphoma, non-Hodgkin lymphoma (NHL), leukemia, and myeloma). We performed complete case analyses since covariate missingness was less than 1% (i.e., ethnicity (n=134) and race (n=28)). SAS software, version 9.3 (Cary, NC) and RStudio, version 0.98.507 were used to perform analyses (207).

3. Results

A total of 39,012 incident cancer patients receiving hemodialysis met eligibility requirements for this study. Demographic and clinical characteristics are presented for selected years (i.e., 2000, 2002, 2004, 2006, 2008, and 2010) in Table 12. The number of eligible patients per year increased from 4,997 in 2000 to 11,219 in 2010. Over time, patients were more likely to be black, Hispanic, or have diabetes as the primary cause of ESRD. Between 2000-2010, mean age at dialysis initiation decreased from 67.9 to 65.8 years, whereas mean age at cancer diagnosis remained constant. The median duration of dialysis at cancer diagnosis was 2.1 years (IQR, 1.3-3.6). The median length of follow-up after cancer diagnosis was 1.0 year (IQR, 0.3-2.4), and 18.6% of patients remained in follow-up at 3 years post-cancer diagnosis.

The distribution of cancer diagnoses by cancer site and year is presented in Figure 11 and Supplemental Table 21 (Appendix B). The most frequently diagnosed cancer sites were prostate, colorectal, and female breast. Cancers of the kidney/renal pelvis had the most notable increase between 2000 and 2010, from 6.1% to 10.9% of diagnosed cancers.

Over the study period, the quarterly proportion of patients that received ESAs remained relatively constant between 92% and 94%. Use of EPO decreased from 94% to 86% between 2002 and mid-2007, and then increased to 88% by early 2010. Use of darbepoetin alfa increased from 0% to 8% between 2002 and mid-2007, and then decreased to 6% by early 2010 (Appendix B, supplemental figure 22). ESA use varied by cancer site. Compared to all cancer patients in the study population, patients with common solid tumors had similar ESA use whereas patients with hematologic malignancies had lower ESA use (figure 12, supplemental figure 23 (Appendix B)).

Among patients receiving EPO, the mean EPO dose increased from approximately 66,000 units/month in early 2001 to 83,000 units/month in early 2004, and then declined to 70,000 units/month by

late 2010. Patients with hematologic malignancies used a higher mean EPO dose compared to patients with solid tumors (~88,000 vs. 73,000 units/month) (figure 13, supplemental figure 24 (Appendix B)).

The quarterly proportion of patients that received transfusions increased from 6% in late 2000 to 9% in late 2010. Use of transfusion was more common among patients with hematologic malignancies compared to patients with solid tumors (quarterly mean, 11% vs 8%) (figure 14, supplemental figure 25 (Appendix B)). Among patients who received transfusion, the mean number of transfusion days per year increased steadily from 1.4 to 1.8 days between 2000-2010, with a steeper increase among patients with hematologic malignancies (1.5 to 2.4 days) compared to solid tumors (1.5 to 1.7 days) (figure 14).

Mean quarterly hemoglobin levels followed a similar pattern to EPO dose. Among patients receiving ESAs, hemoglobin levels increased from 11.3 g/dL in early 2000 to 11.9 g/dL in late 2006, and then declined to 11.2 g/dL in late 2010. Patients with hematologic malignancies had slightly lower mean quarterly hemoglobin levels compared to patients with the most common solid tumors (11.5 vs. 11.6 g/dL) (figure 15, supplemental figure 26 (Appendix B)).

The quarterly proportion of chemotherapy receipt decreased from 6.4% in quarter 1 of 2000 to 4.7% in quarter 4 of 2010. Figure 16 presents quarterly trends in anemia treatment by chemotherapy use. Compared to cancer patients who did not receive chemotherapy, patients who received chemotherapy had higher mean quarterly ESA use (93% vs. 96%) and higher mean EPO dose (~74,000 vs. 98,000 units/month). Almost twice as many patients on chemotherapy received quarterly transfusions compared to patients who did not receive chemotherapy (15% vs 8%). Mean quarterly hemoglobin levels were lower among patients who received chemotherapy compared to patients who did not receive chemotherapy (11.4 vs. 11.6 g/dL).

Analyses stratified by demographic and clinical characteristics revealed several meaningful differences in anemia treatment patterns (Appendix B, supplemental figures 27-32). ESA use was lower among patients who were male, non-African American, receiving dialysis for <2 years, or with primary cause of ESRD due to polycystic kidney disease. EPO dose was lower among patients who were older, non-African American, Hispanic, receiving dialysis for <2 years, or with primary cause of ESRD due to polycystic kidney disease. Transfusion use was lower among patients who were non-Hispanic, receiving

dialysis for ≥2 years, or with primary cause of ESRD due to polycystic kidney disease. Hemoglobin levels did not vary substantially by subgroups.

4. Discussion

In this national study of anemia treatment patterns among U.S. hemodialysis patients diagnosed with incident cancer, we observed extremely high and constant ESA use between 2000 and 2010, even during the years of negative safety reports, product labeling changes, black box advisories, revised anemia management guidelines, and reimbursement changes. EPO dosing increased until 2004, and then declined steadily. Hemoglobin levels followed a similar pattern to EPO dose, with a delayed peak of 2006. We also observed an increase in the use of transfusions over the study period. This study provides novel information on trends in anemia treatment that have not been described in the national dialysis population with cancer.

In contrast to our findings of constant ESA use over time in our hemodialysis population with cancer, the oncology literature reports drastic decreases in ESA use (i.e., both EPO and darbepoetin alfa) in the years surrounding the 2007 FDA black-box warning. Among VA cancer patients, ESA use plateaued in late 2003 and sharply declined from 38% (2006) to 12% (2008) among colon cancer patients and from 23% (2006) to 5% (2008) among lung cancer patients (45). Another study of cancer patients undergoing chemotherapy across 39 sites in seven states reported a decline from 41% to 30% between 10-month intervals before and after the 2007 FDA black-box warning (200). Two studies of cancer patients treated at MD Anderson Comprehensive Cancer Center reported decreases in ESA use between 2006 and 2008 of 17% to 5% and 4% to 1% (199, 201). Thus, compared to our hemodialysis population with cancer, the oncology population seems to be characterized by higher variability in ESA use by calendar year, cancer site, and chemotherapy receipt.

Although ESA use remained constant among dialysis patients with cancer over the study period, we observed an 8% decrease in EPO use between 2002 and 2007 that corresponded with an equivalent increase in darbepoetin alfa use. The timing and magnitude of the decline in EPO use follows a pattern similar to that previously documented in the hemodialysis population (123). In both studies, EPO use

declined steeply after the emergence of ESA-related safety concerns and continued to decline for years. However, the data on darbepoetin alfa use presented in our study suggest that the decline in EPO may be due to increased uptake of darbepoetin alfa rather than recent clinical and policy events. It is also noteworthy that in our hemodialysis population with cancer we observed slightly lower EPO use and hemoglobin levels and slightly higher EPO dosing compared to the larger hemodialysis population.

Current guidelines conflict regarding appropriate treatment in the subgroup of dialysis patients with cancer who do not receive chemotherapy. The guidelines for dialysis patients are similar to the guidelines for cancer patients, except the ESA indication for treatment of anemia is restricted to cancer patients undergoing myelosuppressive chemotherapy (13, 14). These evidence-based guidelines were influenced by studies of cancer patients that consistently reported modification of mortality risk associated with ESAs by chemotherapy use (205). As expected, we observed that patients who did not receive chemotherapy had higher hemoglobin levels and less intensive anemia treatment, including lower ESA use, EPO dose, and transfusion use, compared to patients that received chemotherapy. Yet, the common ESA use in this subgroup of patients not receiving myelosuppressive chemotherapy is noteworthy. These findings highlight discrepancies between guideline-recommended therapy and actual practice.

Transfusion avoidance remains an important goal due to dangerous transfusion-related complications including hyperkalemia, fluid overload, iron overload and allosensitization (208). Between 2000 and 2010, we observed an increasing proportion of hemodialysis patients with cancer that received transfusions and an increasing mean number of transfusion days per year. Since transfusion avoidance provided the formal reason for the original approval and use of ESAs, it seems paradoxical that transfusion use is increasing despite constant ESA use (209). One likely explanation for the increase in transfusion use is the recent paradigm shift towards lower ESA dosing and lower hemoglobin levels. A recent study reported that Medicare hemodialysis patients with 3-month mean hemoglobin levels <10 g/dL received transfusions at a rate approximately 4 times higher than the rate for patients with hemoglobin levels maintained at ≥10 g/dL. Although transfusion rates among patients with hemoglobin levels <10 and ≥10 g/dL remained relatively constant between 1999 and 2010, the proportion of patients with hemoglobin levels <10 g/dL began to increase after 2006, and consequently, the absolute number of patients receiving transfusions also began to increase (203).

Our findings are subject to several limitations. First, our results may not be generalizable to non-dialysis patients with chronic kidney disease, patients on peritoneal dialysis, patients with a non-Medicare primary payer, or patients who died within 9 months of dialysis initiation. Second, claims-based cancer definitions have not been validated in the ESRD population. Third, we cannot exclude the possibility of misclassifying prevalent cancer cases as incident cases. However, identification of prevalent cancer cases during the 6-month baseline period minimized the possibility of misclassification. Fourth, use of claims-based definitions made it impossible to determine whether cancers identified as incident cases were truly new primaries, metastases, or histories of cancer that were miscoded as new primaries. Fifth, we analyzed the number of transfusion days per year rather than the actual number of transfusions, because all transfusions administered on any single day are covered by a single procedural code. Sixth, ESA claims are provided from outpatient dialysis claims but not from hospital claims. Since ESRD patients require several hospital days per year on average, this missing data may yield lower estimates of ESA use and dose. Lastly, we may be missing a small proportion of chemotherapy use due to lack of access to some specific chemotherapy agent codes (i.e., National Drug Codes).

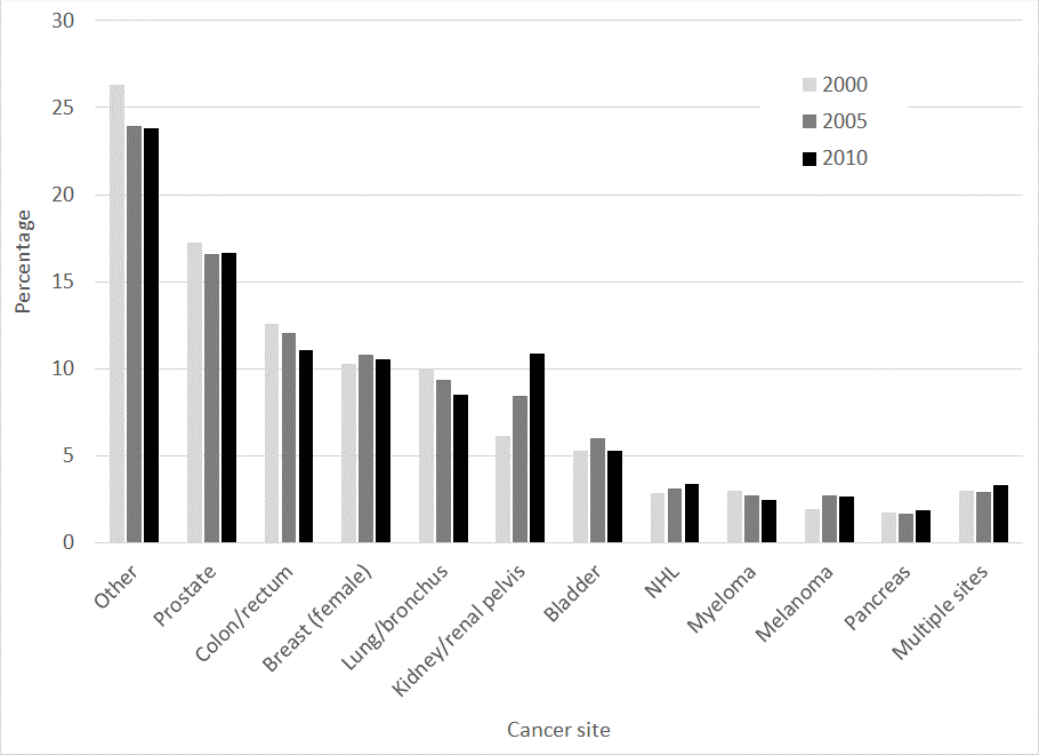
Strengths of our study include more than a decade of data on the large and representative population of U.S. ESRD patients diagnosed with cancer after hemodialysis initiation. The large sample size allowed the novel characterization of anemia management patterns within subgroups, including cancer site and chemotherapy use.

In conclusion, our results suggest that ESA use is extremely common in hemodialysis patients with cancer, and robust to recent clinical and policy events driven by safety concerns. The potential risks associated with ESA use must be balanced with its known benefits, such as alleviating anemia-related symptoms and avoiding transfusion. Although the risks and benefits of ESA use and dosing practices have been documented in the dialysis population, little is known about the safety and effectiveness of ESA use in the dialysis population with cancer. In addition, the impact of ESA use on health-related quality of life needs to be explored in this population. Additional research in the dialysis population with cancer is necessary to examine the risk-benefit profile, to understand impact on quality of life, and to inform clinical practice.

Table 12. Demographic and clinical characteristics of the study population in 2000, 2002, 2004, 2006, 2008, and 2010

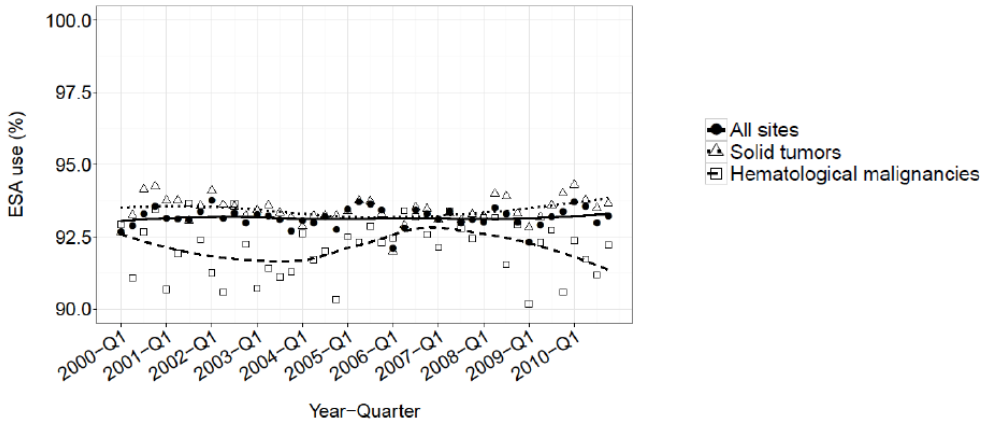
	Year					
Characteristics	2000	2002	2004	2006	2008	2010
Patients (n)	4,997	6,827	8,289	9,620	10,726	11,219
Age at dialysis initiation (years), mean (sd)	67.9 (11.7)	67.4 (11.7)	67.4 (11.9)	66.8 (12.3)	66.4 (12.5)	65.8 (12.8)
Age at first cancer diagnosis (years), mean (sd)	69.9 (11.6)	70.1 (11.5)	70.4 (11.5)	70.2 (11.9)	70.0 (12.0)	69.8 (12.2)
Male gender (%)	55.8	56.2	56.2	55.8	56.4	56.0
Race (%)						
White	60.9	60.7	60.2	59.1	58.5	57.4
Black	35.8	35.9	35.9	36.8	37.7	38.5
Asian	1.8	2.1	2.4	2.3	2.3	2.6
Native American	0.8	0.8	0.9	0.9	1.0	1.1
Other	0.6	0.5	0.6	0.8	0.5	0.4
Unknown	0.1	0.0	0.0	0.0	0.0	0.0
Ethnicity (%)						
Non-Hispanic	90.7	90.4	89.8	89.0	88.8	88.4
Hispanic	8.6	9.1	9.8	10.7	11.0	11.5
Unknown	1.0	0.6	0.6	0.4	0.3	0.2
Reported cause of ESRD (%)						
Diabetes	41.0	41.0	40.9	43.2	44.1	44.6
Hypertension	34.0	34.5	35.6	34.9	34.6	34.1
Glomerulonephritis	10.9	10.5	9.8	9.3	8.8	8.9
Polycystic kidney	1.9	1.9	1.9	1.8	1.9	1.8
Other	12.3	12.1	11.9	10.9	10.7	10.7

Figure 11. Distribution of cancer diagnoses among U.S. hemodialysis patients with cancer, by first cancer site and year, 2000-2010



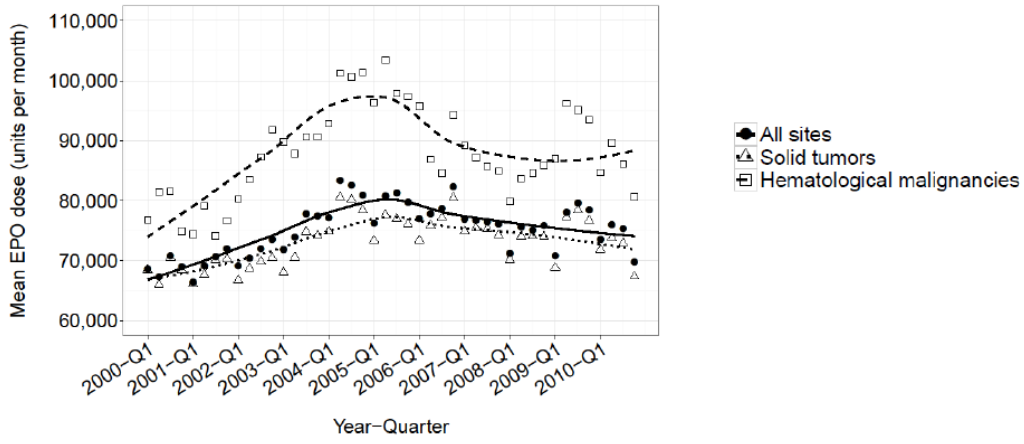
Other cancers were defined as all other site-specific cancers not listed (e.g., cancers of the esophagus, stomach, liver, etc.). Multiple sites indicates patients diagnosed with first cancer at ≥2 sites on the same date.

Figure 12. Mean quarterly ESA use by cancer site among U.S. hemodialysis patients with cancer, 2000-2010



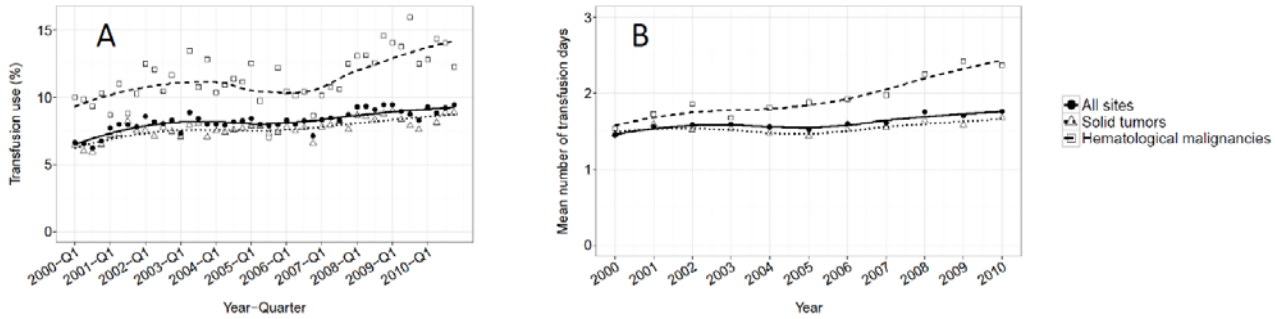
a) All cancer sites; b) most common solid tumors in our study population (i.e., cancers of the prostate, female breast, colon/rectum, lung/bronchus, kidney/renal pelvis, bladder, and pancreas); and c) hematologic malignancies (i.e., Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, and myeloma). Quarterly data points were adjusted for age, sex, race, ethnicity, cause of ESRD, and dialysis vintage. Trend lines represent smoothed conditional means.

Figure 13. Mean EPO dose (units/month) by cancer site among U.S. hemodialysis patients with cancer, 2000-2010



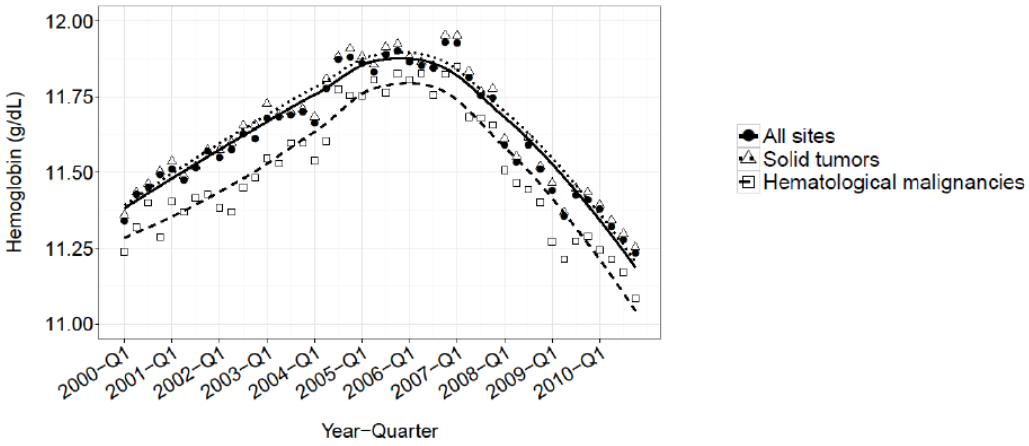
a) All cancer sites; b) most common solid tumors in our study population (i.e., cancers of the prostate, female breast, colon/rectum, lung/bronchus, kidney/renal pelvis, bladder, and pancreas); and c) hematologic malignancies (i.e., Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, and myeloma). Patients treated at a hospital-based facility were excluded to remove the possibility of simultaneous treatment with EPO and darbepoetin alfa. Quarterly data points were adjusted for age, sex, race, ethnicity, cause of ESRD, and dialysis vintage. Trend lines represent smoothed conditional means.

Figure 14. Use of blood transfusions by cancer site among U.S. hemodialysis patients with cancer, 2000-2010



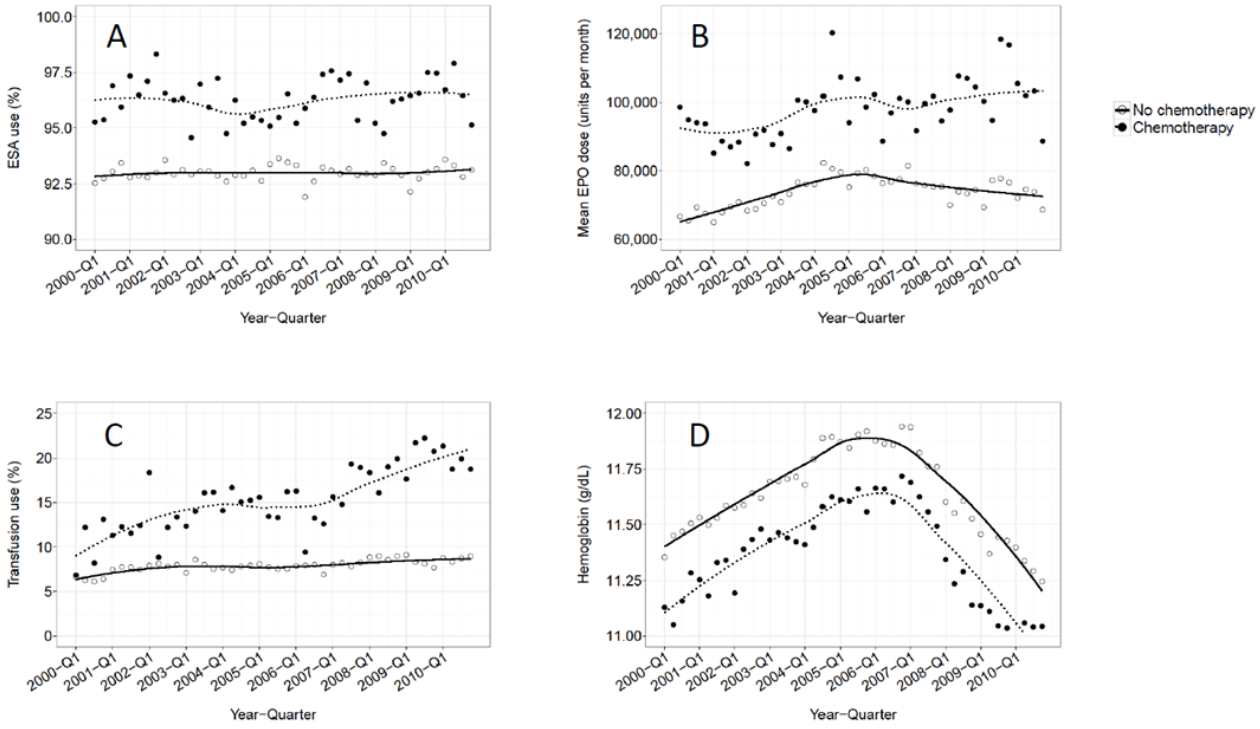
a) Mean quarterly use of blood transfusions and b) mean number of blood transfusion days per year among patients who received blood transfusions, by cancer site. Categorical cancer sites were defined as 1) all cancer sites; 2) most common solid tumors in our study population (i.e., cancers of the prostate, female breast, colon/rectum, lung/bronchus, kidney/renal pelvis, bladder, and pancreas); and 3) hematologic malignancies (i.e., Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, and myeloma). Data points were adjusted for age, sex, race, ethnicity, cause of ESRD, and dialysis vintage. Trend lines represent smoothed conditional means.

Figure 15. Mean quarterly hemoglobin levels by cancer site among U.S. hemodialysis patients with cancer, 2000-2010



a) All cancer sites; b) most common solid tumors in our study population (i.e., cancers of the prostate, female breast, colon/rectum, lung/bronchus, kidney/renal pelvis, bladder, and pancreas); and c) hematologic malignancies (i.e., Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, and myeloma). Quarterly data points were adjusted for age, sex, race, ethnicity, cause of ESRD, and dialysis vintage. Trend lines represent smoothed conditional means.

Figure 16. Quarterly trends in anemia management by chemotherapy use among U.S. hemodialysis patients with cancer, 2000-2010



a) Mean ESA use; b) mean EPO dose (units/month); c) mean use of blood transfusions; and d) mean hemoglobin levels. Patients treated at a hospital-based facility were excluded from the EPO dose calculation to remove the possibility of simultaneous treatment with EPO and darbepoetin alfa. Quarterly data points were adjusted for age, sex, race, ethnicity, cause of ESRD, and dialysis vintage. Trend lines represent smoothed conditional means.

CHAPTER V. DISCUSSION

A. Summary of Findings

This dissertation research examined the cancer burden among ESRD patients on hemodialysis as well as patterns of anemia treatment among ESRD patients on hemodialysis with cancer using national data from the Medicare ESRD program. The research had two main objectives: 1) to characterize the overall and site-specific cancer burden among ESRD patients without cancer at hemodialysis initiation, across demographic and clinical subgroups (*Aim 1*); and 2) to examine trends in anemia therapy in ESRD patients diagnosed with cancer after hemodialysis initiation, for a time period before, during, and after ESA-related negative safety reports, product labeling changes, black box advisories, revised anemia management guidelines, and reimbursement changes (*Aim 2*).

In this large national study of U.S. ESRD patients undergoing hemodialysis, we observed a high cumulative incidence of cancer, even after accounting for the substantial competing risk of death in this population. Between 1996 and 2009, we observed higher rates of incident cancer diagnoses in the dialysis population compared to the U.S. general population, suggesting that ESRD patients are uniquely at risk for developing cancer while receiving hemodialysis treatment. Our results demonstrate varying patterns of cancer incidence across subgroups, after accounting for measured patient characteristics.

Among ESRD patients diagnosed with incident cancer after hemodialysis initiation, we observed extremely high and constant ESA use between 2000 and 2010 despite safety concerns about ESAs in both the ESRD and cancer populations. Even though transfusion avoidance provided the reason for the original approval of ESAs, we observed an increasing quarterly proportion of cancer patients who received transfusions and an increasing mean number of transfusion days per year. This paradigm shift is likely due to the decreasing EPO dose (units/month) and decreasing quarterly hemoglobin levels that we observed in the second half of the study period. Both patients with hematological malignancies and patients who received chemotherapy had higher ESA use, EPO dose, and transfusion use as well as lower hemoglobin levels. Anemia treatment patterns also varied across demographic and clinical subgroups.

B. Public Health Implications

The results of this dissertation research have several implications for public health and clinical practice. First, our estimate of the cumulative incidence of cancer that accounts for the high competing risk of death in the dialysis population provides useful information on the total amount of cancer diagnoses that will occur in the population. This estimate is valuable for health care policy and planning in the dialysis population characterized by very high mortality. Realistic estimates of the cancer burden are essential for allocation of resources to cancer prevention, screening, and treatment programs, which is of critical importance in the federally funded Medicare population.

Additionally, the higher cancer incidence documented in certain subgroups of the population warrants re-evaluation of cost-effectiveness analyses for cancer screening practices in the dialysis population. There are currently no standard recommendations for cancer screening in the dialysis population, as previous cost-effectiveness analyses have suggested general cancer screening in this population would be a relatively inefficient allocation of financial resources, and would add minimal days of life saved per person. However, knowledge of higher cancer risk among subgroups may help to target at-risk groups that may benefit from more frequent prevention or screening interventions.

Finally, understanding temporal trends in anemia therapy among dialysis population with cancer is important for a number of reasons. National data on patterns of use of ESAs and blood transfusions inform providers about standard practice in the absence of formal guidelines regarding appropriate anemia therapy in dialysis patients with cancer. Also, the extremely high and constant ESA use and increasing blood transfusion use calls for further research in this population to examine ESA-related safety, effectiveness, and impact on health-related quality of life.

C. Strengths

Use of the USRDS data

We used data from the USRDS which contains inpatient and outpatient information on the large, representative population of U.S. ESRD patients on hemodialysis. The large sample size of the population allowed characterization of the overall and site-specific cancer burden as well as anemia

treatment within various subgroups, including age, sex, race, ethnicity, primary cause of ESRD, number of years on dialysis, and chemotherapy receipt. This dissertation research improves upon existing estimates of cancer incidence in the ESRD population which are primarily focused on all cancer sites combined or a limited number of cancer sites, and determined from small, select groups of dialysis patients. In addition, this research provides the first data on anemia treatment patterns in the dialysis population with cancer.

Exclusion of prevalent cancer cases

We used a strict definition of incident cancer to avoid bias in our estimates of cancer incidence. Although previous studies have consistently excluded patients with a malignancy-related primary cause of ESRD from the population at risk, misclassification of prevalent cancer cases has remained a possible source of bias. In addition to this exclusion criteria, we required patients to remain cancer-free until 9 months post-dialysis initiation to prevent misclassifying prevalent cancer cases as incident cases.

Advanced analytic methods

The use of advanced analytic approaches improved upon previous work on the cancer burden in the dialysis population. First, we estimated 5-year cumulative incidence of overall and site-specific cancer accounting for the competing risk of death prior to receipt of a cancer diagnosis. The use of competing risks methodology is an innovative approach that is appropriate for the inherent competing risks problem in the dialysis population due to the high annual proportion of death. Second, we used inverse probability weights to calculate 5-year cumulative incidence estimates stratified by patient characteristics that were standardized to the total study sample at baseline with respect to age, sex, race, ethnicity, primary cause of ESRD, and calendar year of dialysis initiation. These analytic approaches combined with the rich data resource of the USRDS enabled quality estimates of the cancer burden.

D. Limitations

Generalizability of results from USRDS

The analytic cohorts were restricted by multiple criteria in order to ensure full healthcare utilization, capture of relevant claims data, and a homogeneous, cancer-free hemodialysis population at

the start of follow-up. Therefore, our results may not be generalizable to non-dialysis patients with chronic kidney disease, patients on peritoneal dialysis, patients with a non-Medicare primary payer, or patients who died within 9 months of dialysis initiation.

Claims-based cancer definitions

Use of claims-based cancer definitions are both a strength and a limitation of this dissertation research. First, claims-based cancer definitions are less stringent than cancer registry data or definitions that require pathology reports. Second, validation of site-specific cancer definitions were conducted in the Medicare general population rather than the ESRD population. Since ESRD patients likely undergo less frequent cancer screening and pursue cancer treatment less aggressively due to high severity of illness and shorter life expectancy, the sensitivity and specificity of these claims-based cancer definitions may be different in the ESRD population. Third, validation has only been performed for a limited number of cancer sites, and the sensitivity varies widely within these sites. Lastly, use of claims-based definitions made it impossible to determine whether cancers identified as incident cases were truly new primaries, metastases, or histories of cancer that were miscoded as new primaries.

Misclassification of prevalent cancer cases

In the absence of pre-dialysis data for the majority of the study population, it is possible that we may have misclassified prevalent cancer cases as incident cancer cases, which may result in a slight overestimate of cancer incidence. However, unlike previous studies, identification of prevalent cancer cases during the 6-month baseline period minimized the possibility of misclassification.

Misclassification of chemotherapy use

The USRDS does not include information on a number of variables that could further characterize the cancer burden in the ESRD population. These include cancer risk factors such as smoking (e.g., cancers of the lung, head/neck, bladder), alcohol (e.g., cancers of the head/neck, esophagus, liver), UV radiation (e.g., skin cancer), and family history (e.g., cancers of the breast, colon/rectum, ovary, prostate). Cancer stage would also be a useful variable.

Inability to capture dialysis information from hospitalizations

Information on ESA use was provided in claims from outpatient dialysis claims but not available from hospital claims. Since ESRD patients require several hospital days per year on average, dialysis

administered during hospitalizations would result in missing claims and ultimately yield lower quarterly estimates of ESA use and dose.

Misclassification of chemotherapy use

For the analysis of patterns of anemia treatment, we stratified the analysis by chemotherapy receipt. Any chemotherapy use (yes/no) was ascertained using ICD-9-CM diagnosis and procedure codes, Healthcare Common Procedure Coding System (HCPCS) codes, and revenue codes(181, 182). Although this approach should capture all chemotherapy use, it is noteworthy that we may be missing a small proportion of chemotherapy use due to lack of access to some specific chemotherapy agent codes (i.e., National Drug Codes) in the USRDS data.

E. Future Directions

Future research is warranted to build upon the findings of this dissertation. First, validation of claims-based cancer definitions using the SEER-Medicare data linkage would be useful for cancer research in the ESRD population. Accurate identification of cancer cases remains the major challenge of studying cancer in the ESRD population because claims-based cancer definitions have not been validated in the ESRD population. Previous validity studies in the elderly general population have evaluated the accuracy of cancer diagnoses in Medicare claims data including breast, colorectal, endometrial, lung, pancreatic, and prostate cancers as well as leukemia and lymphoma (179, 210-216). However, the validity of claims-based cancer definitions is likely different in the ESRD population due to higher severity of illness, worse functional status, shorter expected lifespan, and more frequent healthcare encounters compared to the general population. The SEER-Medicare data linkage, which comprises cancer registry data and Medicare claims for inpatient and outpatient services, is uniquely positioned to validate claims-based cancer definitions in the ESRD population. Second, a re-evaluation of cancer screening practices in this population may be warranted given the updated estimates yielded by this dissertation work. Third, additional research is necessary to examine the risk-benefit profile of ESA use in the dialysis population with cancer. To date, no studies have been conducted on the safety or effectiveness of ESA use in the dialysis population with cancer. For example, ESRD patients with cancer may be at exceptionally high risk

of thrombotic events, which could be explored using this dissertation data set with the addition of thrombotic outcome variables derived from Medicare claims data. In addition, the impact of ESA use on health-related quality of life ought to be explored in this population. Results from these additional research studies would be useful to inform clinical guidelines and practice.

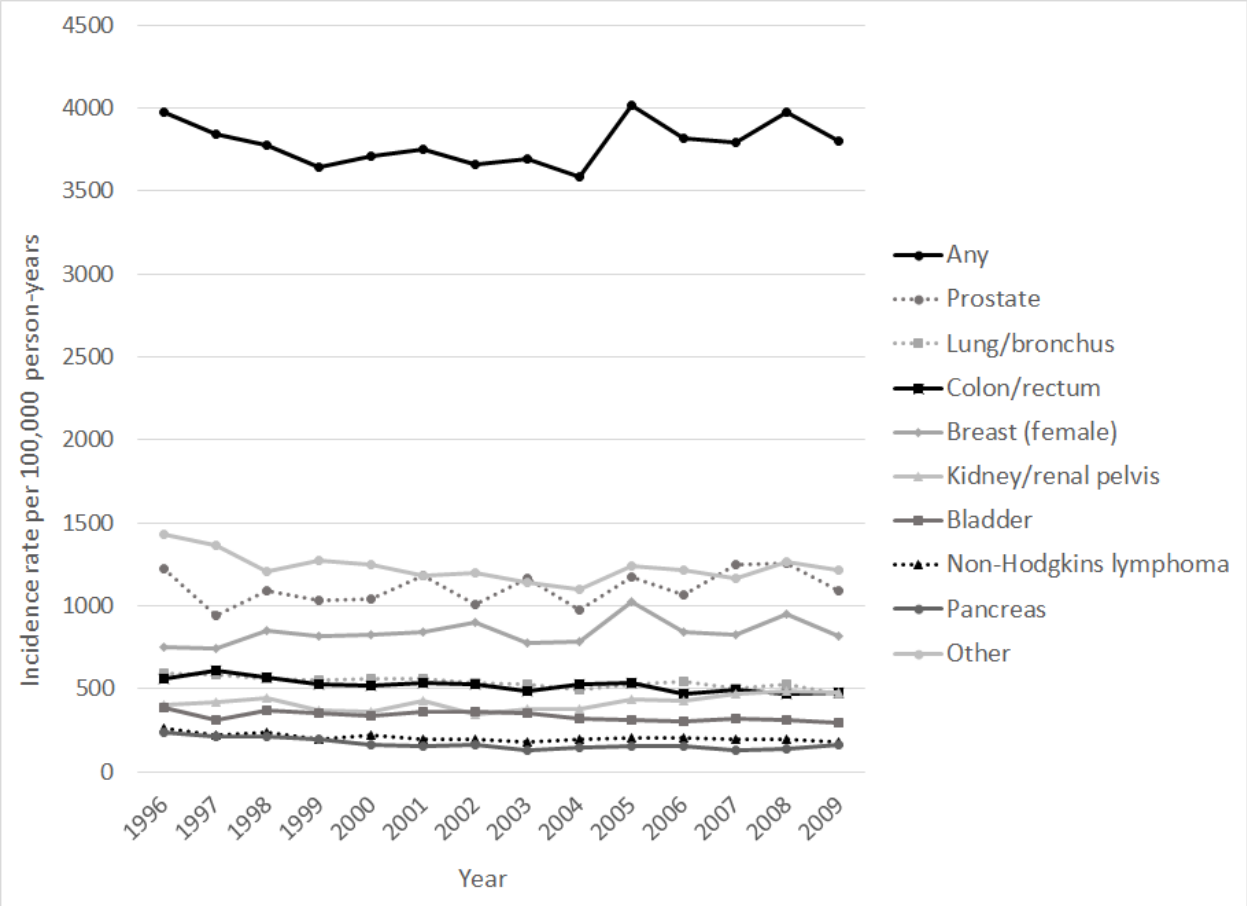
F. Conclusions

Claims-based cancer definitions identified a high and constant overall burden of cancer among the U.S. ESRD population receiving hemodialysis, with certain subgroups of the population exhibiting a particularly elevated cancer risk. Despite safety concerns about ESAs in both the ESRD and cancer populations, ESA use remained extremely common and constant among hemodialysis patients with cancer between 2000 and 2010. In addition, transfusions have increased in frequency despite an effort to avoid transfusions due to dangerous health complications. These results warrant additional research to examine the risk-benefit profile of ESA use in the dialysis population with cancer.

APPENDICES

Appendix A. Supplemental analyses for Chapter IV

Figure 17 (Supplemental). Crude annual incidence rates of cancer diagnoses among U.S. hemodialysis patients by cancer site, 1996-2009



Other cancers were defined as all other site-specific cancers (e.g., cancers of the esophagus, stomach, liver, etc.). The sum of the site-specific cancer rates exceeds the rate for any cancer, due to patients diagnosed with multiple cancer sites on the same date.

Figure 18 (Supplemental). Flow diagram of eligibility criteria among U.S. hemodialysis patients

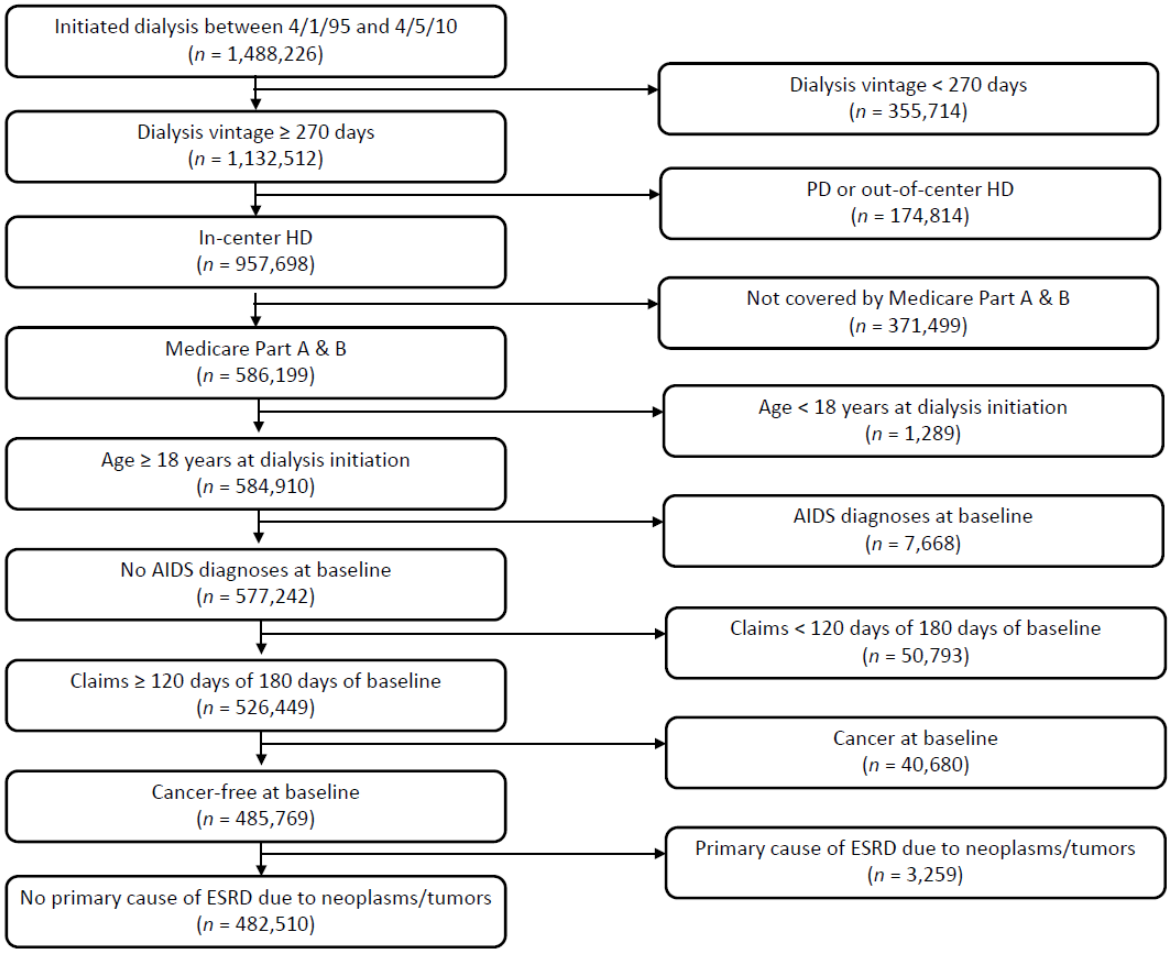
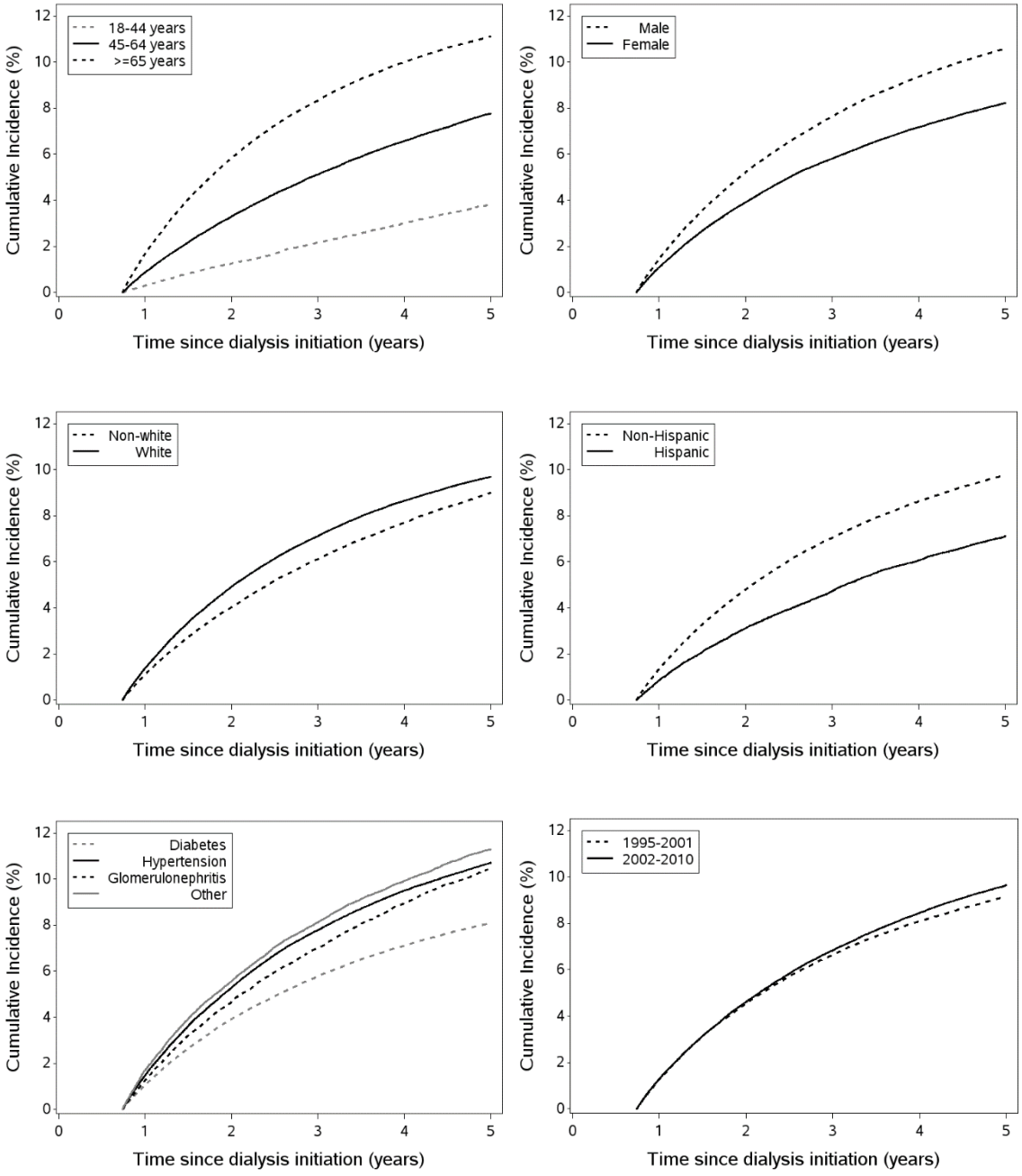
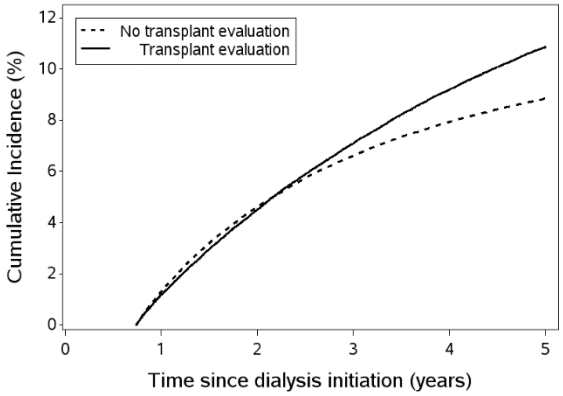


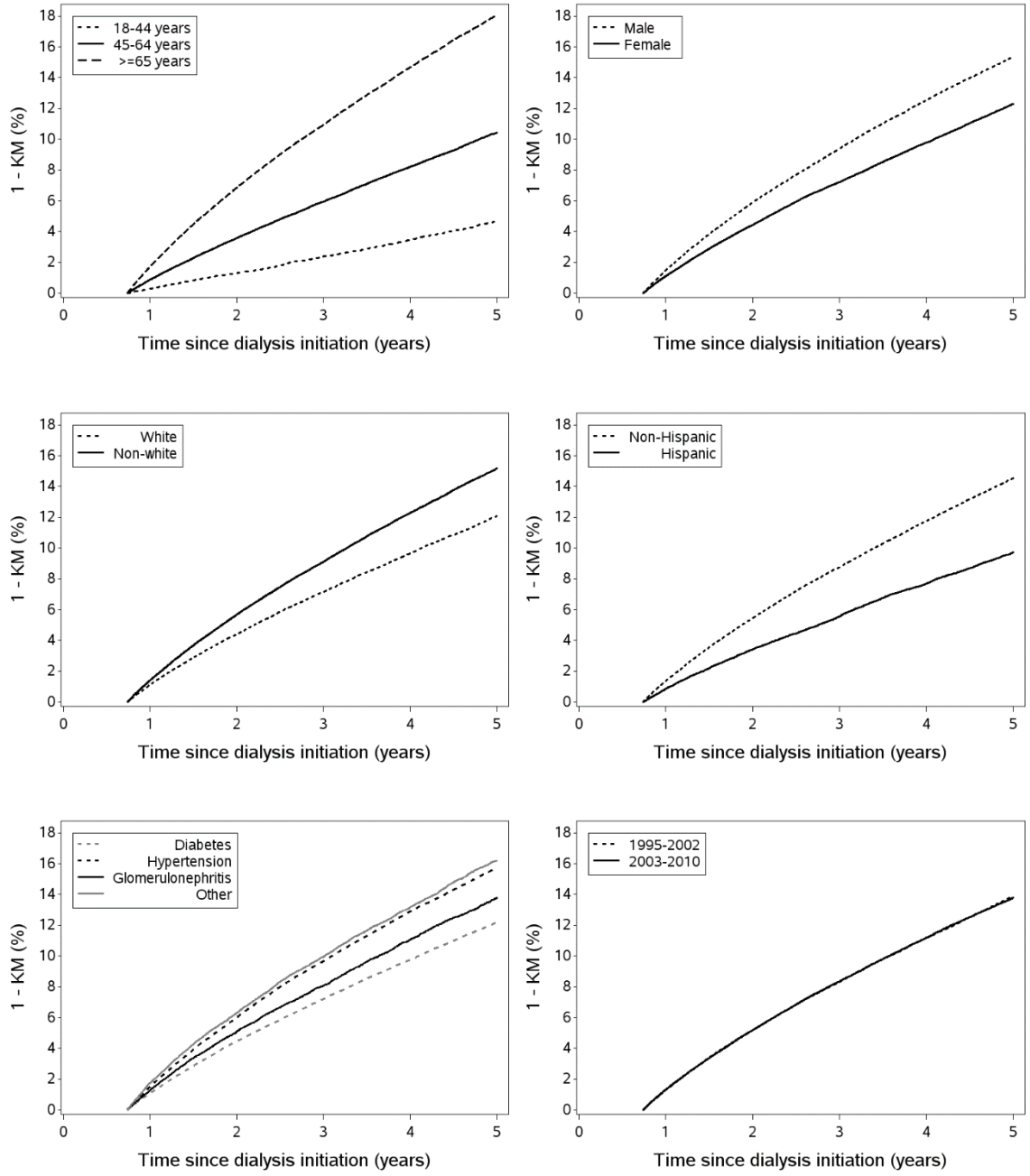
Figure 19 (Supplemental). The crude cumulative incidence of any cancer by time since dialysis initiation, accounting for the competing risk of death, by demographic and clinical characteristics

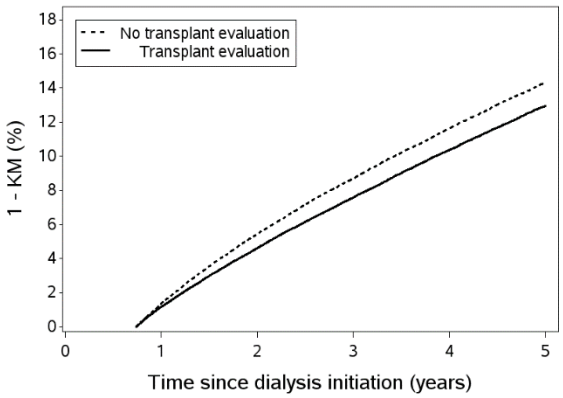




Figures were stratified by patient characteristics including (A) age at dialysis initiation; (B) sex; (C) race; (D) ethnicity; (E) primary cause of ESRD; (F) year of dialysis initiation; and (G) history of kidney transplant evaluation.

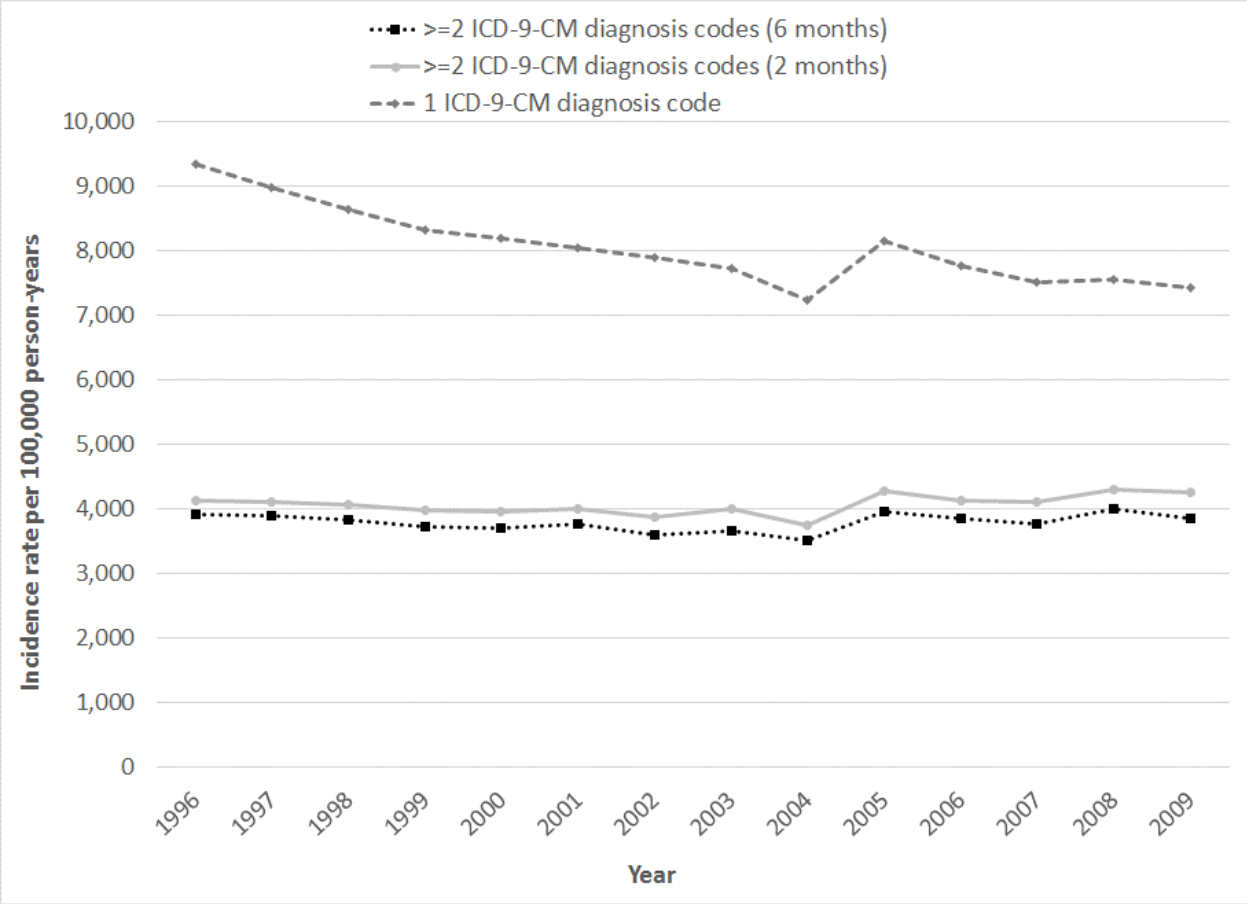
Figure 20 (Supplemental). The crude cumulative incidence of any cancer by time since dialysis initiation, censoring deaths, by demographic and clinical characteristics





Figures were stratified by patient characteristics including (A) age at dialysis initiation; (B) sex; (C) race; (D) ethnicity; (E) primary cause of ESRD; (F) year of dialysis initiation; and (G) history of kidney transplant evaluation.

Figure 21 (Supplemental). Adjusted annual incidence rates of cancer diagnoses by cancer definition among U.S. hemodialysis patients, 1996-2009



Rates were adjusted for age, sex, race, cause of ESRD, and years on dialysis. Incident cases were defined as the first cancer diagnosis of the year among patients without a history of cancer in the last 6 months of the previous calendar year.

Table 13 (Supplemental). Age-, sex-, and race-standardized incidence rates of cancer in the U.S. general population, using the U.S. hemodialysis population as the standard, 1996-2009

Cancer site	Standardized incident cancer rate per 100,000 person-years (SEER) [a]	Unadjusted incident cancer rate per 100,000 person-years (USRDS)	Rate ratio
All sites [b]	1464	3874	2.6
Prostate	604	1209	2.0
Lung/bronchus	224	548	2.4
Colon/rectum	173	523	3.0
Breast (female)	405	778	1.9
Kidney/renal pelvis	41	419	10.3
Bladder	70	353	5.1
NHL	52	231	4.4
Pancreas	44	169	3.9

[a]Standardization was performed using the age, sex, and race distribution of the USRDS study population in year 2000 and age-, sex-, and race-specific incident cancer rates in the U.S. population (seer.gov). Analysis was limited to whites and blacks due to limited availability of rate estimates for other race in SEER general population.

[b]The category for all sites includes all cancer sites diagnosed during the study period, including sites not listed in the table (e.g., liver, stomach, esophagus, etc).

Table 14 (Supplemental). Demographic and clinical characteristics of 482,510 USRDS patients who initiated dialysis between April 1, 1995 and April 5, 2010

Characteristics	No. (%) of patients	Person-years at risk[a] Total	Mean (SD)
Calendar period of dialysis initiation			
1995-1999	127,532 (26.4)	292,669	2.3 (1.5)
2000-2004	168,338 (34.9)	392,798	2.3 (1.5)
2005-2010	186,640 (38.7)	303,050	1.6 (1.3)
Age at dialysis initiation (years)			
18-29	10,739 (2.2)	23,769	2.2 (1.5)
30-39	22,278 (4.6)	51,979	2.3 (1.5)
40-49	45,694 (9.5)	109,087	2.4 (1.5)
50-59	75,599 (15.7)	171,307	2.3 (1.5)
60-69	119,906 (24.9)	255,411	2.1 (1.5)
70-79	139,490 (28.9)	269,050	1.9 (1.4)
≥80	68,804 (14.3)	107,914	1.6 (1.3)
Sex[b]			
Female	233,597 (48.4)	486,139	2.1 (1.5)
Male	248,912 (51.6)	502,376	2.0 (1.5)
Race[c]			
White	302,518 (62.7)	574,321	1.9 (1.4)
African American	154,478 (32.0)	357,748	2.3 (1.5)
Other	25,357 (5.3)	56,129	2.2 (1.5)
Ethnicity[b, c]			
Hispanic	62,765 (13.1)	139,559	2.2 (1.5)
Non-Hispanic	416,901 (86.7)	843,486	2.0 (1.5)
Reported cause of ESRD			
Diabetes	243,279 (50.4)	498,067	2.0 (1.5)
Hypertension	147,157 (30.5)	299,560	2.2 (1.5)
Glomerulonephritis	38,583 (8.0)	83,957	2.2 (1.5)
History of kidney transplant evaluation**			
No	360,602 (74.7)	627,976	1.8 (1.4)
Yes	121,908 (25.3)	360,541	2.8 (1.4)

[a]Person-years at risk were calculated from 9 months post-dialysis initiation to the first of the following: the event of interest (i.e., first cancer diagnosis); or censoring event (i.e., kidney transplantation; death; end of Medicare as primary payer status; change of modality; lost-to-follow-up; 5-years post-dialysis initiation; or end of study on December 31, 2010).

[b]Values were missing for: sex (n=1), ethnicity (n=1,378).

[c]Values were unknown for: race (n=157), ethnicity (n=1,466).

Table 15 (Supplemental). The crude 5-year cumulative incidence of less frequent site-specific cancers among U.S. hemodialysis patients

Cancer site	No. of patients[a]	5-year cumulative incidence % (95% CI) Death treated as censoring event	Death treated as competing event
Lip, oral cavity, and pharynx			
Lip	110	0.04 (0.03, 0.06)	0.03 (0.02, 0.04)
Salivary gland	102	0.04 (0.04, 0.06)	0.03 (0.02, 0.03)
Other lip, oral cavity, and pharynx	64	0.03 (0.02, 0.04)	0.02 (0.01, 0.02)
Digestive system			
Small intestine	148	0.06 (0.05, 0.07)	0.04 (0.03, 0.05)
Anus	64	0.03 (0.02, 0.04)	0.02 (0.01, 0.02)
Other digestive system	129	0.05 (0.04, 0.06)	0.04 (0.03, 0.04)
Respiratory system			
Nasal cavity, middle ear, and sinus	46	0.02 (0.01, 0.03)	0.01 (0.01, 0.02)
Trachea	26	0.01 (0.01, 0.02)	0.01 (0.01, 0.01)
Other respiratory system	74	0.03 (0.02, 0.04)	0.02 (0.02, 0.03)
Skin/connective tissue[b]			
Kaposi sarcoma	68	0.03 (0.02, 0.04)	0.02 (0.01, 0.02)
Reproductive and genitourinary			
Breast (male)[c]	59	0.02 (0.02, 0.03)	0.02 (0.01, 0.02)
Placenta[d]	3	--	--
Vagina	37	0.02 (0.01, 0.02)	0.01 (0.01, 0.01)
Vulva	90	0.03 (0.03, 0.04)	0.02 (0.02, 0.03)
Uterine adnexa, not including ovaries	17	0.01 (0.00, 0.01)	0.00 (0.00, 0.01)
Other female genital organs[d]	2	--	--
Testis	72	0.03 (0.02, 0.04)	0.02 (0.02, 0.02)
Penis	67	0.03 (0.03, 0.04)	0.02 (0.02, 0.03)
Other male genital organs	12	0.01 (0.00, 0.01)	0.00 (0.00, 0.01)
Ureter	44	0.01 (0.01, 0.02)	0.01 (0.01, 0.01)
Other urinary system	49	0.02 (0.01, 0.03)	0.01 (0.01, 0.02)
Neurological			
Eye	111	0.05 (0.04, 0.06)	0.03 (0.03, 0.04)
Mesothelioma	74	0.03 (0.02, 0.04)	0.02 (0.02, 0.03)
Endocrine			
Other endocrine glands and structures	146	0.06 (0.05, 0.07)	0.04 (0.03, 0.05)
Hematological			
Hodgkin's disease	135	0.05 (0.04, 0.06)	0.04 (0.03, 0.04)

Data presented for cancer sites with <150 cases over the study period. Table 10 presents results for cancer sites with ≥150 cases.

[a]667 patients were diagnosed with multiple cancer sites on the same date.

[b]Excludes non-melanoma skin cancer

[c]Malignant and carcinoma *in situ*

[d]Results not presented for cancer sites with <5 cases.

Table 16 (Supplemental). ICD-9-CM diagnosis codes used to identify site-specific cancer cases from Medicare claims

Cancer site	ICD-9 codes
Lip, oral cavity, and pharynx	
Lip	140.XX
Tongue	141.XX
Salivary gland	142.XX
Mouth	143.XX-145.XX
Pharynx	146.XX-148.XX
Other and ill-defined sites within the lip, oral cavity, and pharynx	149.XX
Digestive system	
Esophagus	150.XX
Stomach	151.XX
Small intestine	152.XX
Colon/rectum	153.XX, 154.0, 154.1, 154.8
Anus	154.2, 154.3
Liver and intrahepatic bile duct	155.XX
Gallbladder and other biliary	156.XX
Pancreas	157.XX
Other and ill-defined sites within the digestive organs and peritoneum	158.XX (except for 158.8),159.XX
Respiratory system and intrathoracic organs	
Nasal cavity, middle ear, and sinus	160.XX
Larynx	161.XX
Lung/bronchus	162.XX (except for 162.0)
Trachea	162.0
Other and ill-defined sites within the respiratory system and intrathoracic organs	163.XX-165.XX (except for 163.9 and 164.1)
Bone and cartilage	170.XX
Skin/connective tissue (excludes non-melanoma skin cancer)	
Melanoma	172.XX
Connective & other soft tissue	171.XX
Kaposi sarcoma	176.XX
Breast	
Breast (female), malignant and *in situ*	174.XX, 233.0
Breast (male), malignant and *in situ*	175.XX, 233.0
Genitourinary	
Cervix uteri	180.XX
Corpus and uterus	179.XX, 182.XX
Placenta	181.XX
Ovary	183.0
Vagina	184.0
Vulva	184.1-184.4
Uterine adnexa, not including ovaries	183.2-183.9
Other and unspecified female genital organs	184.8-184.9
Prostate	185.XX
Testis	186.XX
Penis	187.1-187.4
Other and unspecified male genital organs	187.5-187.9
Bladder, malignant & *in situ*	188.XX, 233.7
Kidney and renal pelvis	189.0, 189.1
Ureter	189.2
Other and unspecified urinary organs	189.3-189.9

Other	
Eye	190.XX
Brain and other nervous system	191.XX-192.XX
Mesothelioma	158.8, 163.9, 164.1
Thyroid	193.XX
Other endocrine glands and structures	194.XX
Hematological	
Lymphoma: Hodgkin's disease	201.XX
Lymphoma: Non-Hodgkin lymphoma	200.XX, 202.XX excluding 202.4
Multiple myeloma	203.0
Leukemia	202.4, 204.XX-208.XX
Ill-defined and unspecified	195.XX-199.XX

Table 17 (Supplemental). Descriptive characteristics of inverse probability of exposure weights by patient characteristic

Characteristic	IP of exposure weights Mean (minimum, maximum)
Age at dialysis initiation	1.001 (0.171, 6.771)
Sex	1.000 (0.689, 1.800)
Race	1.013 (0.444, 35.804)
Ethnicity	1.013 (0.306, 51.936)
Reported cause of ESRD	0.999 (0.135, 7.083)
Calendar period of dialysis initiation	1.002 (0.676, 2.199)
History of kidney transplant evaluation	1.000 (0.549, 25.308)

Appendix B. Supplemental analyses for Chapter V

Table 18 (Supplemental). ICD-9-CM diagnosis codes used to identify site-specific cancer cases from Medicare claims

Cancer site	ICD-9-CM diagnosis codes
Lip, oral cavity, and pharynx	
Lip	140.XX
Tongue	141.XX
Salivary gland	142.XX
Mouth	143.XX-145.XX
Pharynx	146.XX-148.XX
Other and ill-defined sites within the lip, oral cavity, and pharynx	149.XX
Digestive system	
Esophagus	150.XX
Stomach	151.XX
Small intestine	152.XX
Colon/rectum	153.XX, 154.0, 154.1, 154.8
Anus	154.2, 154.3
Liver and intrahepatic bile duct	155.XX
Gallbladder and other biliary	156.XX
Pancreas	157.XX
Other and ill-defined sites within the digestive organs and peritoneum	158.XX (except for 158.8),159.XX
Respiratory system and intrathoracic organs	
Nasal cavity, middle ear, and sinus	160.XX
Larynx	161.XX
Lung/bronchus	162.XX (except for 162.0)
Trachea	162.0
Other and ill-defined sites within the respiratory system and intrathoracic organs	163.XX-165.XX (except for 163.9 and 164.1)
Bone and cartilage	170.XX
Skin/connective tissue (excludes non-melanoma skin cancer)	
Melanoma	172.XX
Connective & other soft tissue	171.XX
Kaposi sarcoma	176.XX
Breast	
Breast (female), malignant and *in situ*	174.XX, 233.0
Breast (male), malignant and *in situ*	175.XX, 233.0
Genitourinary	
Cervix uteri	180.XX
Corpus and uterus	179.XX, 182.XX
Placenta	181.XX
Ovary	183.0
Vagina	184.0
Vulva	184.1-184.4
Uterine adnexa, not including ovaries	183.2-183.9
Other and unspecified female genital organs	184.8-184.9
Prostate	185.XX
Testis	186.XX
Penis	187.1-187.4
Other and unspecified male genital organs	187.5-187.9
Bladder, malignant & *in situ*	188.XX, 233.7

Kidney and renal pelvis	189.0, 189.1
Ureter	189.2
Other and unspecified urinary organs	189.3-189.9
Other	
Eye	190.XX
Brain and other nervous system	191.XX-192.XX
Mesothelioma	158.8, 163.9, 164.1
Thyroid	193.XX
Other endocrine glands and structures	194.XX
Hematological	
Lymphoma: Hodgkin's disease	201.XX
Lymphoma: Non-Hodgkin lymphoma	200.XX, 202.XX excluding 202.4
Multiple myeloma	203.0
Leukemia	202.4, 204.XX-208.XX
Ill-defined and unspecified	195.XX-199.XX

Table 19 (Supplemental). Administrative codes used to identify anemia treatment

Anemia treatment	Codes
Epoetin alfa	USRDS summarized variables: epo, epoadmin, epodose, n_epo
Darbepoetin alfa	HCPCS: J0880, J0881, J0882, Q0137, Q4054
Blood transfusions	ICD-9-CM procedure codes: 99.03, 99.04 HCPCS: P9010, P9011, P9016, P9021, P9022, P9038, P9039, P9040, 36430

Table 20 (Supplemental). Administrative codes used to identify receipt of any chemotherapy from Medicare claims

Medicare claims code type	Codes
ICD-9-CM diagnosis codes	V58.1, V66.2, V67.2
ICD-9-CM procedure codes	99.25
HCPCS	964xx, 965xx, C1167, C9127, C9205, C9213, C9214, C9215, C9257, C9414, C9415, C9418, C9420, C9421,C9425, C9427, C9431, C9432, C9440, J8520, J8521, J8530, J8560, J8565, J8610, J9000-J9999, G0355-G0362 (for 2005 only), Q0083-Q0085, Q2024, S0116, S1016
Revenue center codes	0331, 0332, 0335

Table 21 (Supplemental). Distribution of site-specific cancer cases among study population by year, 2000-2010

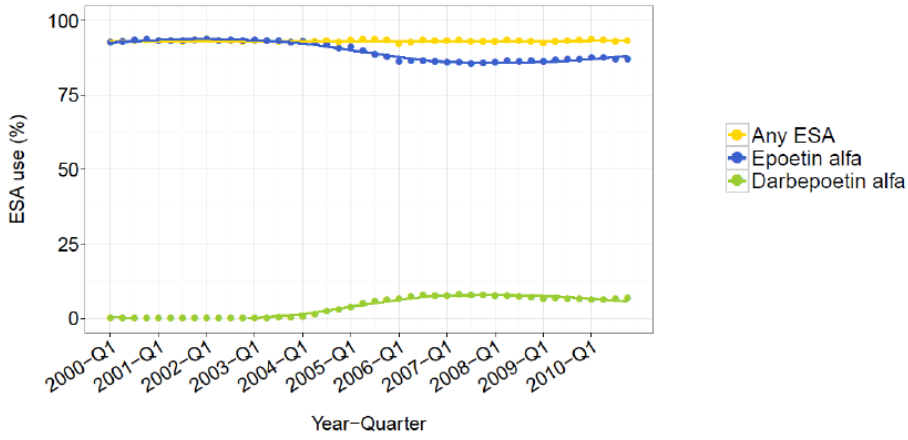
Cancer Site	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Breast (female)	513	627	720	802	876	975	995	1062	1115	1176	1177
Colon/rectum	627	762	840	912	1027	1083	1081	1191	1209	1205	1241
Kidney/renal pelvis	305	414	455	531	657	761	861	997	1066	1152	1218
Leukemia	123	161	181	198	201	212	252	251	272	292	298
Lung/bronchus	497	607	695	759	797	844	890	889	947	931	954
Hodgkin lymphoma	12	10	14	25	29	35	38	36	36	47	41
Myeloma	149	163	195	204	217	243	238	233	270	284	269
NHL	142	186	194	203	231	279	311	342	384	381	377
Pancreas	85	107	125	109	132	146	180	164	178	186	205
Prostate	859	1048	1164	1277	1401	1496	1620	1687	1783	1882	1864
Bladder	263	362	404	440	515	541	559	596	611	606	590
Other**	1,273	1,475	1,659	1,792	1,958	2,159	2,319	2,387	2,522	2,621	2,620
Multiple sites***	149	165	181	217	248	260	276	301	333	343	365
Total (including patients with missing race/ethnicity information)	4,997	6,087	6,827	7,469	8,289	9,034	9,620	10,136	10,726	11,106	11,219
Total patients missing race/ethnicity	19	17	14	9	16	15	16	14	13	15	14
Total (excluding patients with missing race/ethnicity information)	4,978	6,070	6,813	7,460	8,273	9,019	9,604	10,122	10,713	11,091	11,205

*Cancer cases may be included in multiple years.

**Other cancers were defined as all other site-specific cancers not listed (e.g., cancers of the esophagus, stomach, liver, etc).

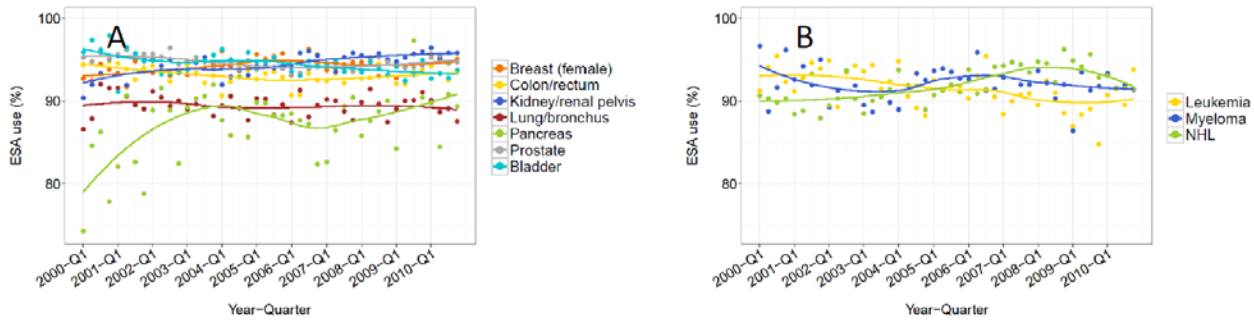
***Multiple sites indicates patients diagnosed with first cancer at ≥2 sites on the same date.

Figure 22 (Supplemental). Mean quarterly ESA use by drug type among U.S. hemodialysis patients with cancer, 2000-2010



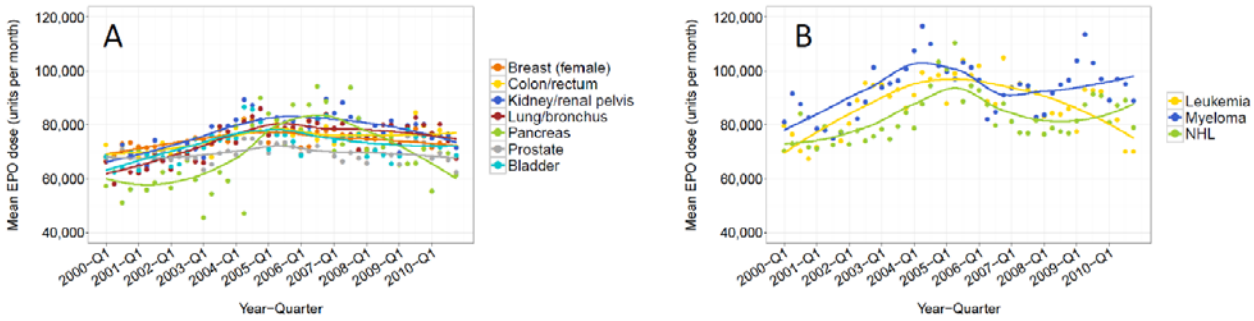
Quarterly data points were adjusted for age, sex, race, ethnicity, cause of ESRD, and dialysis vintage. Trend lines represent smoothed conditional means.

Figure 23 (Supplemental). Mean ESA use by cancer site among U.S. hemodialysis patients with cancer, 2000-2010



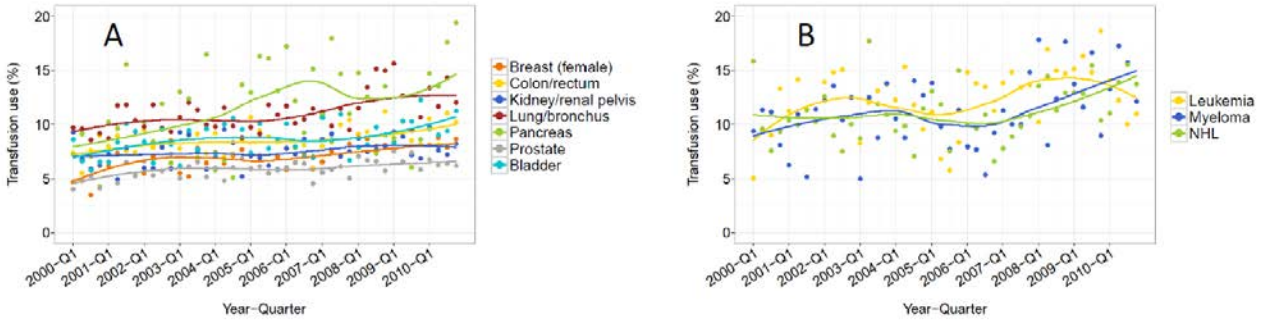
a) Common solid tumors; and b) hematologic malignancies. Hodgkin lymphoma was not presented due to small sample size. Quarterly data points were adjusted for age, sex, race, ethnicity, cause of ESRD, and dialysis vintage. Trend lines represent smoothed conditional means.

Figure 24 (Supplemental). Mean EPO dose (units/month) by cancer site among U.S. hemodialysis patients with cancer, 2000-2010



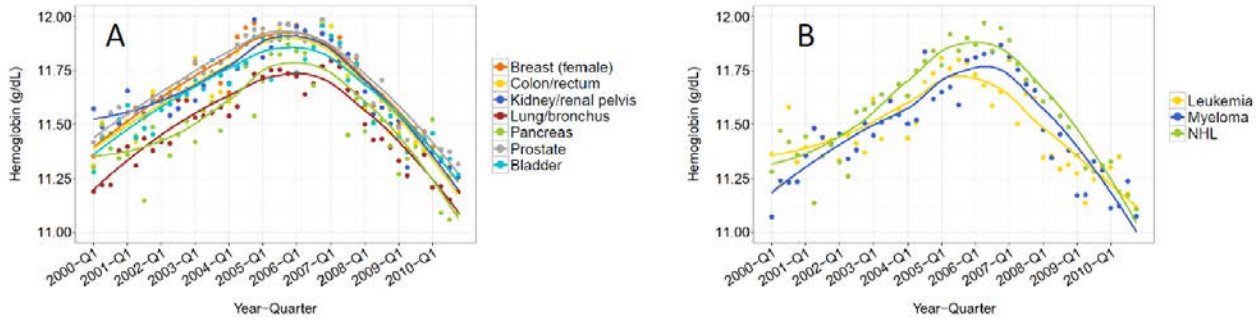
a) Common solid tumors; and b) hematologic malignancies. Hodgkin lymphoma was not presented due to small sample size. Patients treated at a hospital-based facility were excluded to remove the possibility of simultaneous treatment with EPO and darbepoetin alfa. Quarterly data points were adjusted for age, sex, race, ethnicity, cause of ESRD, and dialysis vintage. Trend lines represent smoothed conditional means.

Figure 25 (Supplemental). Mean use of blood transfusions by cancer site among U.S. hemodialysis patients with cancer, 2000-2010



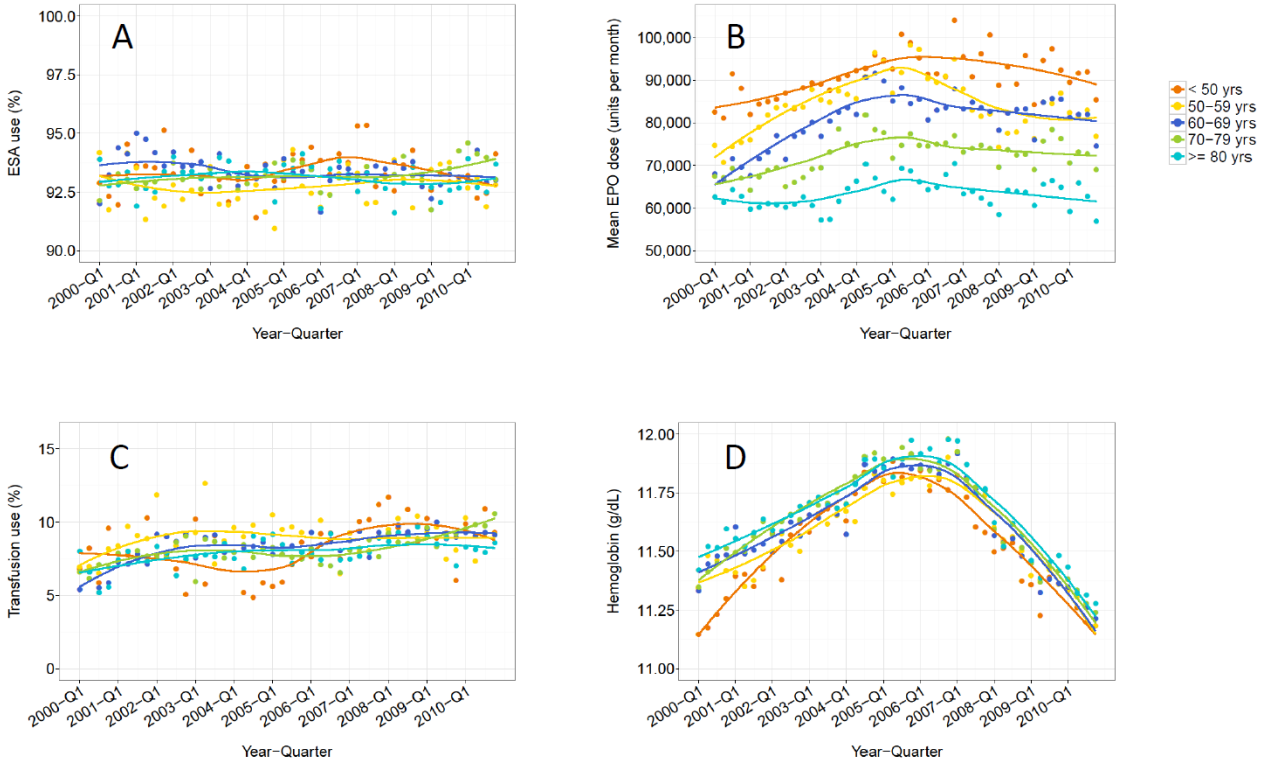
a) Common solid tumors; and b) hematologic malignancies. Hodgkin lymphoma was not presented due to small sample size. Quarterly data points were adjusted for age, sex, race, ethnicity, cause of ESRD, and dialysis vintage. Trend lines represent smoothed conditional means.

Figure 26 (Supplemental). Mean quarterly hemoglobin levels by cancer site among U.S. hemodialysis patients with cancer, 2000-2010



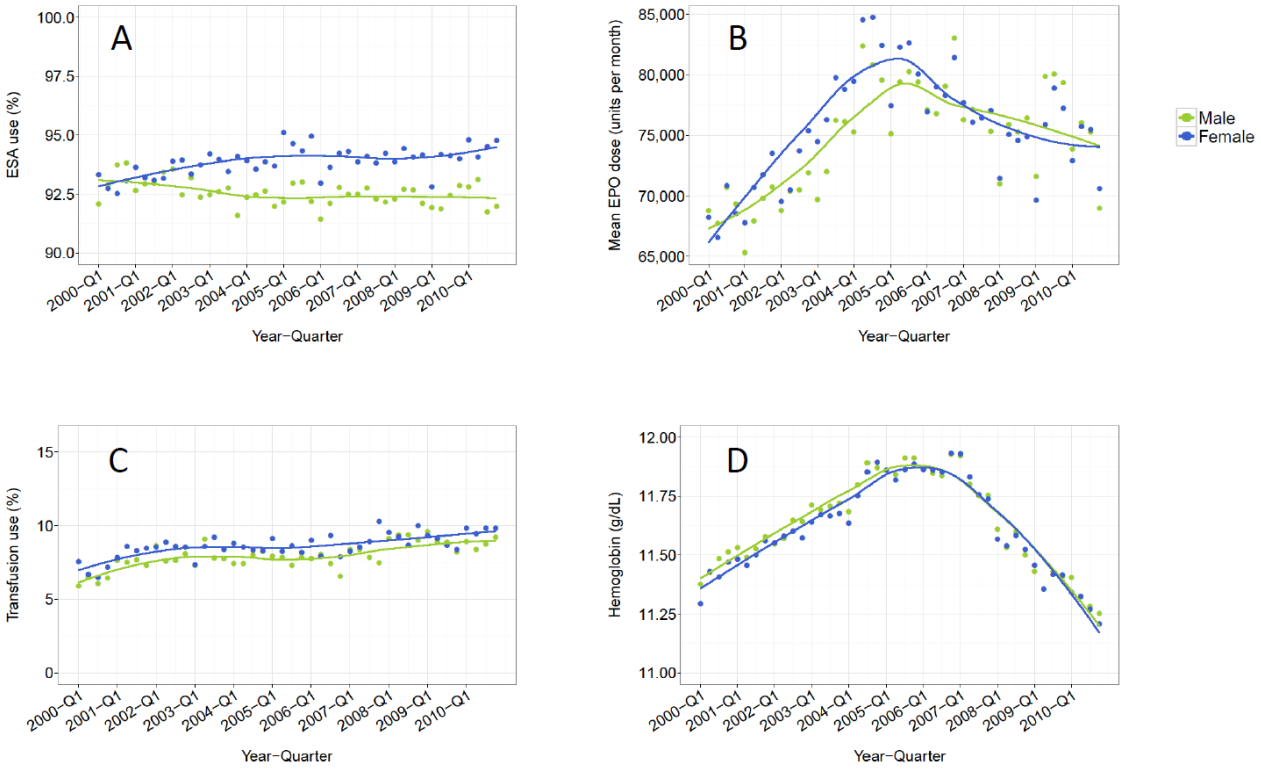
a) Common solid tumors; and b) hematologic malignancies. Hodgkin lymphoma was not presented due to small sample size. Quarterly data points were adjusted for age, sex, race, ethnicity, cause of ESRD, and dialysis vintage. Trend lines represent smoothed conditional means.

Figure 27 (Supplemental). Quarterly trends in anemia management by age among U.S. hemodialysis patients with cancer, 2000-2010



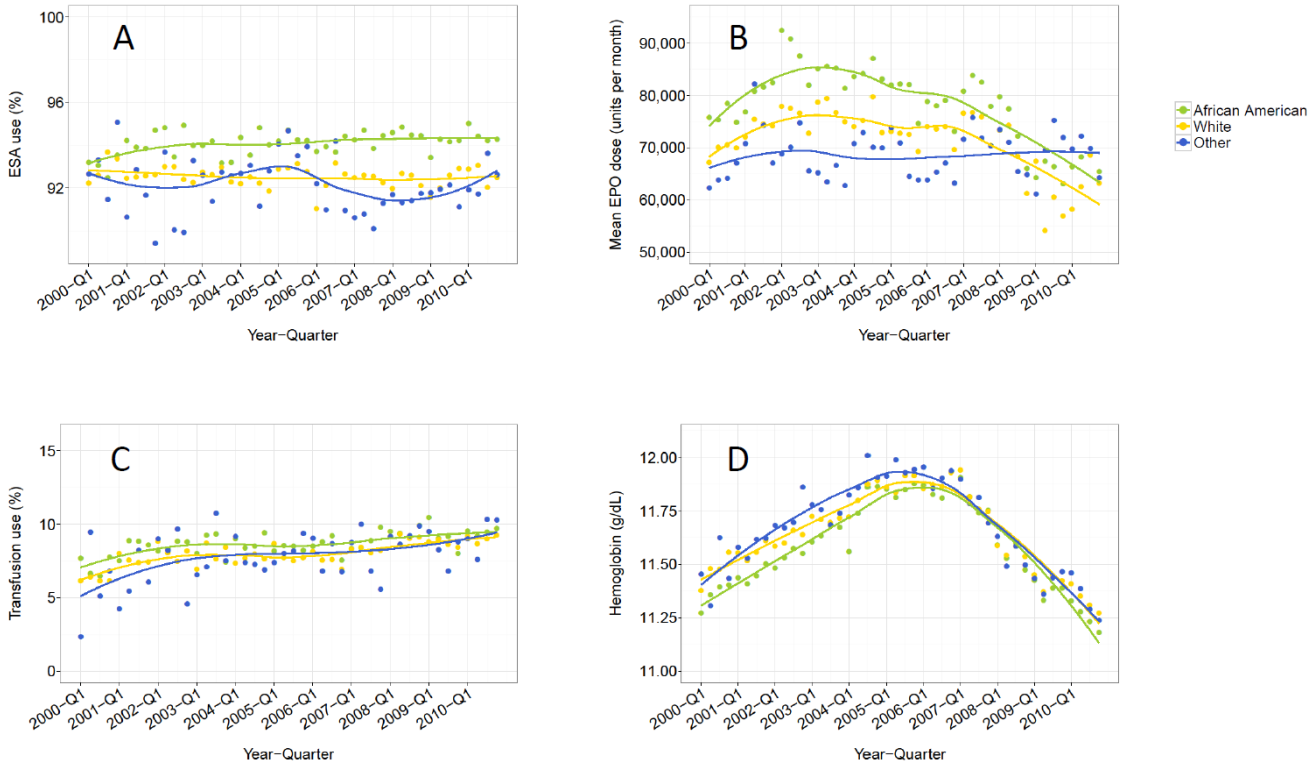
a) Mean ESA use; b) mean EPO dose (units/month); c) mean use of blood transfusions; and d) mean hemoglobin levels. Patients treated at a hospital-based facility were excluded from the EPO dose calculation to remove the possibility of simultaneous treatment with EPO and darbepoetin alfa. Quarterly data points were adjusted for age, sex, race, ethnicity, cause of ESRD, and dialysis vintage. Trend lines represent smoothed conditional means.

Figure 28 (Supplemental). Quarterly trends in anemia management by sex among U.S. hemodialysis patients with cancer, 2000-2010



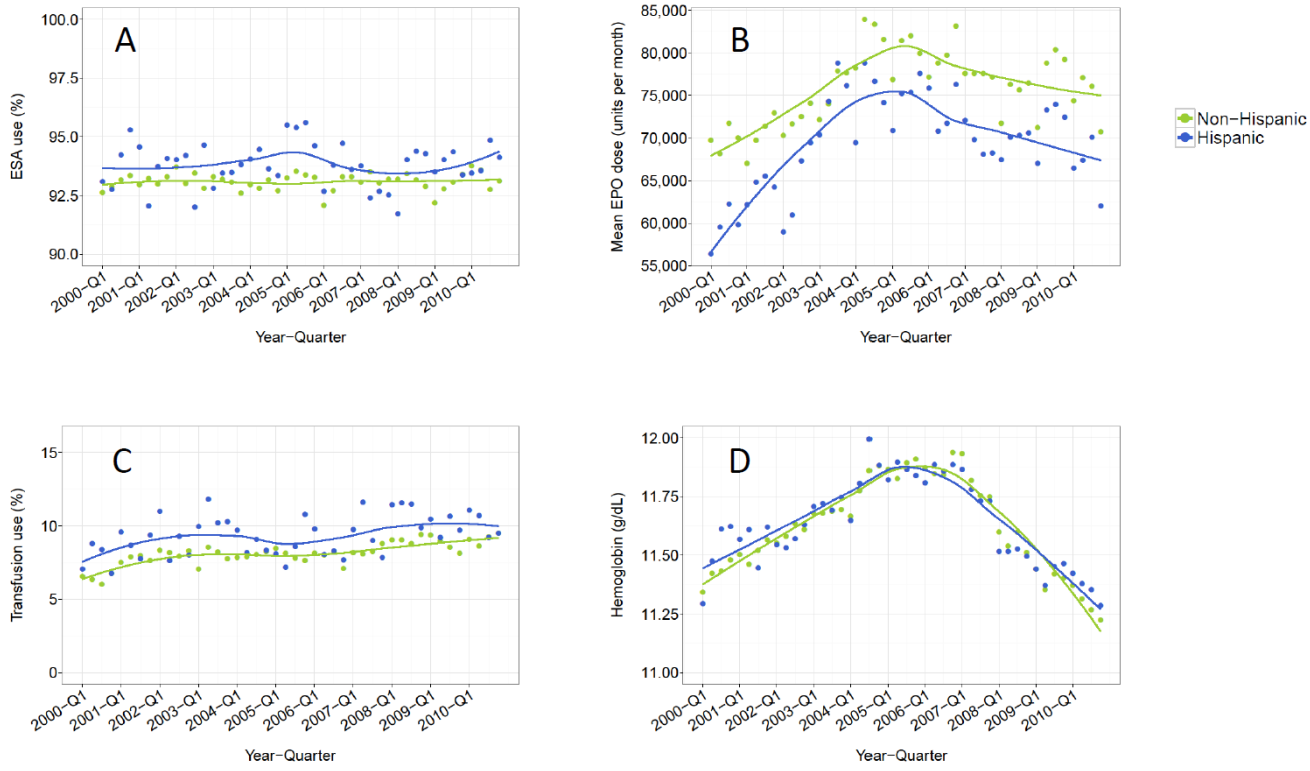
a) Mean ESA use; b) mean EPO dose (units/month); c) mean use of blood transfusions; and d) mean hemoglobin levels. Patients treated at a hospital-based facility were excluded from the EPO dose calculation to remove the possibility of simultaneous treatment with EPO and darbepoetin alfa. Quarterly data points were adjusted for age, sex, race, ethnicity, cause of ESRD, and dialysis vintage. Trend lines represent smoothed conditional means.

Figure 29 (Supplemental). Quarterly trends in anemia management by race among U.S. hemodialysis patients with cancer, 2000-2010



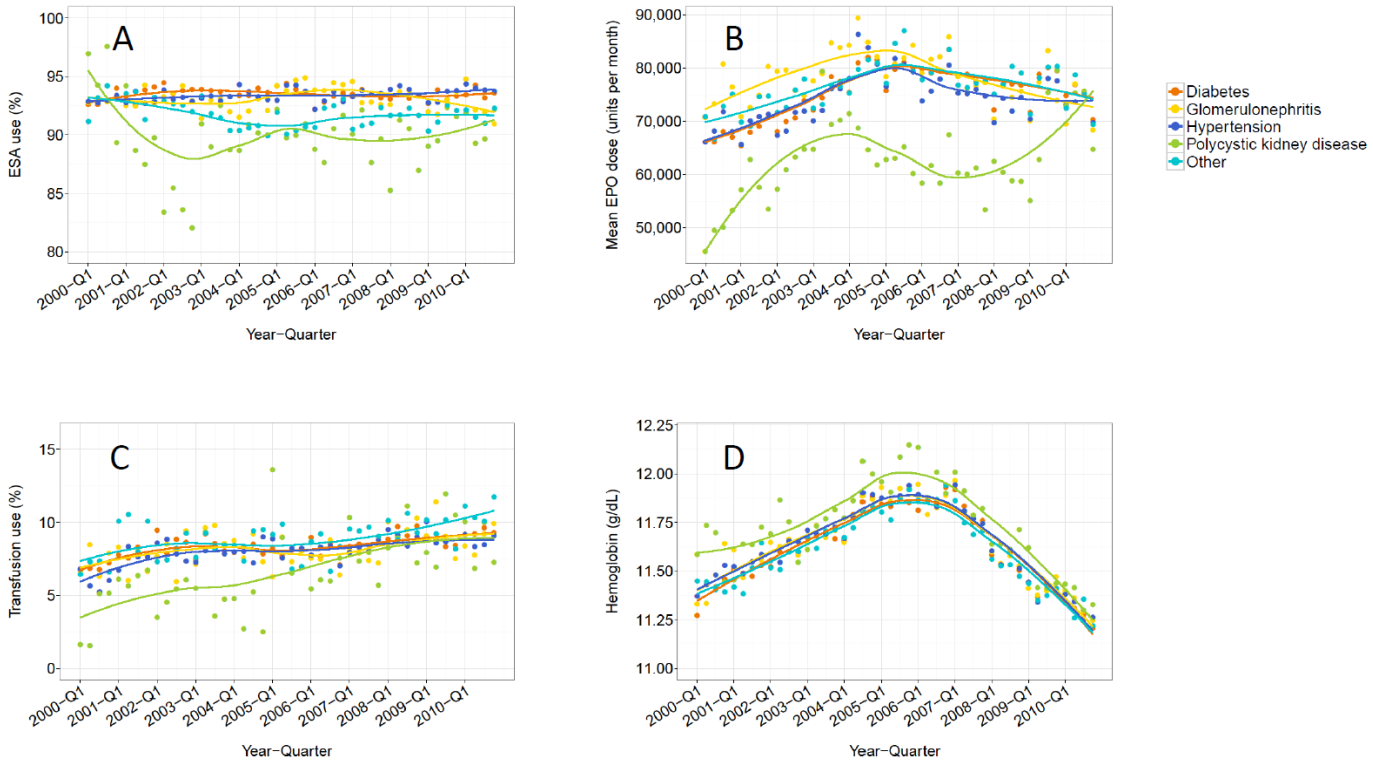
a) Mean ESA use; b) mean EPO dose (units/month); c) mean use of blood transfusions; and d) mean hemoglobin levels. Patients treated at a hospital-based facility were excluded from the EPO dose calculation to remove the possibility of simultaneous treatment with EPO and darbepoetin alfa. Quarterly data points were adjusted for age, sex, race, ethnicity, cause of ESRD, and dialysis vintage. Trend lines represent smoothed conditional means.

Figure 30 (Supplemental). Quarterly trends in anemia management by ethnicity among U.S. hemodialysis patients with cancer, 2000-2010



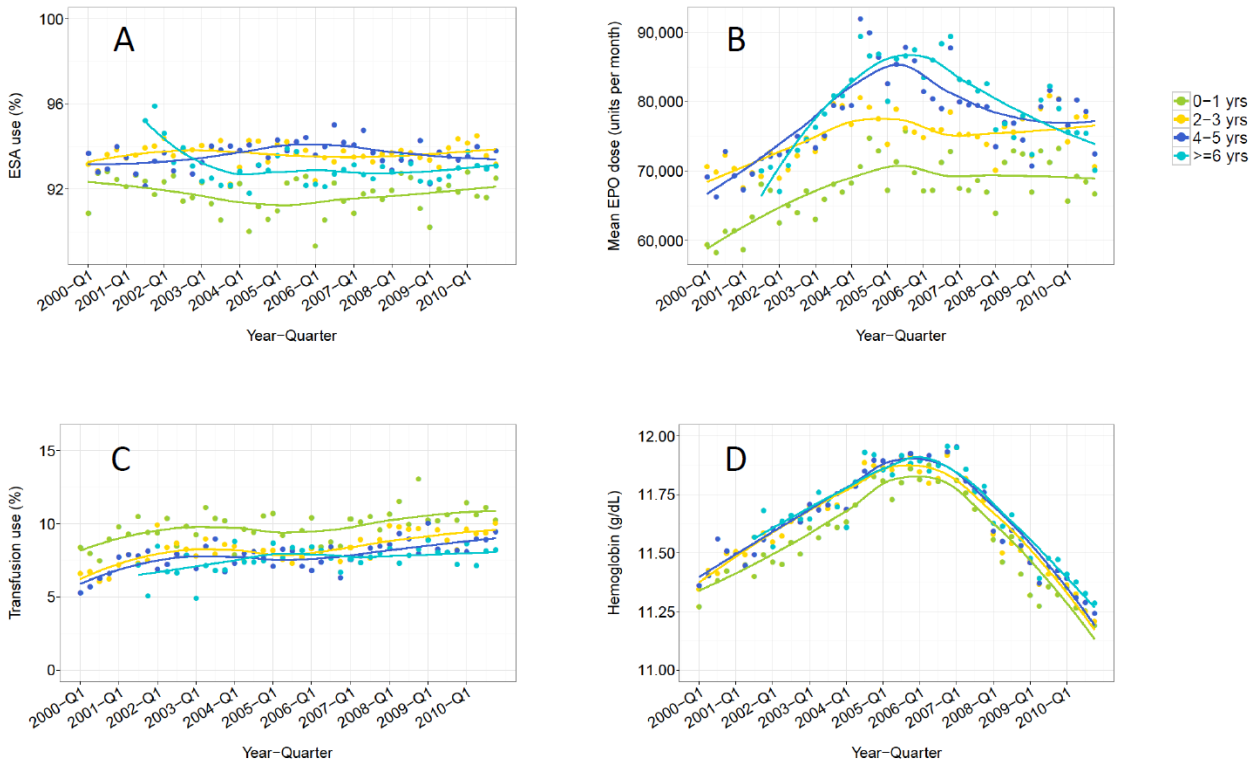
a) Mean ESA use; b) mean EPO dose (units/month); c) mean use of blood transfusions; and d) mean hemoglobin levels. Patients treated at a hospital-based facility were excluded from the EPO dose calculation to remove the possibility of simultaneous treatment with EPO and darbepoetin alfa. Quarterly data points were adjusted for age, sex, race, ethnicity, cause of ESRD, and dialysis vintage. Trend lines represent smoothed conditional means.

Figure 31 (Supplemental). Quarterly trends in anemia management by primary cause of ESRD among U.S. hemodialysis patients with cancer, 2000-2010



a) Mean ESA use; b) mean EPO dose (units/month); c) mean use of blood transfusions; and d) mean hemoglobin levels. Patients treated at a hospital-based facility were excluded from the EPO dose calculation to remove the possibility of simultaneous treatment with EPO and darbepoetin alfa. Quarterly data points were adjusted for age, sex, race, ethnicity, cause of ESRD, and dialysis vintage. Trend lines represent smoothed conditional means.

Figure 32 (Supplemental). Quarterly trends in anemia management by dialysis vintage among U.S. hemodialysis patients with cancer, 2000-2010



a) Mean ESA use; b) mean EPO dose (units/month); c) mean use of blood transfusions; and d) mean hemoglobin levels. Patients treated at a hospital-based facility were excluded from the EPO dose calculation to remove the possibility of simultaneous treatment with EPO and darbepoetin alfa. Quarterly data points were adjusted for age, sex, race, ethnicity, cause of ESRD, and dialysis vintage. Trend lines represent smoothed conditional means.

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