FACTORS ASSOCIATED WITH CHEMOTHERAPY-RELATED UNPLANNED HOSPITALIZATION AND ADVERSE EVENTS IN PATIENTS WITH LUNG AND COLORECTAL CANCER

by

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ABSTRACT OF THE DISSERTATION

Factors Associated with Chemotherapy-Related Unplanned Hospitalization and Adverse Events in Patients with Lung and Colorectal Cancer

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Chemotherapy for non-hematologic cancers is primarily administered and managed in the outpatient setting, and little is known about factors associated with hospitalizations for patients experiencing treatment-related adverse events so severe as to require inpatient care. This retrospective analysis conducted within the SEER-Medicare linked dataset in the non-metastatic lung and colorectal cancer populations revealed predictors related to the likelihood of initial unplanned hospitalization, as well as those predictive of the number of hospitalizations experienced. The tumor types were selected to allow study among two of the most frequently admitted solid tumors identified in the literature, from a nationally validated, population-based dataset comprised of patients over age 65, a group that is underrepresented in clinical trials.

Factors including patient age, sex, race, marital status, degree of residential urbanization, median income, educational level, cancer type, stage, receipt of radiation therapy and comorbidities were studied and considered as predictive factors. Two separate tumor-based cohorts, lung (n = 2457) and colorectal cancer (n = 1485), were

constructed and analyzed in parallel. Patient eligibility included those age greater than 65 years at the time of diagnosis, non-metastatic lung or colorectal cancer as their first malignant primary tumor, uninterrupted Medicare Part A and B coverage with no HMO enrollment, and those who received intravenous chemotherapy at least one time prior to experiencing a cancer-related, non-surgical hospitalization.

The cohorts were analyzed using advanced statistical models that accounted for the potential within-region effects of geography at the SEER registry level. Decreasing age, non-white race, lower rates of high school graduation, higher median income, degree of urbanization, receipt of radiation therapy and number of comorbidities were significant predictors of the likelihood of an initial unplanned hospitalization for lung cancer. Non-white race, receipt of radiation therapy, degree of urbanization and number of comorbidities were factors associated with an increased number of hospitalizations.

For colorectal cancer, female sex, decreasing age, higher rates of high school graduation, lower median income, degree of urbanization and number of comorbidities were significant predictors of initial unplanned hospitalizations. Non-white race, receipt of radiation therapy, degree of urbanization and number of comorbidities were factors associated with increased number of unplanned hospitalizations.

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The pursuit of a PhD degree is not for the faint of heart – based upon my experience, it requires a combination of superior faculty mentorship, extensive patience and flexibility on the part of family and friends to tolerate repeated absences (both physical and mental…), and unflagging persistence on the part of the candidate. Over the course of many years while supporting the important clinical research work of colleagues, I realized that I had unique questions and perspectives to contribute, and decided to pursue an academic doctorate to gain the necessary skills and knowledge to finally be the principal investigator.

In speaking to other colleagues, it seems that the overarching goal of the baccalaureate degree may be to teach the nurse to care for each individual patient well, whereas the master's degree process encourages a population-based view. To me, much of the PhD program was about learning to deconstruct ideas down to their most clear, unambiguous units, then identifying and building upon what is or is not known about how they fit into the world. This process, though somewhat painful and unfamiliar at first, has become a routine and essential part of my thinking and discussions, and I am very grateful to the faculty at Rutgers College of Nursing for the excellent teaching and guidance I received to achieve this perspective.

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During the conduct of this project, two immediate family members were diagnosed with cancer within months of each other – I am immensely grateful that they are both recovered, and am humbly reminded of the experiences of those on the other side of the exam table. I dedicate this work to you both.

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Chapter I. The Problem

Contemporary cancer treatment is predominantly administered and managed on an outpatient basis, but due to crises related to disease progression or intractable symptoms, some patients will require hospital admission. In some cases, the patient may be admitted on multiple occasions over the course of their disease trajectory, interrupting potentially curative treatment regimens and negatively impacting quality of life. The demographic, clinical and setting of care factors associated with an initial inpatient stay, or the characteristics of the subpopulation of patients that are repeatedly admitted to manage severe symptomatology during cancer treatment are not well understood, and the predominance of small, single institution retrospective data sources currently available do not fully inform the pursuit to identify predictors for unplanned single or multiple hospitalizations. This study uses a large, nationally representative, population-based database to overcome this limitation in a population of older adults, and nurses and other providers will be able to utilize findings to target interventions towards patients at the highest risk for these negative outcomes.

History of Cancer and Cancer Therapy

The first uses of the terms “carcinoma” and “cancer” have been credited to Hippocrates (460-370 BC) and Celsus (28-50 BC), though descriptions of similar disease processes are found in ancient Egyptian literature as early as 3000 BC (American Cancer Society, 2011; Garrison, 1926). Treatment at the time, though noted to be generally futile, often consisted of cautery and the application of vegetable or arsenic-based pastes (Riordan, 1949). Despite centuries of increasingly detailed recorded observations of the many types and behaviors of this group of diseases, the treatment of cancer consisted

primarily of surgery until the 1800's when early therapeutic use of radiation and oophorectomy as a hormone-deprivation strategy for breast cancer treatment began (American Cancer Society, 2011).

During World Wars I and II, the discoveries that exposure to nitrogen mustard gas compounds suppressed bone marrow and lymphatic function led to the advent of modern cancer chemotherapy as it is known today (Goodman et al., 1946). Though the term "chemotherapy" may be most widely understood to consist of any chemical in use to treat disease (Ehrlich, 1911), throughout this paper, it will be used to describe several classes of systemic therapies administered with the intent to destroy cancer cells.

Lung and Colorectal Cancer

This study focused on two tumor types, lung and colorectal cancer, as these appear in the literature as the most frequently hospitalized, non-gender based cancers (Gonzalez et al., 2005; Grant, Ferrell, Rivera, & Lee, 1995; Hassett et al., 2011; C. Weaver et al., 2006), and the typical treatment regimens do not involved planned hospitalizations after any indicated initial surgical resection (Azzoli et al., 2011; National Comprehensive Cancer Network, 2012a; National Comprehensive Cancer Network, 2012b; Pisters et al., 2007).

According to the National Cancer Institute's SEER (Surveillance, Epidemiology and End Results) Program statistics, an estimated 226, 160 people in the US were expected to be diagnosed with cancer of the lung or bronchus in 2012, and 160, 340 patients were estimated to die of the disease (Howlader et al., 2011). Approximately 87% of patients are diagnosed with non-small cell lung cancer (NSCLC), and 13% with small-cell lung cancer (SCLC); these major class diagnostic labels are a reference to the

histopathologic appearance of the tumor cells under microscopy (National Cancer Institute, 2012f). The median age at diagnosis is 70, and expected 5 year survival ranges from approximately 52% when disease is diagnosed at a localized stage to less than 4% when the patient presents with metastasis (Howlader et al., 2011).

Approximately 143, 460 patients were estimated to be diagnosed with cancer of the colon or rectum in the US in 2012, and 51, 690 patients were expected to die of these diseases (Howlader et al., 2011). The median age at diagnosis is 69, and expected 5 year survival ranges from nearly 90% when disease is diagnosed at a localized stage to about 12% when the patient presents with metastasis to other sites in the body (Howlader et al., 2011).

Older Adult Population

Though myriad genetic and environmental factors may contribute to the development of a cancer diagnosis, advancing age is considered to be a primary risk factor for most tumors (Howlader et al., 2011). The ACS projected approximately 1.6 million new cancer diagnoses of any type in 2012, with more than 577,000 deaths expected in the same year (Siegel, Naishadham, & Jemal, 2012). Approximately 59% of these patients were expected be older than 65 years, with 30% over age 75 (Scher & Hurria, 2012). In addition to a greater incidence of cancer, aging is also associated with a variety of normal physiologic changes, such as a decrease in blood cell production capacity and renal clearance, which may impact ability to tolerate treatment and toxicity rates (Balducci & Extermann, 2000).

Cancer Treatment

Cancer may arise from nearly any type of tissue within the body, and chemotherapy regimens have been tailored to treat a tumor with a number of drugs found to be active against a particular cancer based upon its histology (i.e. previously normal cell type) and stage, meaning amount and location of disease throughout the body (DeVita et al., 2008). For example, combination regimens to treat colon cancers generally include the drugs 5-fluouracil (5-FU), leucovorin, oxaliplatin and/or irinotecan in varying doses and schedules (National Comprehensive Cancer Network, 2012a). In contrast, patients with lung cancer are more likely to receive combinations of drugs from the taxane, platinum and vinca alkaloid classes (National Comprehensive Cancer Network, 2012b). To optimize tumor cell kill according to theoretical logarithmic growth curves (Simon & Norton, 2006), maintenance of the full prescribed amount and schedule of chemotherapy, known as dose intensity, is often aggressively pursued in patients with early stage disease in an effort to achieve cure or a long-lasting remission in those with advanced disease (Takimoto & Calvo, 2005). It is important to note that the toxicities associated with most chemotherapy agents are positively associated with dose and schedule (Hryniuk & Goodyear, 1990), therefore efforts to manage treatment-associated symptoms are paramount to maintain the ability to provide uninterrupted therapy as well as acceptable quality of life.

Cancer treatment in the older adult. Due to a lack of evidence to clarify the risks of harm and likelihood of benefit to treatment receipt in older adults with cancer, confidence in the safety of offering potentially curative treatment regimens to this population has been low (Balducci & Extermann, 2000). Though a growing body of

evidence generated over the past decade by geriatric oncology specialists has illustrated that physiologic age, as assessed by functional status, comorbidities and other factors may be more important to clinical decision making than chronologic age (Balducci & Extermann, 2000; Langer et al., 2003), many oncologists continue to utilize chronologic age alone in the decision whether or not to offer chemotherapy (Wang et al., 2012).

The strongest level of evidence illustrating the type and incidence of adverse events in elderly patients should ideally be generated through participation in controlled, randomized clinical trials, providing evidence to guide subsequent community-based therapy. This body of knowledge is less robust due to the scarcity of patients over age 65 that enroll in trials, though efforts to purposefully enrich this population began in the 1980's (Begg, Cohen, & Ellerton, 1980). Due to acknowledged physiologic differences in older adults, simple extrapolation of adverse event and survival data from younger patients may not be appropriate. For example, dedicated pediatric and women's health research initiatives have illustrated the need for individualized trials and population-tailored interventions (Boklan, 2006; Women's Health Initiative Study Group, 1998). The paucity of this type of data in older adults not only hampers risk assessment and decision making, but reinforces an erroneous impression that chemotherapy may only be appropriate for a small subset of older patients.

Outpatient versus Inpatient Care

With the advent of white blood cell colony stimulating factors (CSFs) to help prevent infection and more advanced anti-nausea drugs in the early 1990's, the majority of chemotherapy administration now takes place in the outpatient setting (Dollinger, 1996), which may include areas such as an ambulatory department in a hospital, a free-

standing clinic or a private, physician-owned office. Beyond the initial surgical interventions for staging and resection, treatment regimens for patients with non-hematologic cancers, including lung and colon cancers as the selected tumor types for this study generally do not include further planned inpatient care (National Comprehensive Cancer Network, 2012a; National Comprehensive Cancer Network, 2012b), and any further hospitalizations may be considered an unplanned event to manage a complication so severe as to require inpatient care.

Unplanned Hospitalization

The concept of an initial unplanned hospitalization is distinct from readmission, where a patient is discharged from an inpatient stay, then must return to the hospital for further planned or unplanned inpatient care (Fessele & Atkins, 2012; Jencks, Williams, & Coleman, 2009; Mulder, Tzeng, & Vecchioni, 2012). Both concepts represent serious clinical issues, and each may be sensitive to nursing interventions to prevent their occurrence, diminish their frequency and/or shorten their duration (Given & Sherwood, 2005). As data regarding the concept are limited, larger scale studies, such as this work are needed to develop predictors for the incidence of initial unplanned hospitalization and multiple readmissions in the patients intended to be treated exclusively in the outpatient setting.

As will be discussed in greater detail in Chapter 2, published studies identifying factors associated with oncology-related unplanned hospitalization are often limited to small datasets derived from cross-sectional single institution retrospective chart reviews, and describe disease progression and treatment-related symptom management crises as primary reasons for hospitalization (Gonzalez et al., 2005; Grant et al., 1995; Hassett et

al., 2011; C. Weaver et al., 2006). An unplanned hospitalization may present a significant clinical disruption in regards to the ability to maintain potentially curative dose intensity, exposure to possible nosocomial and iatrogenic complications, financial burdens associated with an inpatient stay and the impact on the patient and family's quality of life.

Hospital readmission has emerged as a focal point for health care reform, as part of the Affordable Care Act's efforts to increase patient-centered quality of care and reduction in avoidable costs (Office of Management and Budget, 2009). An important subpopulation to consider are those patients that are repeatedly readmitted, sometimes semi-humorously referred to as "frequent fliers" (Mulder et al., 2012). There is scant literature describing the features of this group, and poor consensus related to unique factors associated with predictors for repeated admissions (Hockenberry, Burgess, Glasgow, Vaughan-Sarrazin, & Kaboli, 2012). Though conceptual and operational clarity between unplanned hospitalization as defined in this study and readmission is essential, a relationship clearly exists on an intra-individual basis in those patients with more than one inpatient stay over the course of their cancer experience. Careful characterization of the factors associated with this problem is critical to the design of policy and practice interventions that not only ameliorate the problem, but avoid unintended consequences, especially in the care of vulnerable elders such as those undergoing cancer therapy (Naylor et al., 2012).

Use of Administrative Databases as a Method of Nursing Inquiry

An alternate method to assess the type and frequency of unplanned hospitalizations and the prevalence of severe toxicity associated with chemotherapy treatment beyond single institution retrospective review designs or secondary analysis of

data from a controlled research project is to query existing electronic data repositories derived from data generated during the care of older adults as they receive treatment in the community setting, providing a "real world" view of care patterns. The number and breadth of large "living" databases, where new cases and observations are continually added as patients interact with the healthcare system are increasing rapidly as electronic health records, health information exchanges, clinical registries and tissue data banks become more widespread (Jacobson, Neuss, & Hauser, 2012; Koh, Judge, Ferrer, & Gershman, 2005). Though the number of citations identified in the literature written by nurses utilizing this method of inquiry is currently small, given the anticipated exponential expansion of digital health information over the next few decades, it behooves the nursing profession to gain skill in this area (Kneipp & Yarandi, 2002; Zeni & Kogan, 2007). The ability to successfully query clinical databases with large numbers of patients allows the researcher an opportunity to not only identify areas of commonality across a majority of cases over time, but also provides sufficient cases and observations to more deeply explore inter- and intra-individual variability among discordant results (Henly, Wyman, & Findorff, 2011).

The exploration of administrative claims-based databases as a method of inquiry is increasingly employed by health services researchers (Koh et al., 2005). The NCI's SEER– Medicare database is a specialized, nationally representative resource that permits researchers to create and follow data derived from cohorts of patients across the United States who have Medicare and a cancer diagnosis (Warren, Klabunde, Schrag, Bach, & Riley, 2002). When cohorts are restricted to those with Medicare benefits due to age greater than 65 years with continuous and primary coverage through this payer, this

database allows longitudinal study of large numbers of patients with cancer as they move through multiple aspects of the health care system, capturing administrative claims data on care provided in any setting by any provider accepting this national coverage (Warren, 2002). The SEER-Medicare database will be discussed in greater detail in Chapter 3.

Statement of the Problem

What factors predict unplanned hospitalizations for serious chemotherapy-related adverse events in patients in the SEER-Medicare linked database with Stage I-III lung and colorectal cancer while receiving ambulatory anticancer therapies? Specifically:

1. What demographic and clinical factors predict **initial unplanned hospitalizations** in separate cohorts of patients with non-metastatic lung and colorectal cancer in the SEER-Medicare linked database?

2. What demographic and clinical factors **predict the number** of unplanned hospitalizations for chemotherapy-related serious adverse events in separate cohorts of patients with non-metastatic lung and colorectal cancer in the SEER-Medicare linked database?

Definition of Terms

Outcome Variable

Unplanned hospitalization is constitutively defined as an inpatient hospital stay that is not part of a patient's intended cancer treatment plan and occurs related to a cancer disease or treatment-related complication that cannot be managed in the outpatient setting (Fessele & Atkins, 2012). Though patients with cancer, like those in the general population may be hospitalized for non-cancer related injury or illnesses, this study

focused on problems related to the cancer diagnosis and treatment trajectory in cohorts of patients where care was intended to be provided exclusively in the outpatient setting.

Operationally, unplanned hospitalizations were defined by identifying all MEDPAR (Medicare Provider Analysis and Review) inpatient claims that specified a cancer diagnosis ICD-9-CM code (*DIAGCD1-10* ='DIAGNOSIS CODE #1-10') in one of the first two diagnostic positions (Mayer, Travers, Wyss, Leak, & Waller, 2011) among patients with at least one preceding billed claim for chemotherapy, as indicated by the presence of a value including the prefix "J9" for the variable *HCPCS* (Healthcare Common Procedure Coding System*)* in the NCH (National Carrier History) or Outpatient files. The J9 HCPCS code series identifies the majority of chemotherapy drugs for billing purposes, including those of interest for this study. The first incidence of such a MEDPAR claim was referred to as the "index" admission, and was the observation included in the analysis for Research Question 1.

Hospital readmission is conceptually defined as an inpatient stay subsequent to an index admission (Jencks et al., 2009). It may be temporally related to the initial unplanned hospitalization, but is not necessarily causally related. It was operationally defined in this study by any MEDPAR claim subsequent to an index admission for the same patient case, using the same variables noted to capture unplanned hospitalizations.

Independent Variables

Demographic. Chronologic age is conceptually defined as the number of years a patient has accrued between birth and a particular time of reference (Merriam-Webster Dictionary, 2012). Operationally, chronologic age was measured as the patient's age at

the time of cancer diagnosis, as derived from the variable *AGEDX65* ='SEER Age at Diagnosis' in the PEDSF (Patient Entitlement and Diagnosis Summary) file.

Sex is conceptually defined as belonging to either the male or female category based on human reproductive functions (Oxford English Dictionary, 2012). Operationally, sex was defined by the value of variable *s_sex* = 'SEER Sex' in the PEDSF file.

Race is conceptually defined as a classification system categorizing biologic and physical differences among humans (Schaefer, 2008). Operationally, it was defined by the variable s*race* = 'SEER Race' in the PEDSF file.

Marital status is conceptually defined as the status of a person as indicated by the marriage laws in their jurisdiction of residence (Organisation for Economic Co-Operation and Development, 2006). It was operationally defined by the value of variable *marst1* = 'Marital Status at diagnosis' in the PEDSF file.

Geography for the purpose of this study is conceptually defined as influence of place on the incidence of disease (Meade & Emch, 2010). Operationally, it was defined by the variables *reg1* = 'SEER Registry Code at Diagnosis' in the PEDSF file.

Clinical. This study was limited to patients with cancers of the lung, bronchus, colon or rectum. Within these broad diagnostic labels, specific histologic subtypes exist that may influence disease behavior and response to treatment, and were therefore included in this analysis. Cancer type is conceptually defined as the patient's specific diagnosis among one of more than 100 categories of diseases characterized by abnormal cell division and metastatic potential (National Cancer Institute, 2012b), and

operationally defined by the variable *hist1* = 'Histologic Type ICD-O-3' in the PEDSF file.

Disease staging varies based on the cancer type, and in non-hematologic cancers is based on the AJCC (American Joint Commission on Cancer) criteria. Appendix II details the criteria for lung and colorectal cancers. Disease stage was conceptually defined for the purpose of this study as the amount and location of the primary tumor and any direct extension or metastatic deposits throughout the body (National Cancer Institute, 2012b). Operationally, disease stage was defined by the value of the variable *dajccstg1*= 'Derived AJCC Stage Group, 6th ed (2004+)' in the PEDSF file.

Comorbidity is conceptually defined as the type and number of illnesses manifest in patient (Fried, Ferrucci, Darer, Williamson, & Anderson, 2004). It was operationally defined through identification of ICD-9-CM diagnostic codes utilized by the NCI Combined Index for producing weighted comorbidity scores found in any inpatient or outpatient Medicare claims (Klabunde, Legler, Warren, Baldwin, & Schrag, 2007) during the 12 month period prior to cancer diagnosis.

Surgery is conceptually defined as any invasive procedure to identify, remove or repair a body part or tumor (National Cancer Institute, 2012d), and may occur initially as an intervention to assist in staging the cancer and resecting as much tumor as possible. Surgery may also be employed later in the course of disease to provide palliative tumor debulking, or for insertion of infusion devices or stents. As surgery is rarely an intervention utilized to manage chemotherapy-related toxicity, hospitalizations were excluded from analysis where surgical resection was noted in one of the first two

diagnostic positions in the MEDPAR file through the value of variables *SRGCDE1-6* = 'SURGICAL PROCEDURE CODE #1-6'.

Radiation therapy is conceptually defined as the use of high-energy external or implanted radiation sources to destroy tumor cells (National Cancer Institute, 2012c). Initially it may be employed following surgical resection to destroy remaining cancer cells in the area of the primary tumor bed and decrease the incidence of local recurrence. Radiation therapy is also an effective intervention to treat sites of metastatic disease, especially painful or unstable bony metastases (Baker, 2010). Operationally, initial therapy was defined by the value of the variable *rad1* = 'Radiation' in the PEDSF file.

Chemotherapy is a major component of cancer treatment for disease with evidence of or at high risk for spread through the lymphatic or blood vessels (DeVita et al., 2008). It is frequently delivered intravenously, with multiple drugs administered in varying combinations of dose and time schedules. It is conceptually defined as the use of drugs to destroy cancer cells (Levine, 2010). Operationally, it was defined through individual drug-specific values of the variable *HCPCS* = 'Hcpcs code' claims located in the Outpatient or NCH files. Appendix IV lists commonly used chemotherapy drugs and combination regimen descriptions.

Delimitations

This study sought to identify predictive factors for chemotherapy-associated unplanned hospitalizations among patients whose therapy was intended to be provided exclusively in the outpatient setting. Patients with stages I-III and histologic subtypes of lung and colorectal cancers met these criteria, and two separate cohorts with similar characteristics were created from these populations. All cases were at least 66 years old at

time of cancer diagnosis, and had continuous Medicare Parts A and B coverage as the primary payer, without an HMO component, for at least 12 months prior to a subsequent initial cancer diagnosis to permit identification of comorbidities. Cohorts were then limited to include those cases where there was at least one billed claim for a chemotherapy drug prior to the initial and subsequent unplanned hospitalizations.

Significance

In the outpatient setting, nurses work in many roles to provide high-quality, patient-centered cancer care. These may include the staff/infusion nurse, the advanced practice nurse, the navigator/case manager, staff educator and nurse manager, and though day to day responsibilities may vary, each maintains a focus on ensuring that every patient receives care in a safe, effective manner with a focus on the proactive management of potential physical and emotional symptoms resulting from the disease and administered treatments. Generally, one or more nurses, in either a formal collaborative role with a specific physician, or as support for a defined population (e.g. by tumor type) follow those patients from the time of diagnosis, throughout their treatment plan and into follow-up or end-of-life care (Cohen, Ferrell, Vrabel, Visovsky, & Schaefer, 2010; Towle et al., 2011). Due to this often long-term relationship, outpatient oncology nurses come to "know" their patients and family members well, recognize and intervene when impending or exacerbating issues arise (Perry, 2006), and are uniquely well-positioned to advocate for them to promote a patient-centered care experience, highlighting the importance of engaging the patient and family in decision-making regarding their care to incorporate their personal goals and preferences (Quality and Safety Education for Nurses, 2012).

Nurse-sensitive patient outcomes (NSPO) are those areas where evidence suggests that care provided by nurses is linked to patient outcomes (Given & Sherwood, 2005; Kurtzman & Corrigan, 2007). In oncology, aggressive symptom management during cancer treatment maintains safe care, permits maintenance of dose intensity in potentially curative situations and promotes the highest degree of quality of life possible for an individual patient during and after cancer treatment. Oncology nurses are responsible to assess risk factors for a potential symptom or clinical problem, tailor the educational messages to the patient and family to ensure adequate vigilance and appropriate action are taken for high-risk issues, and to employ an appropriate degree of clinical monitoring to identify an emerging or exacerbating problem at stage where it can be reversed or managed (Cohen et al., 2010; Perry, 2006). Ideally, such proactive management will occur while the patient remains in the outpatient setting, though realistically not all complications can be controlled safely without the intensive resources available upon hospital admission (Dollinger, 1996).

Identification of predictors for unplanned hospitalizations in patients receiving outpatient chemotherapy presents a significant benefit to nurses and the patients under their care at multiple points in the disease trajectory. During the treatment planning period, a patient-centered treatment approach requires an informed discussion about the potential risks of harm and likelihood of benefits associated with treatment options. Information about potential risks beyond those reported in the clinical trial literature, previously noted to be limited due to the smaller proportion of older adults enrolled, supports decision-making and goal setting among the patient, family and the treatment team.

In addition, identification of patient-related factors predictive of increased incidence of serious events leading to unplanned hospitalization allows a proactive treatment planning approach for generalist and advanced practice nurses. Individualized/increased toxicity monitoring and focused patient education can be implemented for those noted to be at higher risk of negative outcomes. From an administrative perspective, should a set of factors that predict a higher risk of severe adverse events and/or hospitalization be identified through this study, prospective validation would allow more specific case mix analysis for a clinical practice, potentially informing staffing needs and program structure.

Chapter II. Review Of The Literature

This chapter will discuss the current state of the literature regarding the concept of unplanned hospitalizations in the context of ambulatory cancer treatment, and factors that may be associated with symptoms so severe as to require inpatient management. The theoretical models that are applicable to the patient symptom experience and its management will be examined, and relevant propositions reviewed. As a major area of exploration in this study regards the incidence of multiple intra-patient hospitalizations, literature discussing potential predictors for repeated admission will be included.

Unplanned Hospitalizations

The outcomes of interest in this study relate to hospitalizations occurring among those patients who received chemotherapy on an outpatient basis. According to a recent Agency for Healthcare Research and Quality (AHRQ) report, there were approximately 4.7 million cancer-related hospitalizations in the US in 2009, and Medicare was the primary payer for 48% of them (Price, Stranges, & Elixhauser, 2012).

Readmission. The concept of readmission, where a patient returns to the hospital after an initial "index" stay, is well documented. In a study of Medicare beneficiaries in 2003-2004, nearly 20% of patients returned to the hospital within a 30 day period, and 34% within 90 days, resulting in an estimated $17.4 billion in costs (Jencks et al., 2009). Patient age, post-operative complications, unstable chronic conditions such as heart failure and asthma, race, geography, and the effectiveness of discharge and interprofessional "hand-off" practices as patients transition among care settings are among factors that have been associated with readmission (Halfon et al., 2002; Henretta, Scalici, Engelhard, & Duska, 2011; Joynt, Orav, & Jha, 2011; Marcantonio et al., 1999).

Depending on the attendant circumstances, hospital stays may be considered planned or unplanned. There is intense interest in this area due to the enactment of the Readmissions Reduction Program of the Affordable Care Act (ACA). CMS is required to reduce the amount of Medicare and Medicaid payments to hospitals with excessive readmission rates for acute myocardial infarction, heart failure and pneumonia as of October 1, 2012 (Centers for Medicare & Medicaid Services, 2012b). Though cancer-specific admissions are not currently under scrutiny in this program, it has been observed that cancer ranks highly among major disease categories associated with increased 30-day readmission rates among Medicaid beneficiaries (Gilmer & Hamblin, 2010). With the movement towards accountable care organizations under the ACA, hospital readmission rates also affect financial and clinical decision-making for affiliated outpatient facilities (Epstein, 2009) and must therefore be explored with an interdisciplinary and cross-setting care perspective.

The American Hospital Association (AHA) has developed a framework to classify readmissions based on their relationship to a prior admission, and whether the stay was anticipated or unplanned (American Hospital Association, 2011).

Figure 1. A Framework for Classification of Readmissions, AHA, 2011 (Adapted with permission)

	***Related* to Initial Admission**	***Unrelated* to Initial Admission**
Planned Readmission	A **planned** readmission for which the reason for readmission is **related** to the reason for the initial admission.	A **planned** readmission for which the reason for readmission is **not related** to the reason for the initial admission.
***Unplanned* Readmission**	An **unplanned** readmission for which the reason for readmission is **related** to the reason for the initial admission.	An **unplanned** readmission for which the reason for readmission is **not related** to the reason for the initial admission.

More work is needed to clearly identify potentially avoidable versus unavoidable admissions. A number of studies discuss methods to identify readmissions that are *unplanned but potentially avoidable*, such as those related to premature discharge, adverse drug events, inadequate home management of symptoms persistent at discharge or post-surgical infections, versus those that are *unplanned and without current methods to detect impending crises* (Halfon et al., 2002; Halfon et al., 2006; van Walraven, Bennett, Jennings, Austin, & Forster, 2011).

Index admission in the outpatient oncology population. For those patients whose cancer care should occur exclusively in the outpatient area, separate attention should be paid to factors associated with the "index" unplanned admission. No oncology studies have been located that explore this area explicitly, and effort should be applied to identify factors associated with a first unplanned admission, as this has been acknowledged as a statistically significant predictor of return to hospital in multiple studies of patients with CHF and COPD (Shipton, 1996). The concept of ambulatory care sensitive conditions (ACSC), those clinical problems "for which hospital admission could be prevented by interventions" (Purdy, Griffin, Salisbury, & Sharp, 2009) is primarily limited to the primary care area. Conditions such as angina, congestive heart failure, asthma, and diabetic complications, among others are considered sensitive to primary care interventions, and rates of hospitalization related to ACSC are federally monitored indicators of quality healthcare (Agency for Healthcare Research and Quality, 2001).

Beyond a single commentary suggesting that colon cancer incidence might be considered an ACSC in light of the long window of opportunity for colonoscopy to remove precancerous lesions, typically performed as a primary care health promotion (Agency for Healthcare Research and Quality, 2001), this concept has not been applied to oncology. Considering that the majority of oncology care is provided in the outpatient setting over a multi-year trajectory, scrutiny of which types of initial unplanned hospitalizations and readmissions are potentially avoidable is valuable.

Methods were developed during data analysis to identify and exclude inpatient episodes related to primary surgical staging as well as delayed resection for those patients (such as those with Stage IIIB NSCLC) who receive neoadjuvant treatment, allowing

surgery to occur later in the treatment course. It was not possible in this study to reliably differentiate treatment- versus disease-related adverse events based on ICD-9-CM coding; patients diagnosed with stage IV (metastatic) disease were therefore excluded to decrease the likelihood that reported adverse effects during hospitalizations were due to cancer burden rather than treatment.

As noted in Chapter 1, the research questions sought to identify factors associated not only with the incidence of an initial "index" unplanned hospitalization, but also for factors that may assist in identifying those patients at high risk of multiple hospitalizations over time. These intra-patient repeated hospitalizations may or may not be related to each other, and though it may not be entirely possible through the use of claims data alone to make assessments about relatedness, the development of a preliminary predictor model will inform future work.

Single institution studies. Few studies have explored hospitalizations among patients with cancer, most as single-institution chart reviews or are conducted within large administrative datasets. Grant and colleagues (1995) performed a descriptive, retrospective chart review of 5772 admissions between October 1989 and September 1990 at an NCI-designated Cancer Center. Fever and sepsis were the most common reasons for admission (14.8 and 11.3% of readmissions, respectively), which is unsurprising given that at that time, white blood cell colony stimulating factors were not yet commercially available. Uncontrolled pain (7.6% of readmissions), dehydration (5.8%) and pneumonia (5.4%) followed as prevalent reasons for inpatient stays (Grant et al., 1995).

The authors focused much of the descriptive discussion on those patients admitted for uncontrolled pain. They observed that 54% of this subgroup returned to the hospital for pain control within 12 days of a discharge, and 26% had also been admitted specifically for uncontrolled pain within the prior 12 months (Grant et al., 1995).

A prospective study performed at a university hospital in Spain accrued 403 patients diagnosed with colorectal cancer between 1996 and 1998, measuring the occurrence of cancer-related hospital readmissions through 2002 (Gonzalez et al., 2005). The patients were readmitted a mean of 2.1 times, and these events were associated with higher disease stage at diagnosis (HR 1.78 for Dukes stage D, 95% CI [1.20-2.64]), receipt of chemotherapy (HR 1.34, CI [0.96-1.86]) or radiotherapy (HR 1.41, CI [1.00-1.99]) and multiple comorbidities (HR 1.31 for $\geq$ 3 comorbidities, [1.01-1.70]). A special focus of the analysis explored gender and association with readmission, and the authors noted that despite evidence from other sources that women experience more toxicity with 5-FU based chemotherapy regimens, the mainstay of treatment for this population, they were found to be readmitted less frequently than men (HR 1.52 for males, CI [1.17-1.96]).

Weaver and colleagues (2006) compared characteristics of patients readmitted to an NCI-designated comprehensive cancer center within 7 days of discharge versus those who did not return. Among the 74 patients in each group, those with GI cancers were most likely to be readmitted, as were those who complained of persistent nausea within 24 hours preceding discharge (73% readmitted versus only 46% of those who did not complain of nausea, $p = 0.01$). Patients with inadequate support at home (living alone or other caregiver insufficiency) were also more likely to be readmitted ($p = 0.045$).

A prospective study performed at a community hospital in New England observed 2068 patients receiving chemotherapy between 2003 to 2006, noting 262 hospitalizations attributed by consensus among the research team to be related to chemotherapy receipt (Hassett et al., 2011). The top three cancer types to be admitted included lymphoma (14.2% of hospitalizations), followed by colorectal cancer (11.9%) and lung cancer (7.2%), and intractable nausea, vomiting and diarrhea were the most common reasons for admission. Predictors for unplanned hospitalization included a score of 3 or higher on a modified Charlson index measuring co-morbidities (Charlson, Pompei, Ales, & MacKenzie, 1987; Romano, Roost, & Jollis, 1993) and an ECOG performance status score of 2 (capable of independent self-care/limited to chair or bed less than 50% of the day) or 3 (capable of limited self-care/limited to chair or bed more than 50% of the day (Buccheri, Ferrigno, & Tamburini, 1996).

Administrative dataset studies. Several authors have explored large administrative datasets to identify factors associated with hospitalization among patients with cancer. Du and colleagues (2002) studied the rate of hospitalization among 35, 060 patients with breast cancer who also received chemotherapy within the SEER-Medicare database between the years 1991-1996. Rates for serious adverse events were noted to be higher than those in clinical trial reports for the administered regimens, suggesting that incidence may indeed differ when explored within a larger, community-based sample that includes older adults, though age alone did not affect risk of hospitalization in this study. There were race-related variations noted in hospitalization rate, in that black patients were nearly twice as likely to be admitted as whites for complications of anemia. Geographically, SEER registry area was also associated with risk of admission, with

more than a two-fold increased likelihood among several of the 11 studied SEER areas. Increasing cancer stage and presence of comorbidity were also predictive for hospitalizations (OR 2.42 for Stage IV disease [1.48-3.96] and 1.43 for a modified Charlson comorbidity score of 1 [0.95-2.16]).

A study among 9361 patients identified within the SEER-Medicare data with ovarian cancer who received chemotherapy during the years 1991 to 2002 also focused on hospitalization risk (Nurgalieva, Liu, & Du, 2009). The authors grouped patients by chemotherapy classes received, focusing on the platinum and taxane classes specifically, and also stratified by increasing age. Predictors of hospitalization for toxicity among patients receiving chemotherapy included the presence of 3 or more comorbidities related to GI toxicity (OR 1.54, CI [1.10-2.14]), infection (2.20, CI [1.55-3.12]), and cardiovascular issues (4.29, CI [2.80-6.58]). Increasing disease stage was also associated with increased risk for GI toxicity (OR 2.11, CI [1.41-3.16; Stage III]; 2.51, CI [1.68-3.74; Stage IV] and infection (OR 1.85, CI [1.18-2.93; Stage III]; 2.26, CI [1.44-3.55]). Though chronologic age alone was noted by the authors not to be a predictor of hospitalization in this study, patients over age 75 receiving chemotherapy were noted in the statistical model to be more likely to experience infection (OR 1.56, CI [1.17-2.08]) and cardiovascular complications (2.09 [1.27-3.44] for ages 75-79 and 3.11 [1.91-5.07] for those over age 80). Though no etiology was posited for the observed variations, in some cases geographic region where care was received predicted hematologic (OR 2.13 [1.21-3.73] for SEER area F) or cardiovascular complications (OR 2.08 [1.10-3.96] for SEER area K).

A single study using SEER-Medicare data exploring hospitalization rates among patients with lung cancer was located. Wisnivesky and colleagues (2011) studied the impact of adjuvant chemotherapy among 3324 patients post-resection for stages II-IIIA NSCLC during the years 1992 (when the evidence began to illustrate potential survival advantage to the addition of chemotherapy for this population) through 2005. Though not a specific trial endpoint, hospitalizations for treatment-associated adverse events were also discussed, and as compared to a control group of patients, those who received chemotherapy were twice as likely to be hospitalized within 12 weeks of receipt of chemotherapy.

Hassett and colleagues (2006) also studied data derived from employer-based insurance claims among younger women (aged 63 or less) with breast cancer. Receipt of chemotherapy was a primary predictor of hospitalization; of the 12, 239 cases, 61% of those who received chemotherapy were hospitalized at least once (actually calculated at 1.41 admissions per person per year) compared to 42% of similarly matched women who did not receive chemotherapy (admitted 1.25 times per person per year; both statistics $p <$ .001). The authors found that toxicity rates were higher in their study than those reported in the clinical trials associated with the administered regimens, validating similar findings by Du et al. (2002).

Emergency room studies. Several studies examined emergency department (ED) use among patients with cancer. There is value in reviewing data generated from this source to support this study, while an ED visit is a patient-initiated (and therefore unstandardized) event, reasons for urgent presentation to the ED may mirror those associated with inpatient care, and a subset of patients are admitted after ED evaluation.

Mayer and colleagues utilized a statewide ED database in North Carolina to identify visits made by patients with cancer, as evidenced by the appearance of an ICD-9-CM cancer diagnosis code in one of the first five of ten available coding positions for the encounter (Mayer et al., 2011). 32,760 ED visits by 27, 644 patients occurred in 2008, with lung and colorectal cancers as the most common diagnostic groups (26.9 and 7.7% respectively). The five most frequently cited chief complaints (patient-reported reasons for presentation; not based on clinician diagnostic or claims data) were pain, respiratory or neurologic issues, gastrointestinal (GI) problems, and malaise. 62.3% of visits resulted in hospital admission, notably higher than the national rate of all-cause admissions post-ED visits in 2007, which was 12.5% (Niska, Bhuiya, & Xu, 2010).

A second retrospective study involving ED visits by patients with cancer performed in Australia combined two methods; a two-institution manual chart review and data mining from a statewide ED dataset (Livingston, Craike, & Considine, 2011). The authors noted that 32.5% of identified ambulatory oncology patients presented to the ED at least once, and among those, 17.6% presented three or more times during the 12 month study period. Though patients with hematologic cancers presented to the ED most frequently (17.5%), of the 58.8% of patients requiring hospital admission, those with lung and stomach/intestinal cancers were the most likely to be admitted (74.5 and 68.8% respectively).

Bozdemir and colleagues (2009) performed a prospective observational study at a tertiary hospital in Turkey, where a convenience sample of 245 patients with a diagnosis of cancer presenting to the ED was accrued over a 6 month period in 2003. Patients were examined at the time of accrual by an oncology fellow, and in addition to demographic

and clinical data, performance status was assessed for study purposes. Performance status, a measure of functional capacity, along with but independent from comorbidity, has been shown to be an important predictor of morbidity and mortality among patients with cancer (Extermann, 2007; Firat, Byhardt, & Gore, 2002; Lilenbaum, Cashy, Hensing, Young, & Cella, 2008), but is unfortunately unavailable among claims data. Of the 324 ED presentations, 23% were made by patients with GI cancers, and 22% by those with respiratory/thoracic cancers. Pain (24%), dyspnea (17%), nausea/vomiting (14%) and fever (13%) were the most common patient complaints. 53% of patients were noted to have a performance status of 3 or 4 (completely disabled/bedbound), and these scores were significant in a model predicting short-term mortality within 3 months after the ED visit (Bozdemir et al., 2009).

A second Australian study examined 12 months of retrospective data regarding ED presentations and resultant hospital admissions in a cancer center in Sydney (McKenzie et al., 2010). Again it was observed that multiple presentations and admissions involved the same patients over the course of the year, with 469 visits made by 316 patients. 73.7% of these patients had received chemotherapy within 6 months of the presentation, and of those, 69.7% had been treated within the past 4 weeks.

Multiply-admitted population. A primary aim of this study is to identify predictors of multiple unplanned hospital admissions, as scant literature is available on this phenomenon in oncology. Henretta et al.(2011) noted in a single institution retrospective review among patients with gynecologic cancers, approximately 11% experienced more than one unexpected readmission. Of the patients with ovarian cancer in the study, 13.5% had two episodes of readmissions, and 7.3% experienced between 3

to 10 episodes. Pertinent to the current study, 35% of these patients were noted to have received chemotherapy within 30 days prior to the index admission (Henretta et al., 2011).

Demographic Factors

Age. Advancing age is one of the primary risk factors for development of lung and colorectal cancers (Jemal et al., 2011). A number of authors have sought to distinguish the relationships among chronologic versus physiologic age on treatment decision-making for and ability to tolerate cancer therapy. Though there are some expected age-related alterations in organ function, such as decreases in glomerular filtration rate and reduction in bone marrow stem cells, influencing ability to tolerate renally-excreted drugs and myelosuppressive agents, geriatric oncology researchers have sought to illustrate that advancing chronologic age alone should not be considered a contraindication to cancer treatment provision in otherwise healthy older adults (Balducci & Extermann, 2000).

A number of studies have illustrated that older adults are less likely to receive chemotherapy than younger patients, even when otherwise clinically eligible, thereby depriving them of the opportunity to benefit (Sargent et al., 2001; Sundararajan et al., 2002). This finding was validated in a number of other studies illustrating similar survival when clinical parameters rather than chronological age were used to determine treatment eligibility (Chrischilles et al., 2010; Giordano, Duan, Kuo, Hortobagyi, & Goodwin, 2006; Kunos, Gibbons, Simpkins, & Waggoner, 2008; Ramsey, Howlader, Etzioni, & Donato, 2004; Wisnivesky et al., 2011). In a study of over 20, 000 patients age 65 and older with NSCLC in the Veterans Affairs (VA) system between 2003 and 2008,

Wang and colleagues (2012) noted that advancing age was a much stronger negative predictor of treatment receipt than increasing comorbidity. In addition, patients over age 65, who comprise nearly two thirds of the incident cancers in the US, participate disproportionally in clinical trials, limiting data on this population's outcomes and ability to generalize study results to older adults (Lewis et al., 2003).

Sex. Though sex is consistently identified as a descriptive variable, it has not frequently been identified as a predictive factor associated with symptom-related outcomes in patients with lung or colorectal cancer. Consistent with the finding that 5-FU, one of the most commonly administered agents to patients with colorectal cancer is cleared at a slower rate in females, Zalcberg and colleagues (1998) noted that females were significantly more likely to experience febrile neutropenia than males in a study of patients with metastatic colorectal cancer receiving 5-fluorouracil and leucovorin. Females were also more likely to experience severe mucositis among 81 patients receiving the same regimen (Nottage et al., 2003). A study by Shayne and colleagues in 2007 explored the impact of gender and other variables on treatment-induced toxicity among 976 patients with lung, colorectal, breast, lymphoma, ovarian and other genitourinary cancers (Shayne et al., 2007). Female gender was again associated with increased incidence of febrile neutropenia, affecting the ability to deliver planned chemotherapy on the desired schedule. Interestingly, when exploring differences in outcomes by gender post-surgery, Gonzalez and colleagues (2005) found that women were less likely to be readmitted to the hospital than men post-resection of colorectal cancers.

Marital status. A number of studies have noted an association between marital status and outcomes. A classic paper found that unmarried patients not only experienced significantly decreased overall survival, but also were also less likely to present with early stage disease, or to receive treatment (Goodwin, Hunt, Key, & Samet, 1987). This finding was affirmed in subsequent studies (Du et al., 2002; Luo, Giordano, Freeman, Zhang, & Goodwin, 2006; Potosky, Saxman, Wallace, & Lynch, 2004; Roetzheim et al., 2000).

Race. Baldwin and colleagues (2005) found that among 5294 patients with Stage III colon cancer in SEER Medicare between 1992 to 1996, blacks were equally likely to see a medical oncologist as whites, but were significantly less likely to go on to receive chemotherapy ($p = <.001$). Interestingly, this disparity was strongest among the younger patients (age 66-70), and longer surgical length of stay (as a proxy for illness severity), unmarried status (an indicator of social support) and residence in a census tract with lower high school graduation rates explained about 27% of the model variance. Though difficult to intuit rationale from claims data, the authors discussed potential cultural factors such as fatalistic attitudes about cancer treatment and social stigma related to the diagnosis.

Evidence suggests yet unexplained physiologic factors may also be at work; Albain and colleagues (2009) studied survival outcomes across eight cancer types in 19,457 patients enrolled across 35 clinical trials in the Southwestern Oncology Group (SWOG) from 1974 through 2001. After controlling for disease stage and treatment received, a significant decrease in survival was noted among African-American patients with breast, ovarian and prostate cancers, but not in hormonally non-specific types,

suggesting an undetermined but clinically important biologic basis for the disparity. Though no significant difference in survival was noted in lung or colorectal cancers, the study design utilized data derived from those patients enrolled on clinical trials since the 1970's, which may not initially have included those from racially disparate backgrounds in sufficient numbers, though more recent reviews have noted improved racial representativeness of accrual to SWOG studies (Hutchins, Unger, Crowley, Coltman Jr, & Albain, 1999; Unger et al., 2004).

Though surgery is the standard primary intervention for early (Stage IIIA or lower) NSCLC, Bach and colleagues (1999) found a statistically significant disparity in the rates in which black versus white patients underwent potentially curative resection (64% vs. 76.7% respectively, $p < .001$) using SEER data. Though the authors acknowledge that claims-based sources cannot inform whether surgery was offered and declined versus not offered when indicated, subsequent correspondence debates the impact of socioeconomic factors, differing rates of concomitant pulmonary conditions and marital status by race (Campbell & Greenberg, 2000). These findings were seen again in a study of 898 newly diagnosed NSCLC patients, where rate of receipt of recommended therapy, including surgical resection was higher among whites (55%) as compared to other racial groups (Potosky et al., 2004).

Few data are available in regards to race as a factor associated with unplanned hospitalization. Du (2002) found an increased rate of hospitalizations related to anemia among African-Americans treated with chemotherapy for breast cancer in a SEER-Medicare study (OR 1.71, CI [1.20=2.46] as compared to whites). Nurgalieva's study of

women with ovarian cancer did not identify race as a significant predictor of severe toxicity or hospitalization among those receiving chemotherapy (2009).

Physiological Factors

Cancer type. Patients with lung and colorectal cancers are frequently admitted to the hospital to manage complications (National Cancer Institute, 2012f). NSCLC arises from epithelial cells, with squamous cell carcinoma, adenocarcinoma and large cell carcinoma as the most common diagnoses (National Comprehensive Cancer Network, 2012b). Therapy for localized disease that has not spread beyond the primary tumor site (Stage 0 to I) is surgery, with the possible addition of radiation therapy, depending on the location of the tumor. Recommended treatment for patients with evidence of lymphatic or regional spread of disease (Stages II through IIIA) may include surgery, radiation and chemotherapy (National Comprehensive Cancer Network, 2012b; Pisters et al., 2007). For patients diagnosed with Stages IIIB to IV (disease spread so widely within or beyond the thoracic cavity that surgery would not be effective), chemotherapy becomes the primary recommended modality (National Comprehensive Cancer Network, 2012b).

Colon cancers arise from polyps in the mucosal lining of the large intestine, and are most commonly adenocarcinomas (Cappell, 2005). Initial therapy for localized (stages 0 and I) disease is surgical resection followed by observation (National Cancer Institute, 2012a). Though chemotherapy may be administered after surgical resection in Stage II disease, where the tumor extends through the intestine and may contact the peritoneum or other organs, but without lymph node involvement, this practice is not considered standard of care (National Comprehensive Cancer Network, 2012a; Schrag, Rifas-Shiman, Saltz, Bach, & Begg, 2002). Treatment for Stage III disease, where

regional spread of disease is evident includes surgical resection followed by chemotherapy. Metastatic (Stage IV) disease is generally treated with chemotherapy and targeted use of surgical resection or ablative therapies for palliation (National Comprehensive Cancer Network, 2012a).

Stage. As noted above, treatment recommendations vary significantly by presenting stage of disease for both lung and colorectal cancers. For example, during the observation period, patients diagnosed with Stage I disease may be less likely to receive chemotherapy, and therefore not be exposed to multiple months of potential toxicity. Patients presenting with Stage IV disease would be unlikely to undergo extensive surgical resection early in the disease course, though a planned hospitalization for palliative debulking might occur.

As noted in the prior SEER Medicare studies, higher stage of disease was significantly associated with unplanned, treatment-related hospitalizations. Among women with breast cancer who received chemotherapy (Du et al., 2002), presentation of Stage III or IV disease was a statistically significant predictor of unplanned hospitalization for neutropenic complications (OR 1.44, CI [1.07-1.94]/1.56, [1.10-2.21] respectively by stage), anemia (OR 2.19 [1.71-2.81]/2.03 [1.49-2.75]), dehydration (OR 2.26 [1.52-3.37] in Stage IV), and delirium (OR 1.60 [1.09-2.34] in Stage IV). In women with ovarian cancer, Stage III or IV disease predicted hospitalizations for GI complications (OR 2.11 [1.41-3.16]/2.51 [1.68-3.74] respectively) and infections (OR 1.85 [1.18-2.93]/2.26 [1.44-3.55]; (Nurgalieva et al., 2009).

Treatments. Adverse events associated with anticancer treatments are varied, and though incidence may be anticipated based on the multi- or single modality

prescribed, toxicity type, frequency and severity may differ widely among multiple patients receiving similar treatments. Chemotherapy may present the greatest variety of possible adverse events due to its systemic administration, compared to the localized application and subsequent effects of surgery and radiotherapy (Drake & Lynes, 2010; Frankel Kelvin, 2010; Levine, 2010). ICD-9-CM codes associated with cancer therapy adverse events have been comprehensively identified across the studies reviewed thus far, and can be viewed in Appendix V.

When presenting with non-metastatic disease in lung and colorectal cancer, surgical resection is generally the initial modality offered, followed by adjuvant chemotherapy, with additional radiation therapy where indicated based upon factors associated with the primary tumor (National Comprehensive Cancer Network, 2012a; National Comprehensive Cancer Network, 2012b). Concurrent chemo- and radiotherapy regimens may be offered to patients with rectal cancers, or in selected patients with NSCLC (National Comprehensive Cancer Network, 2012b). Efforts will be made during analysis to identify adverse events occurring related to combined modality therapy, such as concurrent chemo-radiotherapy, or use of antiangiogenic agents such as bevacizumab in close temporal proximity to surgical procedures, which is acknowledged to increase risks related to wound healing (Phernambucq et al., 2011).

Preexisting conditions and comorbidities. It is well accepted that pre-existing or concurrent medical conditions may impact cancer treatment selection and overall survival, but a mechanistic understanding of these interactions is not clear (Geraci, Escalante, Freeman, & Goodwin, 2005). Certainly specific comorbid conditions may present contraindications to effective interventions, such as extensive pulmonary or

cardiac dysfunction precluding surgical resection, or poor hepatic or renal function preventing administration of a highly effective chemotherapeutic agent.

Pertinent to this study, Hernandez and colleagues (2009) explored the relationship between comorbidity and number of hospital admissions. In a cross-sectional retrospective analysis of 19, 192 discharges for all patients from a university hospital over a 12 month period in 2004, it was found that 58.8% of patients had at least one chronic condition, the most prevalent primary diagnoses of which were cancer (9.7%), ischemic heart disease (5.1%) and liver cirrhosis (2.2%). 9% of those with a chronic condition (n=1656) experienced 2 or more hospitalizations over the prior 12 month period, and those with cancer were the most prevalent in this subset (13% of the multiply admitted population).

Patients with Stage III colon cancer and comorbidities such as CHF, COPD and DM were found to receive a reduced amount of chemotherapy (Gross, McAvay, Guo, & Tinetti, 2007; Lemmens et al., 2005; Luo et al., 2006), with similar findings noted in patients with NSCLC (Janssen-Heijnen et al., 2005). As noted above, multimorbidity was noted to be significantly associated with increased risk of cancer-related hospitalizations (Du et al., 2002; Gonzalez et al., 2005; Hernandez et al., 2009; Nurgalieva et al., 2009).

Situational Factors

Geography. Treatment variation in relation to geographic area where care is received has been observed in breast cancer related to breast conserving surgery versus mastectomy rates (Cheung et al., 2009), chemotherapy receipt in patients with ovarian cancer and prostate cancer (Desch et al., 1996). Several studies have noted significant associations between geographic variables such as SEER registry or state and outcomes

(Du et al., 2002; Earle et al., 2000; Nurgalieva et al., 2009), though few offer hypotheses to explain these findings.

Summary of Literature Review

In sum, we have an incomplete understanding of the predictors of hospitalization in patients receiving chemotherapy, and that study designs involving large administrative datasets such as SEER-Medicare provide researchers with the opportunity to develop knowledge that improves the health of patients receiving chemotherapy. Based upon the high incidence of lung and colorectal cancer diagnosed in the US Medicare-eligible population, and the reported high frequency with which these patient groups are admitted for cancer-related complications, selection of these diagnostic categories as the focus of this study is appropriate.

Two studies (Du et al., 2002; Hassett et al., 2006) note that the type and frequency of chemotherapy-related toxicity differed in their studies conducted within large, community-based administrative datasets, as compared to the adverse event rates described in the associated clinical trials. This observation is an important one as it relates to the expected generalizability of the typical clinical trial result, especially given the low participation of patients over age 65. Use of the SEER-Medicare dataset provides an optimal environment to study type and frequency of adverse events in the population of interest when applied to lung and colorectal cancers, where the median age at diagnosis matches well with entry into coverage eligibility.

The available data illustrates that although there are expected age-related declines in organ function over time, factors impacting physiologic age and/or functional status, such as multiple comorbidities may be more appropriate predictors of tolerance to

therapy and overall survival than chronologic age. Clinical factors such as advanced stage of disease may also be important predictors of unplanned hospitalization.

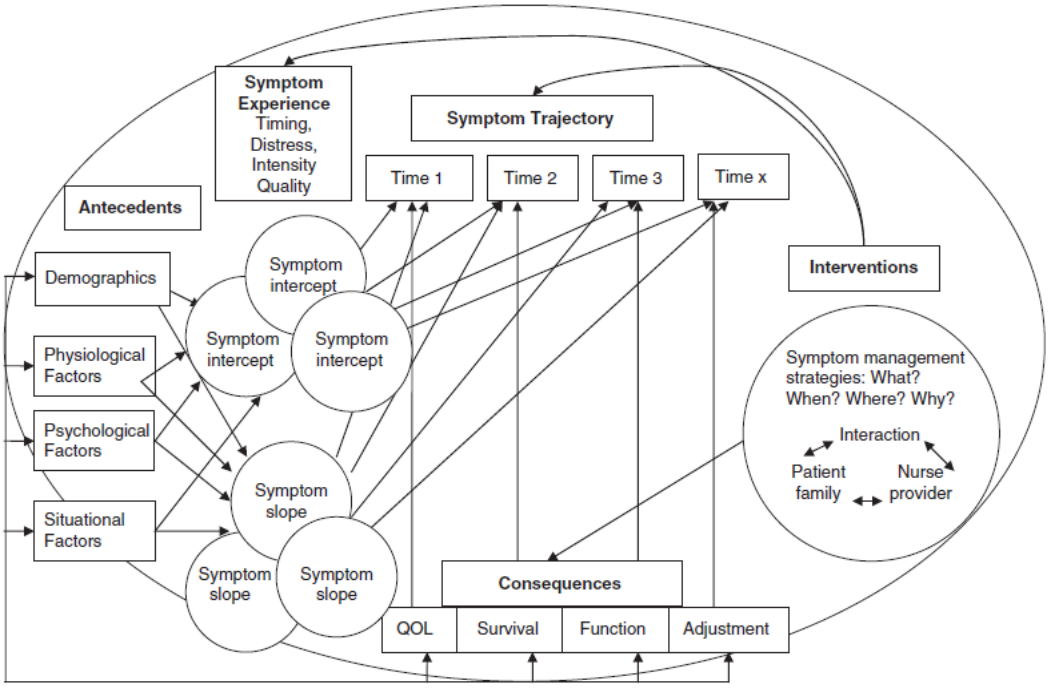
Evidence suggests that demographic factors such as gender and race may impact tolerance to chemotherapy through mechanisms such as drug metabolism that are not yet fully understood. Marital status and geographic location where care is offered have also been shown to be associated with variations in hospitalization rates, and should be evaluated within the context of this study.

Theoretical Rationale

Hospitalizations among patients receiving outpatient anticancer treatments are likely to be motivated by symptoms so severe as to warrant inpatient resource use. A number of models explore concepts associated with symptoms, including the theory of unpleasant symptoms (TUS; (Lenz & Pugh, 2008)), the symptom experience model (SEM; (T. S. Armstrong, 2003)), the symptom management model (Brant, Beck, & Miaskowski, 2010), the symptom experience in time model (SET; (Henly, Kallas, Klatt, & Swenson, 2003)) and the University of California, San Francisco (UCSF) symptom management theory (Dodd et al., 2001). Each model has been studied within the context of cancer, and a number of common elements are noted. Most pertinent to this study is the identification of antecedents (Brant et al., 2010; Lenz & Pugh, 2008), also known as contextual variables (Dodd et al., 2001), influencing factors or qualities of the person, their health and environment that may moderate or mediate symptom input (Henly et al., 2003). Each theory proposes some relationship between these factors and the experience and trajectory of incident symptoms. Though still in early development, Brant's SMM guides this study, as it intentionally builds upon the TUS, SET and SEM, adding

exploration of the influence of symptom clustering and more detail regarding the trajectory of symptoms over time. These concepts are critical to this study, as we seek factors associated with single or multiple unplanned hospitalizations, likely due to severe disease or treatment-related symptoms across an intra-patient multi-year perspective.

Figure 2. Symptom management model. (Brant et al., 2010). Reprinted with permission



Note: QOL, quality of life.

The SMM antecedents include Demographics, Physiological, Psychological and Situational Factors. Variables in this study that align with the SMM antecedents include age, sex, marital status, and race as Demographic Factors; disease type and stage, treatments (surgery, radiation therapy, and chemotherapy), pre-existing comorbidities and other clinical problems identified during the observation period as Physiological Factors; geography and setting of care as Situational Factors. The SMM proposes that antecedent factors both provide input to and form the context within which the patient experiences

symptoms (Brant et al., 2011). While the current study aimed to provide a preliminary exploration of the weight of these multiple factors associated with unplanned hospitalization for severe symptoms, research beyond the scope of this study is needed to understand how differences among these values might influence the multiple domains of single and clustered symptom experiences, such as incidence, severity, burden and meaning, among others.

Hypotheses

Based on the literature reviewed above, we hypothesized that:

1. Initial unplanned hospitalizations in separate cohorts of patients with non-metastatic lung and colorectal cancer in the SEER-Medicare linked database are associated with advanced disease stage, one or more comorbidities, age greater than 70 years, and unmarried status.

2. The number of unplanned hospitalizations for serious adverse events in separate cohorts of patients with non-metastatic lung and colorectal cancer in the SEER-Medicare linked database receiving ambulatory anticancer therapies are positively associated with increasing disease stage, an increasing number of comorbidities, increasing age greater than 70 years, and unmarried status.

CHAPTER III. METHODS

This chapter will discuss the use of the SEER-Medicare linked database as the research setting and main instrument for this study, including its origin, representativeness to the desired population, and content. The proposed sample and data analysis plan will be discussed.

The Research Setting

Data for this study originate from the NCI's SEER – Medicare linked database. This database combines information from two sources, the NCI SEER program and the Center for Medicare-Medicaid Services claims data through a linking process to allow researchers to view clinical and administrative data for a single patient across time and settings of care.

SEER

Since 1973, the SEER program has collected data on all incident cancer cases diagnosed within 17 cancer registries across the United States, capturing approximately 28% of all national cases (National Cancer Institute, 2012e). SEER data includes patient demographics, cancer type, stage, initial treatments and survival status, and the quality of data is considered highly valid according to the North American Association of Central Cancer Registries (Bray & Parkin, 2009). The SEER database is focused on collecting information on new cancer cases and associated initial treatments (those initiated within 4 months of diagnosis) and long-term mortality, which is reconciled with the National Center for Health Statistics. Data on treatments occurring later than 4 months post-diagnosis and long-term status of cancers for patients still living is not collected. Details

related to chemotherapy regimens provided as initial or subsequent treatment is not collected.

Medicare

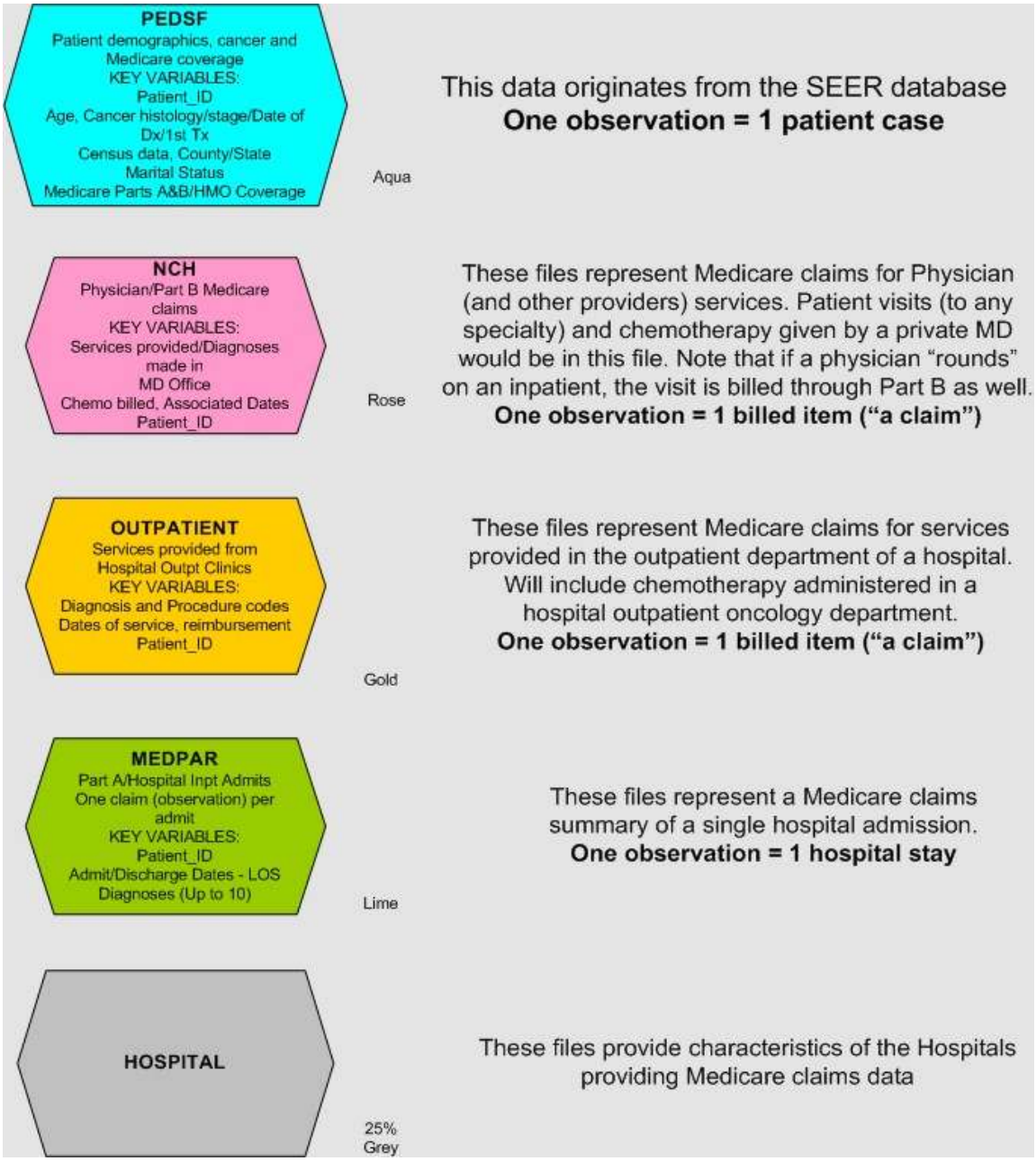
Medicare is a federally administered health insurance program. Individuals may become eligible for Medicare benefits due to a number of reasons, including end-stage renal disease (ESRD), certain other disabilities and most commonly by attaining 65 years of age. Approximately 97% of Americans over age 65 are covered by Medicare (Warren et al., 2002), which automatically includes Part A benefits that provide for hospital and skilled-nursing facility costs, as well as hospice and some other home health services. About 96% of covered beneficiaries choose to obtain Part B benefits, which cover physician and outpatient services. Part C and D benefits cover Health Maintenance Organization (HMO) plans for which CMS is payor, and prescription drug coverage, respectively (Centers for Medicare & Medicaid Services, 2012a).

SEER-Medicare dataset linkage. In 1991, the NCI, SEER Registries and CMS collaborated to link each SEER case diagnosed since 1973 with the corresponding Medicare patient data for the first time. Through use of a protocol to carefully match demographic data such as Social Security Numbers, date of birth, gender and name (Potosky, Riley, Lubitz, Mentnech, & Kessler, 1993) between the SEER and Medicare records, a single merged record is created, along with a new, unique case identifier that is applied across each of the SEER-Medicare linked database file types. Warren and colleagues (2002) studied the generalizability of SEER-Medicare data by comparing socioeconomic characteristics, levels of Medicare HMO participation (Part C) and cancer mortality rates among those over age 65 in the SEER registries contributing data to those

nationally, using Census data and other resources. At the time, age and sex were found to be comparable, though some disparities were noted. SEER areas were noted to contribute a higher proportion of cancer cases from people with non-white race, from more affluent, urban areas, though it was noted that the analysis preceded the addition of four new SEER registries to the program in 2001 that were expected to minimize these differences (Bach, Guadagnoli, Schrag, Schussler, & Warren, 2002). The authors also reported that in the 1990's, Medicare HMO enrollment in SEER areas exceeded the nation as a whole, but the trend was steadily decreasing over time. Last, overall cancer mortality was lower among cases derived from SEER areas compared to the national average (Bach et al., 2002).

SEER-Medicare claims data files. The SEER-Medicare database is comprised of several file types, each generated from a separate source. Figure 3 illustrates the main file types in this study, including the unit of measurement in each file. The Patient Entitlement and Diagnosis Summary File (PEDSF) originates from the SEER registry information, and is formatted as one observation per patient case. Should a patient experience more than one cancer diagnosis over their lifetime, up to ten primary cancers would be described within this single record. The availability of PEDSF data at the start of this study included incident cancers from 1973 through 2007 across all tumor types.

Figure 3. SEER-Medicare File Types



At the time of study start, claims-derived data was available for cases through 2009; for example, the record of a patient diagnosed with lung cancer in 2005 would be found in the PEDSF file for that tumor type and year, and will include all of the SEER registry information. A researcher might then wish to explore the patient's associated

Medicare-derived files from 2004 (prior to the cancer diagnosis to identify pre-existing comorbid conditions) through the end of available data in 2009.

The Medicare Provider Analysis and Review file (MEDPAR) is derived from the Medicare Part A claims data generated during a hospitalization. Each observation within MEDPAR represents a single hospital stay for a SEER-Medicare patient. The National Carrier History (NCH) and Outpatient (OUTPT) files describe services such as provider visits and treatments administered in the ambulatory setting. The two files are very similarly formatted. NCH data represents provider claims from physicians, nurse practitioners and physician assistants empaneled as independent Medicare providers, as well as claims from laboratory and freestanding ambulatory care centers. OUTPT data represents claims from the outpatient departments within hospitals, and are separate in nature and structure from the MEDPAR claims.

Each observation in the NCH and OUTPT files represents a single billed line item. Using a hypothetical scenario to illustrate a one-day chemotherapy administration in a private oncologist's office, the researcher might note several separate observations for the same date in the NCH file, including the provider exam, a complete blood count to assure patient eligibility prior to treatment, each individual drug charge and an administration charge (Lamont et al., 2005). The initial variable in the PEDSF, MEDPAR, NCH and OUTPT files is the Patient ID assigned by SEER-Medicare, allowing desired data to be obtained for a particular patient as he or she receives care and generates claims to Medicare at various locations over time.

There are acknowledged limitations of claims data use. For example, a condition must be formally diagnosed as an element of the bill for the professional service

rendered. Conditions that are chronic may not be noted in every claim, or may be reported in an isolated "rule out" context that may bias detection methods. Therefore many researchers look for at least two incidences of a particular diagnosis code across the patient record to verify its validity (Klabunde, Potosky, Legler, & Warren, 2000). In addition, claims data illustrate what the patient received, but no information about what other options may have been offered, but possibly refused by the patient, or considered by the provider, but not implemented due to anticipated clinical or financial obstacles. Though the cohorts in this study were carefully selected to ensure consistent use of Medicare coverage as the primary payer (by including only those with Part A and B coverage each month without interruption during the period of interest, and excluding those with HMO (Part C) coverage), some patients may elect to use other coverage for some services, such as Veteran's Administration or other benefits, in which case the data related to any such claims will not be evident in the SEER-Medicare data.

Instruments

The SEER-Medicare files serves as the main "instrument" in this study. The rationale for, and exact variables selected for each concept are explained in chapters 1 and 2. The NCI Combined Index (Klabunde, Warren, & Legler, 2002; Klabunde et al., 2007) was utilized during analysis to provide a weighted comorbidity score for each patient case.

The NCI Combined Index is based upon the Charlson Comorbidity Index (CCI; (Charlson et al., 1987)), originally developed through retrospective chart review of 685 patients with breast cancer, which uses a weighted index of 19 common conditions to predict 1-year all-cause mortality. In 1993, Deyo and colleagues adapted the CCI to

enable use of administrative data in the form of ICD-9-CM and Common Procedural Terminology (CPT; (American Medical Association, 2012)) codes. The Charlson/Deyo method remains in common use today (Fedewa, Ward, Stewart, & Edge, 2010; Lang et al., 2009; Walter et al., 2009), but is limited to analyses focused solely on inpatient data. The NCI Combined Index was developed specifically to extend use of the Charlson/Deyo method to study designs inclusive of both the inpatient and outpatient areas. The presence (initially assigned a score of 1) or absence (assigned a score of 0) of 14 non-cancer conditions is detected from either the inpatient or outpatient claims data. Each condition score is then multiplied by a coefficient estimate for 2-year non-cancer mortality through use of a Cox proportional hazards model derived during method development (Klabunde et al., 2000). The weighted scores are then summed to provide a single value. Extensive SAS (SAS Institute, 2012) programming to reliably perform the calculations is provided to the researcher on the SEER-Medicare website (National Cancer Institute, 2011).

Procedure for Data Collection

Though SEER-Medicare data are de-identified, they are not public use files, and researchers must utilize a formal application process to obtain data through Information Management Services (IMS), Inc. in Silver Spring, MD. IMS is the contracted administrator for SEER-Medicare, and requires submission of a detailed research project description, proof of Institutional Review Board approval or exemption, and a signed data use agreement. Each application is peer-reviewed by a panel selected by the IMS administrator prior to data release to ensure the project is feasible, that each type and years of the data files requested are necessary to the proposed research questions and analysis, that the research team is qualified to perform the work and able to adequately

protect the data during the analysis and dissemination periods. Once approved, the researcher forwards the calculated data preparation fee and receives the compressed files on a series of encrypted computer disks.

Per the Rutgers University Institutional Review Board, use of de-identified SEER-Medicare data for this study does not require formal review, and approval to proceed was obtained on September 1, 2011. See Appendix VI for a copy of the determination letter.

Rationale for data file type and year selection. The selected tumor types for this study, lung and colorectal cancers, were chosen due to their reported frequency of hospital admission (Gonzalez et al., 2005; Grant et al., 1995; Hassett et al., 2011; C. Weaver et al., 2006), a median age of diagnosis that falls within Medicare eligibility parameters and a high incidence in both genders. The cohorts were created and maintained separately, but once developed we were able to efficiently apply similar SAS programming to both, enabling comparison of the results between the two groups.

To capture treatment regimens comprised of traditional chemotherapy agents (see Appendix IV for list of regimens by tumor type and stage) as well as off label use of the monoclonal antibodies that have more recently become standard of care for metastatic disease (bevacizumab, approved by the Food and Drug Administration (FDA) in 2004 and 2006 for advanced colon cancer and advanced lung cancers, respectively and cetuximab, approved in 2004 for advanced colon cancer), the years 2005 – 2009 were examined for lung cancer, and 2003-2009 for colorectal cancer. This date range allowed ample time for identification of comorbidity data prior to cancer diagnosis, and continued through the current end of available data. Though another novel drug class, the orally-

administered tyrosine kinase inhibitors has also impacted treatment of these tumor types over the past decade, claims from Medicare Part D (which includes billing for oral therapies) became available to SEER-Medicare researchers only as of 2007, and therefore cannot be included in this study.

The Population

Two separate, parallel cohorts were constructed by tumor type, and analyzed in a similar manner, allowing comparison of predictors between the two cancer types. Cases were included initially if the patient was 66 years of age or greater at the time of cancer diagnosis, and had continuous Parts A and B Medicare coverage during the period of observation, but no participation in Part C (HMO). Cases diagnosed on autopsy or by death certificate only were excluded.

Data Preparation and Cohort Construction

Prior to analysis, extensive preparation of the bulk data utilizing SAS programming from the multiple file types was required. Due to the extremely large file sizes involved, variables not intended for analysis were trimmed to increase processing efficiency, and similar variables among file types were recoded as needed prior to merging observations.

Though an attractive feature of the use of SEER-Medicare data is the ability to follow an individual patient case across care settings utilizing the unique patient identification number assigned by the NCI database administration, this necessitates careful planning and attention to detailed procedures for properly locating and merging cancer-specific data from the PEDSF file with claims data from multiple settings across the MEDPAR, NCH and OUTPT files. An observation is formatted differently dependent

on the file type, preventing simple merge procedures using the unique patient identifier alone. For example, a single observation in the MEDPAR file summarizes one inpatient hospitalization, regardless of length or complexity, whereas a single observation in the NCH or OUTPT file represents a claim for one billed item, such as an individual chemotherapy drug. On a typical chemotherapy administration visit, there may be multiple observations in the these files representing billed claims for each individual premedication, chemotherapy drug, hydration, clinician charges, etc.

Files are initially provided inclusive of the entire population of Medicare-eligible patients diagnosed in contributing SEER registry areas with the desired cancer type for the years requested. Cohort construction was designed to produce a group of patient cases that represent those with non-metastatic lung or colorectal cancer who have received chemotherapy and experienced a subsequent hospitalization.

This writer deliberately selected a dissertation project using a large, administrative dataset to build experience in the management of "big data" as a method of nursing inquiry, and personally designed and executed the majority of the SAS programming necessary to prepare and analyze these files. Detailed program logs and schematics related to file manipulation and management were retained to supplement the final dissertation report sufficient to enable reproducibility at each step.

Chapter IV. Analysis of the Data

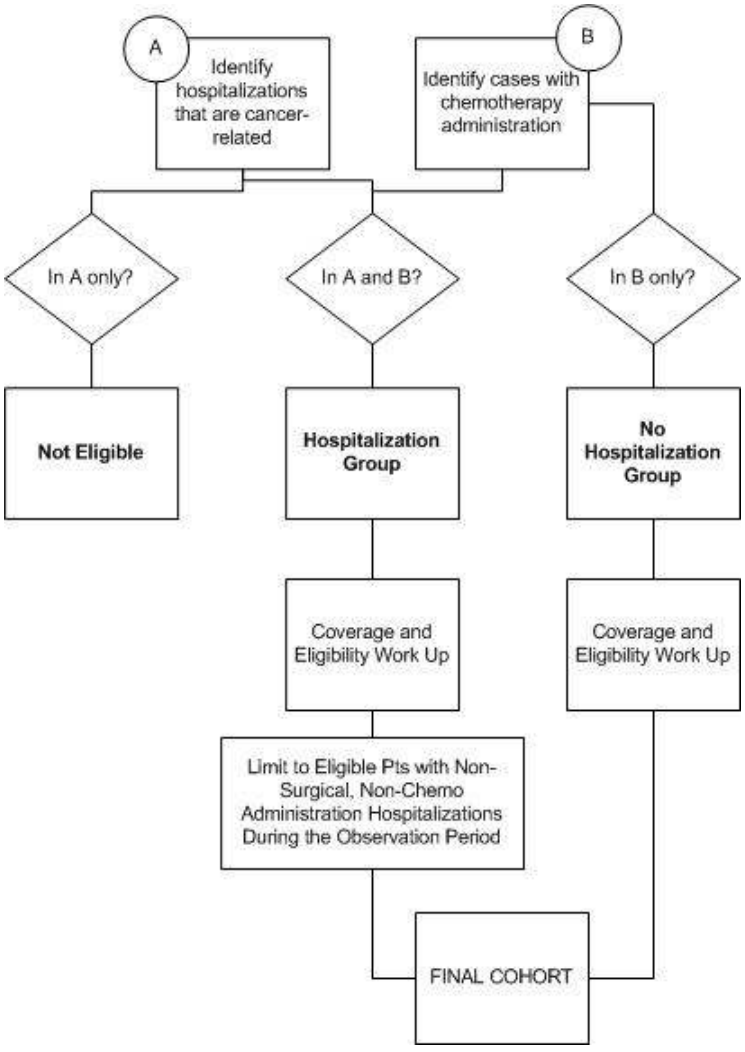
The purpose of this study was to identify risk factors predictive of initial and increasing numbers of unplanned hospitalizations among patients in the SEER-Medicare linked database receiving outpatient chemotherapy for the treatment of lung or colorectal cancer. Factors examined included age, comorbidity, sex, marital status, receipt of radiation therapy, race, urbanization, and SEER registry. The study plan originally intended to include disease stage and setting of care factors such as NCI cancer center designation, hospital teaching status and participation in cooperative oncology research groups by the provider, but inequities in availability of these data across all cases in the cohorts prevented unbiased inclusion. Data were collected on parallel cohorts of patients with lung or bronchus cancer (n = 2,457) and colorectal cancer (n =1,485). A major aspect of skill building for the dissertation candidate related to achieving a study design with careful attention at every point to properly manipulate the large and varied amounts of raw study data. Each of the five file types supplied data in a different structure and with different units of measurements, with respect to number of patients, claims and hospitalizations. As the analysis progressed, the unit of measurement varied for the task at hand, and in some cases, hospitalizations were aggregated by patient. This chapter presents findings from analysis of that data.

Data Selection and Initial Preparation

The SEER-Medicare database served as the research setting in this exploratory study. As described in Chapter 3, the National Cancer Institute provides this data according to tumor type in the form of several file types, where observations are derived

either from billed Medicare claims or the patient's main SEER Registry summary, which provides demographic, insurance coverage and clinical information regarding the cancer diagnosis and initial surgical and radiation treatments provided. To perform most analyses, it is necessary to carefully select and thoughtfully combine information from different file types regarding the patient cases at numerous points throughout the cohort formation. Figure 4 illustrates the logic model used to form the final analysis cohorts.

Figure 4. Cohort Formation Logic Model



As was noted in chapter 2, lung and colorectal cancers were selected for this study as the literature indicated that patients in these populations were most frequently admitted to the hospital during their cancer trajectory (Gonzalez et al., 2005; Grant et al., 1995; Hassett et al., 2011; C. Weaver et al., 2006). The SAS programming code developed for a single tumor type could be rapidly implemented in a second disease setting, accomplishing the important goal of replication, and providing comparative data to further support or refute the hypotheses of interest. Though the years selected for each disease site, including patients diagnosed with colorectal cancers in 2003-2007, and those with lung cancers diagnosed in 2005-2007 may appear different, they were chosen for two reasons. First, the total number of cases receiving chemotherapy is roughly similar in both groups among those years (see Table 1), and second, a planned subset analysis which will follow this study is intended to focus on adverse events among these two disease sites in the first years of monoclonal antibody usage (Avastin®, bevacizumab, Genentech; Erbitux®, cetuximab, Imclone/Roche and Vectibix®, panitumumab, Amgen) post-FDA approval, which occurred in 2004 in colorectal cancer and 2006 in lung cancer (one year of patient claims data prior to cancer diagnosis is required to facilitate calculation of comorbidity scores, hence data purchase starting in 2003 and 2005, respectively) . Both of these factors influenced selection of the data years purchased, and as no major changes to the regimen of traditional chemotherapy drugs were recommended in the literature during that time, controlling each group for the introduction of the monoclonal antibodies was a deciding factor.

Table 1. Number of Cases in Selected Years in SEER-Medicare Dataset

Tumor Type	Incident SEER Years Included	Total Cases	Cases with at least 1 billed claim for chemotherapy
Lung	2005-2007	104,388	31,789
Colorectal	2003-2007	133,833	32,717

Initial receipt of the data included several compressed and encrypted disks, arranged by year of cancer diagnosis and tumor type. Step one of data preparation was to combine each year of the claims files into a single multi-year file per data source. Next, initial demographic and diagnostic eligibility criteria were applied to the PEDSF (SEER Registry data) file to include only patient cases where age was greater than at 65 at diagnosis, with lung or colorectal cancer as the first primary malignancy (to avoid the residual effects of prior cancer treatments) and those with no Medicare Health Maintenance Organization (HMO) enrollment from one year prior to cancer diagnosis through the end of the hospital observation period (30 days after the last billed chemotherapy administration). Cases diagnosed at autopsy or by death certificate only were excluded, and any observations listing the "Month of Diagnosis" value as unknown were recoded to default as January, allowing patient retention and the most conservative option during the subsequent review for uninterrupted Medicare Part A and B coverage.

Patients who received chemotherapy were identified by searching the multiyear ambulatory claims files (NCH and Outpatient) for observations with a HCPCS value containing a J9 code, which designates chemotherapy agents (Lamont et al., 2005).

Cancer-related hospitalizations were identified by searching the multiyear hospital claims file (MEDPAR) for the tumor type of interest in either the first or second position of 10 possible ICD-9-CM diagnostic codes assigned to the admission. Within each cohort, two groups were created in preparation to examine Research Question 1, comparing factors associated with initial unplanned hospitalization. When a patient identification number was located in both the "received chemotherapy" and "had a cancer-related hospitalization" files, that case was assigned to the "Hospitalized" group. Where a case was found in the "received chemotherapy" file only, that patient was assigned to the "No Hospitalization" group. Tables 2 and 3 describe the characteristics of these groups for both cohorts, and Figures 6 and 7 illustrate the steps of cohort formation including attrition of cases at each stage of development.

Table 2. Characteristics of the Colorectal Cohort

	Hospitalized (*n* = 1152)			**Non-Hospitalized (*n* = 333)**		
		n	**%**		***n***	**%**
Age at diagnosis (years)						
Mean	77.3			78.9		
Std Dev	5.0			5.7		
Range	65 , 97			65 , 97		
Sex						
Male		505	43.8		201	60.4
Female		647	56.2		132	39.6
Comorbidity score						
0		477	41.4		198	59.5
1		300	26.0		83	24.9
2		197	17.1		33	9.9
≥3		178	15.4		19	5.7
Range (pre-recode)	0 , 9			0 , 5		

Number of Hospitalizations[1]	1522				
Mean	1.8				
Std Dev	1.3				
Range	1-17				
Length of Stay Median/Range	5 (1 , 120)				
Marital Status					
Married		630	54.7	176	52.9
Not Married		522	45.3	157	47.2
Urbanization[2]					
Big Metro		618	53.7	181	54.4
Metro/Urban		386	33.5	126	37.8
Less Urban/Rural		147	12.8	26	7.8
SEER Registry Region					
1- NJ		249	21.6	79	23.7
2 - West (CA, Hawaii, Seattle)		317	27.5	114	34.2
3 - Southern (KY, LA, GA)		262	22.7	60	18.0
4 - Mid/NE (MI, CT, Iowa, NM, UT)		324	28.1	80	24.0
Race (percent)					
White		1025	89.0	289	87.0
Non-White		127	11.0	43	13.0
Census Tract Median Income (in dollars)	45333			45857	
Range	7 , 200008			7887 , 200008	
Census Tract Percent of Residents without HS diploma					
Mean	19.9			19.0	
Median	16.3			15.5	
Std Dev	13.4			13.0	
Range	0 , 68.8			0.71 , 71.7	
Disease Stage					
0		4	0.4	27	8.1
I		101	8.8	102	30.6
II		294	25.5	43	12.9
III		658	57.1	67	20.1
Unknown (Not Missing)		95	8.3	94	28.2

Total	*1152*	*100*	*333*	*100*
Radiation Treatment				
External Beam	280	24.8	100	30.6
None, incl. Refused	849	75.2	227	69.4
Missing	*23*		*6*	
Chemotherapy Classes Received[3]				
5-FU	1010	87.7	166	49.9
Oxaliplatin	586	50.9	61	18.3
Monoclonal Antibodies	439	38.1	62	18.6
Irinotecan	295	25.6	23	6.9
Toxicity[4]				
Dehydration	84	5.5		
Abdominal pain	70	4.6		
Diarrhea	68	4.5		
Nausea with vomiting	55	3.6		
Unspecified intestinal obstruction	40	2.6		
Fever	40	2.6		
Other malaise and fatigue	39	2.6		
Care involving other specified rehabilitation procedure	36	2.4		
Syncope and collapse	32	2.1		
Pneumonia organism unspecified	24	1.6		
Venous embolism	22	1.4		
Hemorrhage of gastrointestinal tract unspecified	20	1.3		
Shortness of breath	19	1.3		
Chest pain	17	1.1		

[1]Non-surgical Hospitalizations without chemotherapy administration occurring during chemotherapy observation period

[2]Rural/Urban Continuum Definitions per the Area Resource File 2004 recode

Big Metro - Counties of metro areas of 1 million population or more

Metro/Urban - Urban population of 20,000 through Counties in metro areas of up to 1 million population

Less Urban/Rural - Completely rural, or less than 2,500 urban population through Urban population up to 19, 999

[3]Indicates % of pts in group that received this drug class. Pts generally received more than one drug during the study period.

[4]Most prevalent adverse events identified as likely to be cancer treatment-related among admitting diagnoses. ICD-9-CM codes from the MEDPAR variable ADMDXCDE with a frequency > 1% are listed.

Table 3. Characteristics of the Lung Cancer Cohort

	Hospitalized (*n*= 1479)			**Non-Hospitalized (*n* = 978)**		
		n	**%**		***n***	**%**
Age at diagnosis (years)						
Mean	76.2			77.5		
Std Dev	5.0			5.1		
Range	65 , 92			65 , 95		
Sex						
Male		823	55.7		510	52.2
Female		656	44.4		468	47.9
Comorbidity score						
0		1149	77.7		443	45.3
1		149	10.1		323	33.0
2		86	5.8		135	13.8
≥3		95	6.4		77	7.9
Range (pre-recode)	0 , 7			0 , 9		
Number of Hospitalizations[1]	2257					
Mean	1.5					
Std Dev	0.9					
Range	1-9					
Length of Stay Median/Range	4 (1 , 432)					
Marital Status						
Married		799	54.0		510	52.2
Not Married		680	46.0		468	47.8
Urbanization[2]						
Big Metro		823	55.65		483	49.44
Metro/Urban		486	32.86		408	41.76
Less Urban/Rural		170	11.49		86	8.8

SEER Registry Region					
1- NJ		268	18.1	125	12.8
2 - West (CA, Hawaii, Seattle)		487	32.9	407	41.6
3 - Southern (KY, LA, GA)		370	25.0	217	22.2
4 - Mid/NE (MI, CT, Iowa, NM, UT)		354	23.9	229	23.4
Race (percent)					
White		1320	89.3	905	92.5
Non-White		158	10.7	73	7.5
Census Tract Median Income (in dollars)	44661.5			44434	
Range	8324 , 200008			7 , 200008	
Census Tract Percent of Residents without HS diploma					
Mean	19.6			18.5	
Median	16.4			15.9	
Std Dev	12.9			12.3	
Range	0.8 , 77.0			0 , 69.9	
Disease Stage					
0		234	15.8	143	14.6
I		108	7.3	57	5.8
II		895	60.5	549	56.1
III		242	16.4	229	23.4
Unknown (Not Missing)		234	15.8	143	14.6
Total		*1479*	*100*	*978*	*100*
Radiation Treatment					
External Beam		718	50.2	484	51.7
None, incl. Refused		711	49.8	453	48.3
Missing		*50*		*41*	
Chemotherapy Classes Received[3]					
Platin		1283	86.8	805	82.3

Taxane	943	63.8	537	54.9
Gemcitabine	417	28.2	195	19.9
Pemetrexed	320	21.6	135	13.8
Topoisomerases	369	25.0	241	24.6
Monoclonal Antibodies	209	14.1	134	13.7
Vinca Alkaloids	138	9.3	69	7.1
Toxicity[4]				
Shortness of breath	191	8.5		
Pneumonia organism unspecified	173	7.7		
Dehydration	83	3.7		
Other malaise and fatigue	69	3.1		
Fever	63	2.8		
Unspecified chest pain	61	2.7		
Respiratory abnormality other	60	2.7		
Unspecified pleural effusion	48	2.1		
Syncope and collapse	46	2.0		
Atrial fibrillation	41	1.8		
Exacerbation of chronic bronchitis	40	1.8		
Care involving other specified rehabilitation procedure	33	1.5		
Nausea with vomiting	32	1.4		
Congestive heart failure unspecified	28	1.2		
Anemia unspecified	27	1.2		
Other pulmonary embolism and infarction	27	1.2		

[1]Non-surgical Hospitalizations without chemotherapy administration occurring during chemotherapy observation period

[2]Rural/Urban Continuum Definitions per the Area Resource File 2004 recode

Big Metro - Counties of metro areas of 1 million population or more

Metro/Urban - Urban population of 20,000 through Counties in metro areas of up to 1 million population

Less Urban/Rural - Completely rural, or less than 2,500 urban population through Urban population up to 19, 999

[3]Indicates % of pts in group that received this drug class. Pts generally received more than one drug during the

study period.

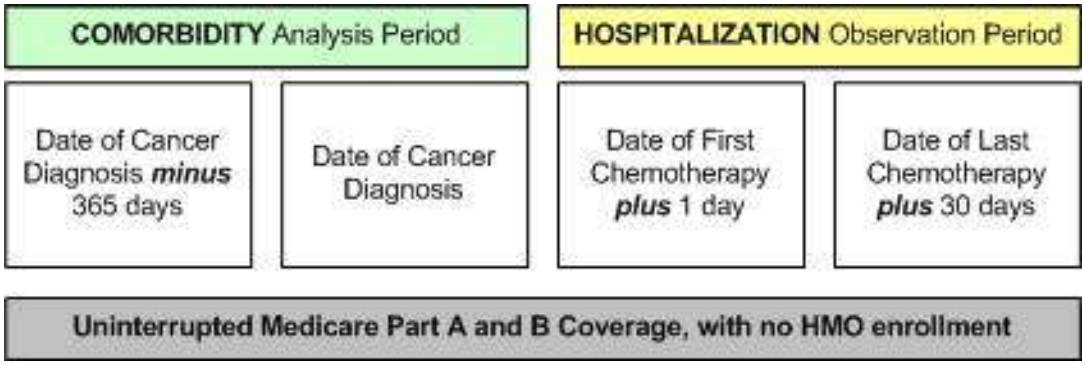
[4]Most prevalent adverse events identified as likely to be cancer treatment-related among admitting diagnoses. ICD-9-CM codes from the MEDPAR variable ADMDXCDE with a frequency > 1% are listed.

Application of Eligibility Criteria

Medicare coverage.

To optimize the capture of billed claims and the associated diagnostic coding information, SEER-Medicare researchers typically apply what is referred to as "Most Likely to Have (Consistent) Claims" criteria (Warren et al., 2002). By ensuring uninterrupted Medicare Part A and B coverage, with no transfer into a Medicare HMO product over the course of the study, the researcher is most able to detect all diagnostic codes and claims for a patient as they receive services from providers and institutions that accept this insurance. Figure 5 illustrates the key time periods associated with the study, including the comorbidity analysis period, which precedes the cancer diagnosis, as well as the post-diagnosis hospitalization observation period. This period ranges from the day after the first chemotherapy administration (to avoid missed data resulting from the method Medicare uses when a patient receives both outpatient and inpatient claims on the same date) through 30 days after the last chemotherapy administration.

Figure 5. Study Observation Periods



Though most of the SAS programming for this study was performed by the dissertation candidate, due to the complexity of the problem, the candidate worked closely and collaborated with Matthew Hayat, PhD, dissertation committee member to design a SAS macro to evaluate continuous Medicare Part A and B coverage. In order to determine patient Medicare coverage, a complicated sequence of logic needed to be applied to the data. Although most dates of interest to the study were associated with already designated variables, such as diagnosis date, or where a date was easily computed by the first or last occurrence of a J9-containing HCPCS code, in the case of Medicare coverage, each patient case possesses a range of values from 0 (no coverage) to 3 (both Part A and B coverage) over a varied number of coded months (e.g. Month 1 – Month 228). This required sophisticated SAS code in order to correctly identify different months to begin and end insurance evaluation. Utilizing information from the PEDSF file, each patient case was assessed in this section of the programming on a month-by-month basis for uninterrupted coverage from the start of the comorbidity assessment period (365 days prior to date of cancer diagnosis) through the end of the hospitalization observation

period (30 days after the last billed J9 HCPCS claim indicating chemotherapy administration).

Figure 6. Colorectal Cancer Cohort Formation

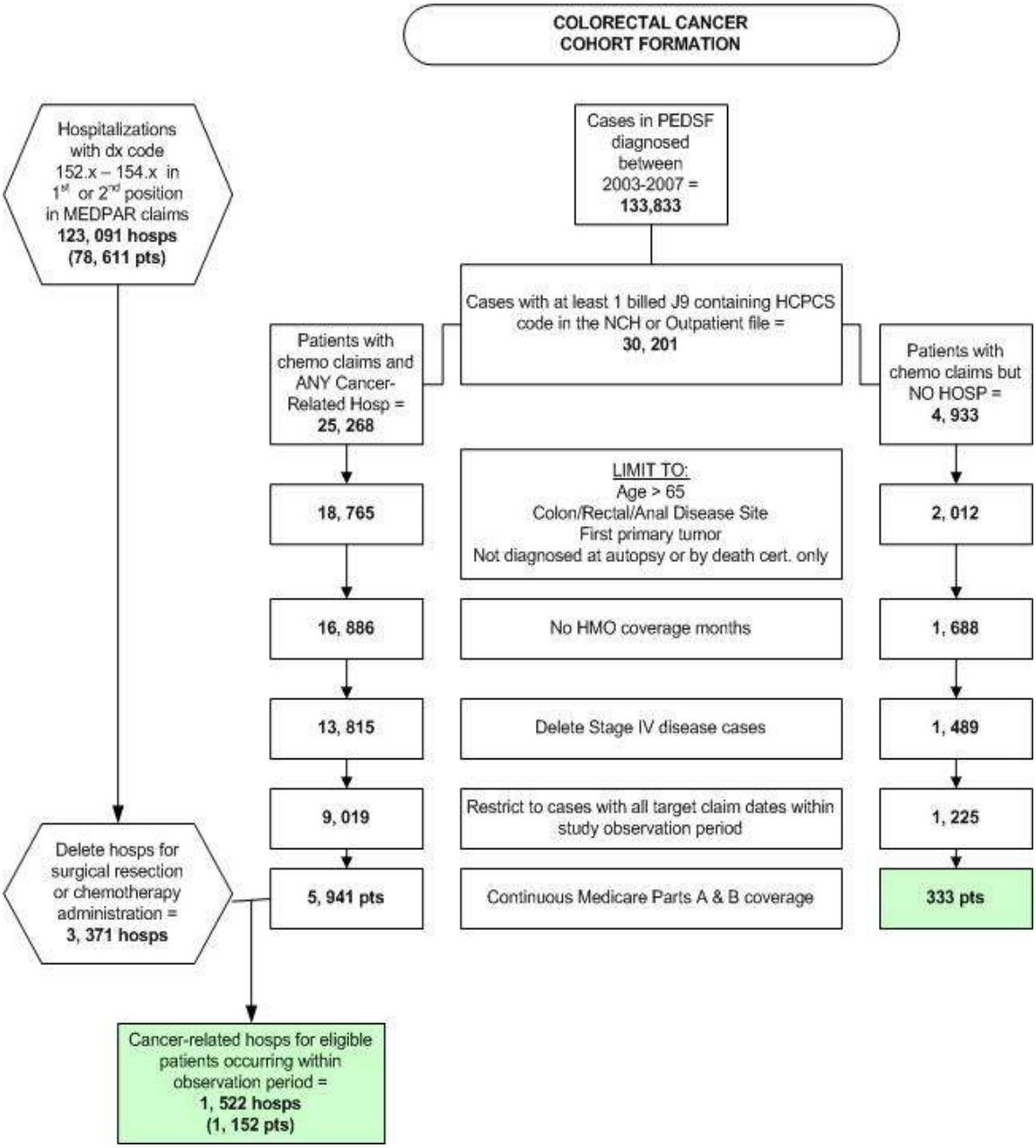
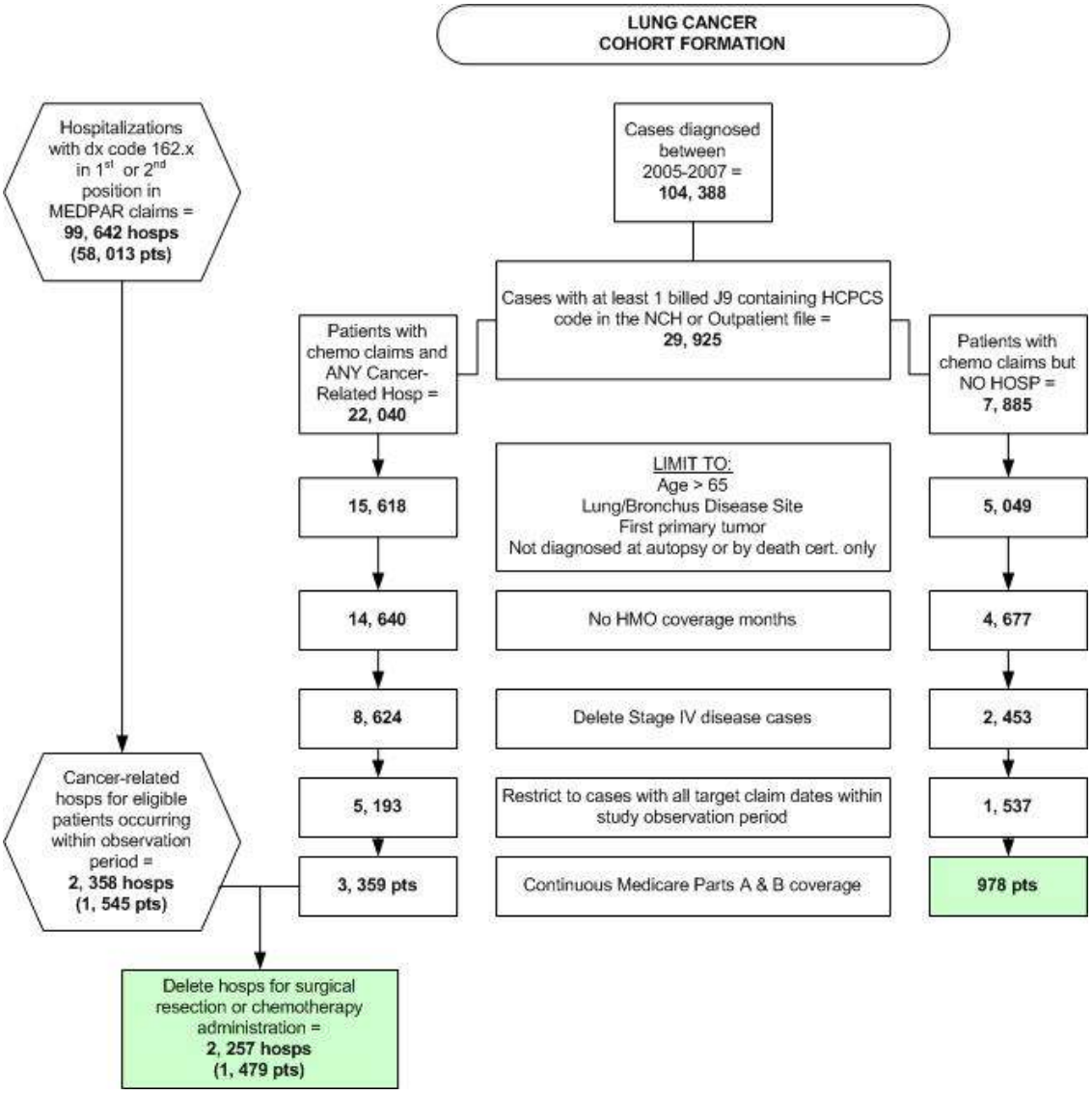


Figure 7. Lung Cancer Cohort Formation



At this point, each cohort was also restricted to remove Stage IV (metastatic) disease cases. As the focus of this study was on unplanned hospitalizations associated with chemotherapy treatment, inclusion of the metastatic disease population would likely add admissions related to disease progression rather than therapy-related adverse events. It can be difficult to ascertain the difference from claims data alone; therefore, it was decided during the dissertation proposal process to exclude this population for this

project. Cases remaining with No Hospitalizations at this point formed that final group segment for comparative analysis (Lung, n = 978; Colorectal, n = 333). The "All Cancer-Related Hospitalizations" file was then restricted to include only admissions associated with dates within the hospitalization observation period (First Chemotherapy Administration plus 1 day through Last Chemotherapy Administration plus 30 days) for the eligible patient cases. The remaining observations formed the final Hospitalization group for analysis.

Comorbidity analysis. Both Hospitalized and Non-Hospitalized cases underwent weighted comorbidity analysis, utilizing the NCI Combined Index (Klabunde et al., 2007). As described in Chapter 3, this index uses ICD-9-CM claims data available from inpatient and outpatient sources to calculate 13 individual disease scores as well as a single weighted score per patient (a measure similar in function to the Charlson Comorbidity index measure), the latter of which was incorporated into the statistical models in this study. The NCI provides templates with SAS syntax to assist research teams in preparing this score, and we used a two-step process to ensure accuracy. Step one involved reviewing claims to remove any ICD-9-CM diagnostic codes that appeared only once in the record to avoid basing scores on information utilized to "rule out" a potential medical condition that did not result in a permanent diagnosis. Step two involved reviewing all in- and outpatient diagnostic codes to produce the individual disease and associated weighted comorbidity scores.

Analytic Methods

Research Question 1, "What demographic, clinical and setting-of-care factors predict initial unplanned hospitalizations in separate cohorts of patients with non-metastatic lung and colorectal cancer in the SEER-Medicare linked database?" entailed the creation and analysis of a binary outcome, defined as hospitalized or not, during the defined study time period. Research Question 2, "What demographic, clinical and setting-of-care factors predict the number of unplanned hospitalizations for treatment-related serious adverse events in separate cohorts of patients with non-metastatic lung and colorectal cancer in the SEER-Medicare linked database?" considers factors associated with count data. In particular, the outcome variable for Research Question 2 was defined as a conditional measure. The dependent variable was defined as the number of hospitalizations in the defined study period, conditional on at least one recorded hospitalization.

Data were available from 16 NCI-SEER registries. Based on geographical considerations, these data were grouped into 4 SEER registry regions. In order to properly account for geographical differences, and the resulting within region correlations that may occur with cases from the same region, advanced statistical modeling techniques were used. Generalized estimating equations (GEE) were applied to account for within region cases.

GEE is a statistical modeling technique that builds on the classical generalized linear model to allow for within region correlated data (Liang & Zeger, 1986). For Research Question 1, the method is used with a binomial distribution and logit link to

predict the probability of a 'case/event' (i.e., hospitalization) as a function of linear predictors, in a similar manner to logistic regression. However, the variance of the binary response is adjusted for the likelihood that cases from the same region are more similar. Results are interpreted in terms of odds ratios, giving the likelihood of hospitalization versus not for each independent variable. For Research Question 2, the GEE model with a Poisson distribution and log link is used to predict the number of hospitalizations, conditional on at least one hospitalization occurrence. Results are interpreted as multiplicative incidence rates. (M. Weaver, 2009). For this study, data step programming in SAS, version 9.3, was used to perform data management, integration, and manipulation. Statistical modeling was completed with the PROC GENMOD SAS procedure. After assessing the characteristics and frequency distributions of the independent variables, bivariate models were fit to assess the association between each independent variable with the dependent variable. Independent variables with statistical results at the alpha = 0.15 level were retained in further modeling stages. Multivariate modeling was then performed. After considering independent variables that were known to be associated with hospitalization, and including in each model by default regardless of statistical significance, two statistical criteria were considered in model building and selection. Statistical results (p-values) and the QIC (quasi-likelihood under the independence model criterion) goodness of fit statistic were used (Pan, 2001). Details of the modeling results are displayed in Tables 4 through 7.

Table 4. GEE with Dichotomous Outcome Model Estimate Versions (*p* values) for Unadjusted Bivariate and Adjusted Multivariate Results for Colorectal Cancer. Distribution = Binomial, Dependent Variable: Hospitalized or Not Hospitalized

Variable	**Unadjusted (Bivariate)**	**Adjusted (Multivariate[1])**					
		Model 1	Model 2	Model 3	Model 4	Model 5	**Model 6 (FINAL)**
Sex	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	**<.0001**
Age	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	**<.0001**
Race	0.3026						**0.2943**
Education	<.0001	0.0312	0.0175	0.1491			**0.0332**
Income	<.0001	0.2325	0.0566				**0.0252**
Urban 1 vs. 3	<.0001	0.0178	0.0009	<.0001	<.0001	<.0001	**<.0001**
Urban 2 vs. 3	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	**<.0001**
Radiation	0.0834	0.2065		0.2021	0.2335		
Marital Status	0.6879						
Comorbidity 0 vs. 3	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	**<.0001**
Comorbidity 1 vs. 3	<.0001	0.0001	<.0001	<.0001	<.0001	<.0001	**0.0002**
Comorbidity 2 vs. 3	0.1459	0.0790	0.0858	0.0665	0.0642	0.0733	**0.1015**
QIC[2]		1441	1466	1442	1454	1478	**1464**

[1]Each model version represents the p values and QIC goodness of fit statistic for that corresponding multivariate model.

[2]Lower QIC is better.

Table 5. GEE with Count Outcome Model Estimate Versions (*p* values) for Unadjusted Bivariate and Adjusted Multivariate Results for Colorectal Cancer.
Distribution = Poisson, Dependent Variable: Number of Hospitalizations

Variable	Unadjusted (Bivariate)	Adjusted (Multivariate[1])				
		Model 1	Model 2	Model 3	Model 4	Model 5 (FINAL)
Sex	.1346	0.1670	0.0641	0.0787	0.0818	
Age	.5537					
Race	.0031	0.0158	0.0191	0.0254	0.0168	**0.0173**
Education	.2041	0.6192	0.6430			
Income	.0940	0.0796	0.0758	0.2214		
Urban 1 vs. 3	.0166	0.0290	0.0341	0.0293	0.0040	**0.0044**
Urban 2 vs. 3	.0002	0.0031	0.0022	0.0020	<.0001	**<.0001**
Radiation	.1505	0.0685	0.0681	0.0607	0.0386	**0.0303**
Marital Status	.0038	0.3719				
Comorbidity 0 vs. 3	.5494	0.4396	0.4374	0.4319	0.2821	**0.4532**
Comorbidity 1 vs. 3	.9734	0.7933	0.8435	0.8369	0.9428	**0.8920**
Comorbidity 2 vs. 3	<.0001	<.0001	<.0001	<.0001	<.0001	**<.0001**
QIC[2]		1914	1912	1912	1909	**1889**

[1]Each model version represents the p values and QIC goodness of fit statistic for that corresponding multivariate model.

[2]Lower QIC is better.

Table 6. GEE with Dichotomous Outcome Model Estimate Versions (*p* values) for Unadjusted Bivariate and Adjusted Multivariate Results for Lung Cancer. Distribution = Binomial, Dependent Variable: Hospitalized or Not Hospitalized

Variable	Unadjusted (Bivariate)	Adjusted (Multivariate[1])			
		Model 1	Model 2	**Model 3 (FINAL)**	Model 4
Sex	0.0598	0.0756	0.1036		
Age	<.0001	<.0001	<.0001	**<.0001**	<.0001
Race	0.0182	0.0089	0.0065	**0.0066**	0.0045
Education	<.0001	0.0077	0.0093	**0.0068**	0.0005
Income	0.5369	0.0236	0.0234	**0.0200**	0.0045
Urban 1 vs. 3	0.4634	0.2179	0.2263	**0.2234**	0.2979
Urban 2 vs. 3	0.0001	0.0008	0.0012	**0.0015**	0.0008
Radiation	0.3127	0.0619	0.0609	**0.0691**	
Marital Status	0.4484	0.8271			
Comorbidity 0 vs. 3	<.0001	<.0001	<.0001	**<.0001**	<.0001
Comorbidity 1 vs. 3	<.0001	<.0001	<.0001	**<.0001**	<.0001
Comorbidity 2 vs. 3	<.0001	0.0003	0.0003	**0.0002**	0.0002
QIC[2]		2850	2849	**2849**	2958

[1]Each model version represents the p values and QIC goodness of fit statistic for that corresponding multivariate model.

[2]Lower QIC is better.

Table 7. GEE with Count Outcome Model Estimate Versions (*p* values) for Unadjusted Bivariate and Adjusted Multivariate Results for Lung Cancer.
Distribution = Poisson, Dependent Variable: Number of Hospitalizations

Variable	**Unadjusted (Bivariate)**	**Adjusted (Multivariate[1])**			
		Model 1	Model 2	**Model 3 (FINAL)**	Model 4
Sex	0.5321	0.8181			
Age	0.1997	0.5518	0.5351		
Race	0.0337	0.0318	0.0375	**0.0420**	0.0338
Education	0.1776	0.8490	0.8275	**0.8199**	
Income	0.3691	0.9898	0.9839	**0.9443**	
Urban 1 vs. 3	0.1570	0.3403	0.3490	**0.2832**	0.1759
Urban 2 vs. 3	0.0001	0.0287	0.0308	**0.0122**	0.0018
Radiation	0.0002	0.0160	0.0215	**0.0170**	0.0099
Marital Status	0.9768	0.8644			
Comorbidity 0 vs. 3	0.1446	0.1361	0.1235	**0.1309**	0.1239
Comorbidity 1 vs. 3	0.0010	0.0008	0.0009	**0.0008**	0.0012
Comorbidity 2 vs. 3	0.1915	0.1969	0.1865	**0.2050**	0.1618
QIC[2]		4533	4536	**4527**	4536

[1]Each model version represents the p values and QIC goodness of fit statistic for that corresponding multivariate model.

[2]Lower QIC is better.

Hypotheses

For Hypothesis 1, we proposed to study initial unplanned hospitalizations in separate cohorts of patients with non-metastatic lung and colorectal cancer in the SEER-Medicare linked database. Our hypothesis is that unplanned hospitalizations will be associated with advanced disease stage, one or more comorbidities, age greater than 70

years, and unmarried status. Hypothesis 2 stated that the number of unplanned hospitalizations for serious adverse events in separate cohorts of patients with non-metastatic lung and colorectal cancer in the SEER-Medicare linked database receiving ambulatory anticancer therapies will be positively associated with increasing disease stage, an increasing number of comorbidities, increasing age greater than 70 years, and unmarried status. The following sections, including Tables 9 through 12, detail results found in the analysis.

Colorectal cancer. Although it was planned to study disease stage, we could not include this measure as an independent variable in this study due to a large proportion of cases where the SEER staging value at diagnosis was entered by the registry as unknown. Statistical modeling results related to Hypothesis 1 were as follows. After controlling for other variables in the multivariate adjusted model, marital status was not found to be a significant predictor of initial unplanned hospitalization and age was significant in a direction inverse to what was predicted. After controlling for other variables in the model, for each year of increasing age, the likelihood of hospitalization decreased by 6.1% [OR=0.9393, 95% CI: (0.9218, 0.9571), p<0.0001]. After adjusting, comorbidity was supported as a predictor, whereas compared with a weighted NCI Combined Index score of 3+, patients with no comorbidities had a decreased likelihood of hospitalization of 78.1% [OR=0.2187, 95% CI: (0.1029, 0.4646), p<0.0001]. After controlling for other variables in the model, those with a comorbidity score of 1 had a decreased likelihood of 63.9% [OR=0.3609, 95% CI: (0.2110, 0.6173) p = 0.0002] and in those with a score of 2, the likelihood of hospitalization decreased by 44.2% [OR=0.5575, 95% CI: (0.2771, 1.1218), p = 0.1015].

However, additional factors were found to predict unplanned hospitalization in the final model for Hypothesis 1. Interestingly, in the multivariate model, an interplay between race and sex occurred, as after including race and other factors in the adjusted model, female patients were more than twice as likely to be hospitalized as males [OR=2.2721, 95% CI: (1.8366, 2.8108), p<0.0001]. After controlling for other variables in the model, for each 10% increment decrease in census tract level rate of high school completion, the likelihood of hospitalization decreased by 6.02% [OR=0.9398, 95% CI: (0.8876, 0.9951), p = 0.0332]. After controlling for other variables in the model, for each $10,000 increment increase in census tract level median income, the likelihood of hospitalization decreased by 5.34% [OR=0.9466, 95% CI: (0.9021, 0.9932), p = 0.0252]. The influence of degree of urbanization as a predictive factor is more complex; as compared to patients living in an area designated as completely rural (urban population less than 20,000), after controlling for other factors, those living in counties metro areas of 1 million or more (Big Metro) have a decreased likelihood of hospitalization of 31.4% [OR=0.6853, 95% CI: (0.5863, 0.8009), p < .0001], and those in areas with an urban population of between 20,000 and 1 million (Metro/Urban) have a decreased likelihood of 41.6% [OR= 0.5840, 95% CI: (0.5664, 0.6021), p< .0001]. In summary, hypothesis 1 was partially supported by the study results.

Data for hypothesis 2 were also limited, as disease stage could not be included in the modeling process due to lack of availability. At the bivariate stage of analysis, neither age nor marital status were found to be significant predictors of the number of hospitalizations experienced. Controlling for other variables in the model, cases designated in the SEER record with a non-white race had 1.1894 times the number of

unplanned hospitalization as compared to whites [Estimate=1.1894 , 95% CI: (1.0312, 1.3720), p<0.0173]. After controlling for other factors, patients who received radiation therapy had an increased likelihood of hospitalization, multiplied by 1.0614 as compared to those who did not undergo that treatment [Estimate=1.0614, 95% CI: (1.0057, 1.1203), p=0.0303], and patients with a comorbidity score of 2 had an increased 1.1351 times the number of hospitalizations as compared to those with a score of 3+ [Estimate=1.1351, 95% CI: (1.0952, 1.1765), p<.0001]. Degree of urbanization again influenced unplanned hospitalization. After controlling for other variables, as compared to those patients living in a completely rural area, those in a Big Metro area had a decreased 0.7970 number of expected hospitalizations [Estimate=0.7970, 95% CI: (0.6819 , 0.9315), p = 0.0044], and those in a Metro/Urban area also have a decreased likelihood, multiplied by 0.7874 [Estimate=0.7874, 95% CI: (0.7137, 0.8686), p<.0001]. In summary, hypothesis 2 was partially supported by the study results.

Lung cancer. Disease stage was again not included in this cohort due to unknown values at diagnosis in a proportion of cases sufficient to introduce potential bias. In bivariate analyses, marital status was not found to be a significant predictor of initial unplanned hospitalization [OR=0.9274, 95% CI: (0.7633, 1.1269), p = 0.4484], and as in colorectal cancer, age was significant in a direction inverse to what was predicted. For each year of increasing age, the likelihood of hospitalization decreased by 5.4% [OR=0.9524, 95% CI: (0.9386, 0.9665), p<.0001]. Comorbidity was supported as a predictor in the multivariate model, whereas after controlling for other factors, compared with a weighted NCI Combined Index score of 3+, patients with no comorbidities had an increased likelihood of hospitalization of 120.67% [OR=2.2067, 95% CI: (1.5339,

3.1746), p<.0001]. Those with a score of 1 had a decreased likelihood of 60.6% [OR=0.3931, 95% CI: (0.2963, 0.5215), p<.0001] and in those with a score of 2, the likelihood of hospitalization decreased by 47.9% [OR=0.5208, 95% CI: (0.3689, 0.7353), p=0.0002].

As in colorectal cancer, additional factors were found to predict unplanned hospitalization in the final model for Hypothesis 1. Controlling for clustered SEER registry, non-white patients experienced an increased likelihood of hospitalization of 58.7% as compared to whites [OR=1.5877, 95% CI: (1.1372, 2.2165), p=0.0066]. After controlling for other factors, for each 10% decrement increase in census tract level rate of high school completion, the likelihood of hospitalization increased by 9.78% [OR=1.0978, 95% CI: (1.0261, 1.1746), p=0.0068]. After controlling for other factors, for each $10,000 increment increase in census tract level median income, the likelihood of hospitalization increased by 8.25% [OR=1.0825, 95% CI: (1.0126, 1.1573), p=0.02]. After controlling for other factors, the influence of degree of urbanization as a predictive factor is again complex; as compared to patients living in an area designated as completely rural (urban population less than 20,000), those in areas with an urban population of between 20,000 and 1 million (Metro/Urban) have a decreased likelihood of hospitalization of 40.9% [OR=0.5905, 95% CI: (0.4266, 0.8174), p=0.0015], but living in counties metro areas of 1 million or more (Big Metro) did not significantly impact likelihood of the event [OR=0.7744, 95% CI: (0.5132, 1.1687), p=0.2234]. In summary, hypothesis 1 was partially supported by the study results.

Disease stage was not included in the modeling process, and neither age nor marital status were found to be significant predictors of the number of hospitalizations experienced. Controlling for clustered SEER registry, education and median income, cases designated in the SEER record with a non-white race had 1.0763 times the number of unplanned hospitalizations as compared to whites [Estimate=1.0763, 95% CI: (1.0027, 1.1553), p=0.0420]. After controlling for other factors, patients who received radiation therapy had 1.0398 times the number of repeated hospitalizations compared to those who did not undergo that treatment [Estimate=1.0398, 95% CI: (1.0070, 1.0736), p=0.0170], and those with a comorbidity score of 2 had 1.1959 times the number of repeated hospitalizations as compared to those with a score of 3+ [Estimate=1.1959, 95% CI: (1.0772, 1.3276), p=0.0008]. Degree of urbanization again influenced the likelihood of increasing numbers of unplanned hospitalizations. After controlling for other factors, as compared to those patients living in a completely rural area, those in a Metro/Urban area had 0.9024 times the number of hospitalizations [Estimate=0.9024, 95% CI: (0.8327, 0.9779), p=0.0122]. In summary, hypothesis 2 was partially supported by the study results.

In addition to applying complete model selection criteria using the QIC goodness of fit statistical test, the statistical models were tested for robustness to covariance structure. GEE models are robust by definition to the covariance structure, and results unaffected in theory by misspecification (Liang & Zeger, 1986). The standard error estimates will still be correct, even in the absence of a theoretically correct specification. Results for all four final adjusted models suggested minimal changes to QIC, confirming

robustness to covariance matrix specification (See Table 8). Compound symmetry was the default structure assumed for all models.

Table 8. Covariance Matrix Specification Test (QIC Results[1])

	Covariance Structure	Lung	Colorectal
Logistic	Independent	2849.6	1477.2
	Compound Symmetry	2849.9	1477.7
	Unstructured	2897.0	Unestimable[2]
Poisson			
	Independent	4527.8	1894.2
	Compound Symmetry	4527.2	1902.7
	Unstructured	4714.2	2320.4

[1] Lower QIC is better.

[2] Unestimable for this model.

Table 9. Lung Generalized Estimating Equation with Dichotomous Outcome Final Model Results. Factors associated with a patient experiencing an unplanned hospitalization during the chemotherapy observation period (*n*=1479) versus chemotherapy receipt but no hospitalizations (n=978).

	Unadjusted (Bivariate) Models				**Adjusted (Multivariate) Model (QIC** = 2849.6012)			
	OR	**95% CI**		***p***	**OR**	**95% CI**		***p***
		Lower	**Upper**			**Lower**	**Upper**	
Sex								
Female	0.87	0.75	1.01	0.0598				
Age	0.95	0.94	0.97	<.0001	0.95	0.94	0.97	<.0001
Race								
Non-White	1.48	1.07	2.06	0.0182	1.59	1.14	2.22	0.0066
Education								
% Non HS Grads	1.05	1.03	1.07	<.0001	1.10	1.03	1.17	0.0068
Median Income	1.02	0.96	1.07	0.5369	1.08	1.01	1.16	0.0200
Urbanization								
Big Metro	0.86	0.58	1.28	0.4634	0.77	0.51	1.17	0.2234
Metro/Urban	0.60	0.46	0.78	0.0001	0.59	0.43	0.82	0.0015
Radiation Therapy	0.95	0.85	1.05	0.3127	0.89	0.79	1.01	0.0691
Marital Status	0.93	0.76	1.13	0.4484				
Charlson Comorbidity								
0	2.10	1.51	2.93	<.0001	2.21	1.53	3.17	<.0001
1	0.37	0.29	0.48	<.0001	0.39	0.30	0.52	<.0001
2	0.52	0.38	0.69	<.0001	0.52	0.37	0.73	0.0002

Table 10. Lung GEE with Count Outcome Final Model Results. Model predictors for number of hospitalizations; data restricted to patients with at least one hospital visit. Patients (n = 1479) with chemotherapy and unplanned hospitalizations during Chemotherapy Observation Period (2257 hospitalizations, range 1-9 per patient, mean 1.53, SD 0.92)

	Unadjusted (Bivariate) Models				**Adjusted (Multivariate) Model (QIC** = 4527.8075)			
	Multiplier	**95% CI**		***p***	**Multiplier**	**95% CI**		***p***
		Lower	**Upper**			**Lower**	**Upper**	
Sex								
Female	1.02	0.95	1.11	0.5321				
Age	0.99	0.98	1.00	0.1997				
Race								
Non-White	1.09	1.00	1.17	0.0337	1.08	1.00	1.15	0.0420
Education								
% Non HS Grads	1.01	0.99	1.02	0.1776	0.99	0.99	1.01	0.8199
Median Income	0.99	0.98	1.01	0.3691	0.99	0.97	1.02	0.9443
Radiation Therapy	1.04	1.02	1.07	0.0002	1.04	1.00	1.07	0.0170
Marital Status	1.00	0.96	1.04	0.9768				
Urbanization								
Big Metro	0.93	0.85	1.02	0.1570	0.93	0.82	1.06	0.2832
Metro/Urban	0.90	0.86	0.95	0.0001	0.90	0.83	0.98	0.0122
Charlson Comorbidity								
0	1.03	0.98	1.08	0.1446	1.04	0.99	1.09	0.1309
1	1.19	1.07	1.32	0.0010	1.19	1.08	1.33	0.0008
2	1.04	0.97	1.12	0.1915	1.04	0.97	1.12	0.2050

Table 11. Colorectal GEE with Dichotomous Outcome Final Model Results. Factors associated with a patient experiencing an unplanned hospitalization during the chemotherapy observation period (*n*=1152) versus chemotherapy receipt but no hospitalizations (n=333).

	Unadjusted (Bivariate) Models				**Adjusted (Multivariate) Model (QIC** = 1464.6376)			
	OR	**95% CI**		***p***	**OR**	**95% CI**		***p***
		Lower	**Upper**			**Lower**	**Upper**	
Sex								
Female	1.95	1.48	2.57	<.0001	2.27	1.83	2.81	<.0001
Age	0.94	0.92	0.96	<.0001	0.94	0.92	0.96	<.0001
Race								
Non-White	0.83	0.59	1.18	0.3026	0.77	0.48	1.25	0.2943
Education								
% Non HS Grads	1.02	1.01	1.03	<.0001	0.94	0.88	0.99	0.0332
Median Income	0.95	0.94	0.96	<.0001	0.94	0.90	0.99	0.0252
Urbanization								
Big Metro	0.60	0.52	0.69	<.0001	0.68	0.58	0.80	<.0001
Metro/Urban	0.54	0.52	0.57	<.0001	0.58	0.56	0.60	<.0001
Radiation Therapy	0.75	0.54	1.04	0.0834				
Marital Status	0.93	0.65	1.33	0.6879				
Charlson Comorbidity								
0	0.26	0.14	0.48	<.0001	0.22	0.10	0.46	<.0001
1	0.38	0.26	0.58	<.0001	0.36	0.21	0.61	0.0002
2	0.64	0.35	1.17	0.1459	0.58	0.27	1.12	0.1015

Table 12. Colorectal GEE with Count Outcome Final Model Results. Model predictors for number of hospitalizations; data restricted to patients with at least one hospital visit. Patients (*n* = 1152) with chemotherapy and unplanned hospitalizations during Chemotherapy Observation Period (1522 hospitalizations, range 1- 17 per patient, mean = 1.78, SD = 1.31)

	Unadjusted (Bivariate) Models				**Adjusted (Multivariate) Model** QIC = 1889.7619			
	Multiplier	**95% CI**		**p**	**Multiplier**	**95% CI**		**p**
		Lower	**Upper**			**Lower**	**Upper**	
Sex								
Female	1.07	0.98	1.17	0.1346				
Age	0.99	0.99	1.00	0.5537				
Race								
Non-White	1.13	1.04	1.23	0.0031	1.19	1.03	1.37	0.0173
Education								
% Non HS Grads	1.02	0.98	1.07	0.2041				
Median Income	0.96	0.92	1.00	0.0940				
Urbanization								
Big Metro	0.81	0.69	0.96	0.0166	0.79	0.68	0.93	0.0044
Metro/Urban	0.79	0.70	0.89	0.0002	0.78	0.71	0.87	<.0001
Radiation Therapy	1.04	0.98	1.10	0.1505	1.06	1.00	1.12	0.0303
Marital Status	1.06	1.02	1.10	0.0038				
Charlson Comorbidity								
0	0.96	0.86	1.08	0.5494	0.96	0.85	1.07	0.4532
1	0.99	0.90	1.10	0.9734	1.01	0.90	1.13	0.8920
2	1.12	1.07	1.16	<.0001	1.13	1.09	1.17	<.0001

CHAPTER V. DISCUSSION OF THE FINDINGS

This study intended to examine predictors of demographic, clinical and setting of care factors as they relate to the negative outcome of unplanned hospitalization over the course of outpatient chemotherapy administration. As discussed in chapter 2, these concepts fit into existing symptom management conceptual models and theories as antecedents (Brant et al., 2010; Lenz & Pugh, 2008), contextual variables (Dodd et al., 2001), or influencing factors or qualities of the person, their health and environment that may moderate or mediate symptom input (Henly et al., 2003). Each model or theory proposes relationships among these factors and others, such as symptom appraisal by the patient and/or caregivers, interventions provided and the temporal components among them. A limitation of a study reliant upon administrative and claims data is an inability to examine many of these areas, or to test many desired theoretical propositions. However, a number of researchers have successfully utilized secondary data analysis methodology to conduct research within population-based health databases using a defined theoretical model, provided attention to conceptual clarity, data quality and validity for the intended purpose and methodological rigor are applied (Doolan & Froelicher, 2009; Kneipp & Yarandi, 2002; Magee, Lee, Giuliano, & Munro, 2006). This chapter will discuss the findings summarized in Figure 8,and possible explanations for the supported and unsupported aspects of the hypotheses originally proposed.

Figure 8. Predictors of Increased Likelihood of Unplanned Hospitalization

Significant Variables (After controlling for other factors in a multivariate model)		
	Colorectal	**Lung**
Dichotomous Outcome (Hospitalized or Not) *Predictors of* ***Increased*** *Likelihood of Unplanned Hospitalization*	**Decreasing Age** **Female Sex** **Living in an area with:** • **Higher HS Grad Rate** • **Lower Median Income**	**Decreasing Age** **Non-White Race** **No Comorbidities*** **Living in an area with:** • **Lower HS Grad Rate** • **Higher Median Income**
Count Outcome (Number of Hospitalizations)	**Non-White Race** **Receipt of Radiation** **Comorbidity Score > 2**	**Non-White Race** **Receipt of Radiation** **Comorbidity Score of 1***

***Needs further exploration due to unexpected distribution of comorbidity scoring in these groups**

Unplanned Hospitalization

Hypothesis 1, stating that initial unplanned hospitalizations in separate cohorts of patients with non-metastatic lung and colorectal cancer in the SEER-Medicare linked database will be associated with advanced disease stage, one or more comorbidities, age greater than 70 years, and unmarried status was partially supported, as noted in chapter 4. Stage of disease has been implicated in increasing the risk of unplanned hospitalization in this population in other studies (Hassett, O'Malley, Pakes, Newhouse, & Earle, 2006; Hassett et al., 2011; Nurgalieva, Liu, & Du, 2009), but was unable to be retained in this

analysis without excluding an unacceptable number of otherwise complete cases, or introducing a selection bias with unknown consequences by including this variable in the modeling process. It should be noted that in both the colorectal and lung cohorts, the proportion of cases where the diagnostic stage was coded as "Unknown" by the contributing cancer registry was significantly higher in the Non-Hospitalized groups (X^2 = 93.76, 1, $p < .0001$ and 25.82, 1, $p < .0001$ respectively). Most cancer registries reside within a hospital setting where direct medical record access is available, as compared to the alternative process of obtaining diagnostic information by mail when the patient is seen only in a private physician office or infusion clinic not owned by a hospital system. The direct access to documents verifying the staging work up is a possible explanation for the higher rate of SEER diagnostic classification among those patients in the Hospitalized group.

Comorbidity

Comorbidity, as measured by an adapted Charlson method via the NCI Combined Index (Klabunde, Legler, Warren, Baldwin, & Schrag, 2007) is an important variable in this study. Numerous sources discuss the impact of the presence of other chronic diseases on the patient's ability to tolerate anticancer treatments and on the natural history of the cancer process itself (Geraci, Escalante, Freeman, & Goodwin, 2005; Gross, McAvay, Guo, & Tinetti, 2007; Hernandez et al., 2009; Janssen-Heijnen et al., 2005; Lemmens et al., 2005). The weighted comorbidity scores for this study were calculated based on data collected regarding chronic diseases in the year prior to cancer diagnosis, so it is important to consider the impact of pre-existing disease on the likelihood of toxicity related to treatment, and do this specifically where possible. For example, a known

adverse effect of the monoclonal antibody bevacizumab is hypertension, observed even in previously normotensive patients (Mohile et al., 2013). A future sub-analysis of this study data may attempt to explore the incidence of new-onset or exacerbated hypertension among patients with and without a prior diagnosis, or a cardiovascular score on the NCI Combined Index. Optimally, such an analysis should include the metastatic population, as Stage IV patients were excluded from this study. For each cohort and both research questions, comorbidity was significantly associated with the outcome.

Indeed, a number of subsequent analyses in this area are indicated based on the findings of this study. In reviewing the characteristics, comorbidities and observed major toxicities during unplanned hospitalizations, numerous questions arise regarding potential interactions. For example, approximately 18% of the observed toxicities in the colorectal cohort were gastrointestinal in nature, which is not surprising given the natural history of the disease and the expected adverse effects of the chemotherapy regimen prescribed. However, a logical sub-analysis would be to explore the toxicity patterns and risk of hospitalization in patients identified to have a diagnosis of diabetes prior to starting colorectal cancer treatments, as the high incidence of nausea and vomiting is likely to heavily impact this population. Identification of such clear-cut predictors will aid nurses to target aggressive education, supportive therapies and patient monitoring to those patients at highest risk of avoidable complications.

In colorectal cancer, there was a clear trend noted in the odds ratios and increasing weighted comorbidity scores and the likelihood of unplanned hospitalization. As compared with patients with a comorbidity score of 3 or higher, a lower odds ratio was observed in each level of decreasing comorbidity. Those who began the process of

cancer treatment with no or fewer additional illnesses requiring management or potentially impairing the function of organ systems to be additionally stressed with the application of chemotherapy were less likely to experience unplanned hospitalization. In the lung cancer cohort, a mixed set of observations was noted. After controlling for other factors in the model, the odds ratio for those patients with a weighted score of zero (indicating no comorbid conditions), one or two as compared with three or more was 2.2, 0.39, and 0.52 respectively, which is not the trend seen in colorectal cancer, nor one we would have expected. These cohorts consisted of early-stage and therefore potentially curable tumors, so it is conceivable that those patients considered healthiest at time of treatment decision making might be selected to receive the most aggressive treatment regimens. Realistically, it is unlikely that this rationale would explain such a large disparity in results, and it is more likely this result is related to a limitation in the data. Among the ultimately eligible cases, there were significant differences (Lung X^2 = 300.31, 3, $p < .0001$ and Colorectal 45.77, 3, p = $p < .0001$) in the comorbidity scoring categories (0, indicating no pre-existing comorbidity, 1, 2 or 3+ weighted comorbid conditions) between the Hospitalized and Non-Hospitalized groups. Unlike the colorectal cohort, where the trend for higher comorbidity scores was seen among the Hospitalized group, the Non-Hospitalized group in the lung cancer cohort appeared to present at the time of cancer diagnosis with more co-existing illnesses, and this may contribute to these unexpected results.

Age

In both tumor types, age was a statistically significant predictor related to the incidence of initial unplanned hospitalization, but not in regards to the number of

hospitalizations experienced. Each year of additional age was associated with a 4.7% and 6% decrease in the likelihood of initial unplanned hospitalization in non-metastatic lung and colorectal cancers, respectively. Though this may appear a counterintuitive result, a bias towards offering less aggressive anticancer treatments to patients based upon their chronologic age is evident in the literature (Hurria et al., 2008; Sargent et al., 2001; Sundararajan et al., 2002) and could contribute towards the appearance of fewer severe toxicities leading to hospitalization. Though the specific drugs administered could be precisely identified through billing data, the exact dose could not. Some research teams have explored attempts to quantify chemotherapy dosing within SEER-Medicare claims data utilizing (Lamont et al., 2005), but thus far the degree of sensitivity appears insufficient to adequately address this issue, as the unit of measurement is at the billed vial size, rather than indicative of true milligram per meter squared dosing. Actual dosing as available in an individual patient's electronic health record would provide the most accuracy, and aggregated data from this source, such as will hopefully soon be available in a rapid learning system such as the American Society of Clinical Oncology's CancerLinQ program (American Society of Clinical Oncology, 2012). Future large-scale studies regarding this important question will be better able to be undertaken when such a resource matures.

Marital Status

Marital status at time of cancer diagnosis was included as a proxy for in-home social support, with precedent for inclusion based on prior studies (Goodwin, Hunt, Key, & Samet, 1987). It is acknowledged that this marker of support is a relatively crude one in a dataset limited to administrative and claims data, and potentially underestimates the

many aspects of the informal caregiver dynamic that informs social support and early care seeking behaviors in the face of escalating treatment related symptoms. Marital status was not found to be a statistically significant predictor for either research question or tumor type. An opportunity exists to perform a subset analysis exploring results when the patient is male versus female, as some authors have described gender differences related to spousal caregiving (Brazil, Thabane, Foster & Bedard, 2009).

Sex

After controlling for other factors, female sex was a significant predictor of the likelihood of unplanned hospitalization in colorectal cancer, which is consistent with the literature (Gonzalez et al., 2005; Nottage et al., 2003; Pal & Hurria, 2010; Sloan et al., 2002; Zalcberg, Kerr, Seymour, & Palmer, 1998); (Pal & Hurria, 2010; Sloan et al., 2002; Sloan et al., 2012). A number of studies have documented more frequent treatment-related toxicities among women (Sloan et al., 2002), and though the supporting data is inconsistent related to the exact mechanism, this may be related to biologic differences in clearance of 5-FU, the most commonly administered drug. In this study, females in the colorectal cohort experienced twice the likelihood of unplanned hospitalization than males, supporting these prior findings. Further studies are necessary to determine the exact biological mechanisms that may underlie this observation, as well as additional related factors.

Geography

Geography was examined as a variable in this study on several levels. Patient cases were originally submitted to the database via one of 16 national SEER registries (See Appendix VII for listing). Prior SEER-Medicare and other studies illustrated some

differences in outcomes associated with geographic variability at the regional or registry level, but the specific areas creating the greatest effects were inconsistent, and may be related to the distance required to travel to seek specialized oncology care. To control for potential within region/registry effects, 4 geographic clusters were formed (1 – New Jersey; 2 – West, including California, Hawaii, Seattle; 3 – Southern, including Kentucky, Louisiana, Georgia and 4 - Midwest/Northeast, including Michigan, Connecticut, Iowa, New Mexico, Utah) and used as a cluster effect within the PROC GENMOD syntax in the SAS programs.

Degree of urbanization. Degree of urbanization was represented through three levels of population density via data from the national Area Resource File system (National Center for Health Statistics, 2012). Many factors may contribute to care seeking and acceptance behaviors, and some health disparities and health services research teams are exploring the impact of distance from place of primary residence necessary to access specialized cancer services (Baade, Youlden, Coory, Gardiner, & Chambers, 2011; Onega et al., 2008; Palacio-Mejía, Rangel-Gómez, Hernández-Avila, & Lazcano-Ponce, 2003; Robertson et al., 2004). Though the three levels of urbanization in this study appear broad, this factor was a statistically significant predictor in each model, and more detailed investigation of this issue is warranted.

Geographic influence on socioeconomic variables. Two of the three socioeconomic variables utilized in this study were derived from census tract level data, thereby contributing additional geographic considerations. Collected in the year 2000, Median Income and Percent of Non-High School (HS) Graduates by Census Tract were selected based on usage in other SEER-Medicare analyses (Bach, Guadagnoli, Schrag,

Schussler, & Warren, 2002) along with race to provide some gauge of socioeconomic status as part of the study. Both factors were statistically significant predictors of the likelihood of initial unplanned hospitalization in non-metastatic lung and colorectal cancer, though neither were significant in the final models predicting the number of hospitalizations experienced, and the directionality of the associations were inconsistent between the tumor types. Of note, the final conditional model in lung model achieved its best goodness of fit statistic (QIC 4527 vs. 4536) by retaining median income and HS education, though all other factors remained significant. Future work should explore the mechanisms of interaction among these apparently related variables.

Future study on disparities in healthcare provision, care seeking behaviors and decision-making by varied patient groups, clinical and psychosocial outcomes and associated biologic/genomic aspects are essential in oncology care, and though an administrative dataset limits the depth and breadth of exploration that can occur, the results derived in this study provide support to pursue more work. Specific follow up to this study should include exploration of a number of additional SES variables available in the PEDSF file to maximize knowledge that can be gained from the cohort already formed.

Race and "Race-based Medicine'

In this analysis, roughly 90% of both tumor cohorts consisted of patients identified as "white" by the contributing SEER registries, yet "non-white" status was a significant predictor for both the likelihood of the initial admission as well as an increased number of unplanned hospitalizations in lung cancer, and was also a significant predictor of the number of hospitalizations in the colorectal group. Historically, race has

been conceptualized as a social construct, but is increasingly considered a potential biologic marker. Prospectively, many opportunities exist to evaluate the biologic and genomic factors that may impact drug handling and treatment tolerance, and may only be hinted at in this analysis through the proxies of race and indicators of socioeconomic status measures. This approach must be taken with careful attention to the complex and multiple implications of the ethical and public policy aspects of such pursuit. Two widely debated examples of so-called "racial drug profiling" include gefinitib (Iressa®, Astra Zeneca) and the combined formulation of isosorbide dinitrate and hydralazine hydrochloride (BiDil® ®, NitroMed).

Gefitinib is an orally administered epidermal growth factor receptor (EGFR) inhibitor that influences tyrosine kinase signaling, one of many potential stimulation pathways for certain malignant cell types, including lung and colorectal cancer. Gefitinib was studied in broad samples of patients with advanced non-small cell lung cancer in the early 2000's until what appeared to be a lackluster (<10%) overall response rate caused the FDA to restrict its use to only those who already exhibited a response and those in ongoing clinical trials in 2005. During attempts to investigate why certain patients enjoyed a good response, a profile emerged illustrating females, never-smokers, an adenocarcinoma histology or Asian patients were most commonly found to possess EGFR mutations predictive of response. Tumors with the two most frequently seen EGFR mutations (exon 19 deletion and a point mutation in exon 21 known as L858R) within these groups were so sensitive to inhibition of this pathway that patients in this category could receive gefitinib as first-line therapy instead of traditional chemotherapy

and expect similar or better anticancer response rates (Ellison et al., 2013; Mok et al., 2009).

The gravity of the diagnosis and optimism associated with the ability to provide a self-administered, comparatively less toxic therapy with clearly superior overall and progression-free response rates led to rapid practice change and implementation of EGFR mutation testing for those newly diagnosed patients that fit the profile. Since that time, several additional mutational markers associated with response that are not so closely linked with a racial group have become available, such as KRAS (Kirsten rat sarcoma-2 viral protein) and ALK (anaplastic lymphoma kinase) that also predict response to EGFR inhibitors, so it is now a recommended practice to test when any patient presents with advanced disease and sufficient tissue is available (Li, Kung, Mack, & Gandara, 2013).

The FDA approval of BiDil® in 2005, a fixed-dose combination of the long-available drugs isosorbide and hydralazine set off vigorous debate in the professional and lay press regarding the appropriateness of "race-based medicine." The study sponsor was NitroMed, a for-profit pharmaceutical company, with co-sponsorship from the Association of Black Cardiologists, and intentionally recruited self-identified African-Americans with hypertension and heart failure for the A-HeFT (African American Heart Failure Trial) after a secondary, retrospective review of a prior study indicated that African Americans appeared to demonstrate greater than expected benefit from the drug combination (Cohn et al., 1991). NitroMed proposed and financed the A-HeFT study, citing the lack of treatment options for this population, and subsequently ended the study early due to obvious benefit for the drug combination in achieving improved clinical outcomes (Taylor et al., 2004). Though some hailed the study as a landmark that

highlighted the need to enhance minority recruitment in clinical trials, and raised the opportunity to clarify the concepts and standardized terminology associated with race, geographic ancestry and population-based therapy approaches on a global scale, others proposed negative connotations and cast aspersions on the financial motivations driving the work (Seguin, Hardy, Singer, & Daar, 2008). It should be noted that despite a follow up study attempting to define a marker of response among BiDil ® responders, no clear genetic marker has been identified (Ferdinand, 2008). In this case, practice change was slow, and despite strong study results indicating efficacy in an underserved population, NitroMed ceased BiDil® marketing in 2008 (Armstrong, 2008) (Armstrong, 2008). Given the burgeoning technology associated with "personalized medicine," and the anticipated exponential expansion of available biologic and genomic tests that will soon guide treatment and supportive care decision making in oncology and other specialties, nurses must increase familiarity with these issues and act as leaders to encourage thoughtful dialogue as both scholars and patient advocates (Jaja, Gibson, & Quarles, 2012).

Radiation

Surprisingly, though receipt of radiation therapy was a statistically significant predictor of the number of hospitalizations in both the lung and colorectal cohorts, it was not significant as a predictor of the initial admission. Radiation therapy is a very localized intervention as compared with the systemic effects of chemotherapy, but may cause intense and lasting effects in the areas treated, and the severity and duration of these effects, alone or in combination with pre-existing conditions or concurrent treatments may exacerbate symptoms to the point that cannot be controlled in the outpatient setting. Site-specific acute adverse effects of radiation to the chest may include esophagitis and

pneumonitis; patients receiving therapy to the abdomen may experience diarrhea, nausea and vomiting, especially when administered concurrently with chemotherapy (Baglan et al., 2002). Depending on the amount of rib, spine or pelvic bone marrow in treatment areas, blood cell production may be reduced, increasing the risk of anemia and leukopenia, and nearly every patient will experience some degree of dermatitis (Wickline, 2004). As in other areas of symptom management, some exploration of individualized biological markers to predict radiation-induced toxicity is underway as well and may assist in proactive identification of those patients most likely to require additional monitoring and supportive care (Henríquez-Hernández et al., 2012).

Limitations

The availability of a National Cancer Institute managed, large-scale dataset such as SEER-Medicare offers many advantages, including access to the entire population of incident cases for certain time periods with a plethora of associated data available for each case. However, there were a number of important limitations to this study. For example, it was anticipated that more detailed analysis of the interactions between the time of chemotherapy administration and the unplanned hospitalization event(s) would be possible, as well as more specific descriptions of the reasons for the hospitalizations. Due to the differently structured file sources and units of measurement for ambulatory claims and inpatient stay data, additional analytic support with SAS expertise dedicated to the research team will be needed for future work to enable this level of analysis.

We were unable to evaluate setting of care factors (hospital teaching status, NCI cancer center designation and participation in cooperative clinical trial groups) as originally planned due to the smaller proportion of cases treated in a hospital outpatient

setting, where these data would be available. A future subset analysis would be possible, especially if the stage IV number of cases were to be added. In addition, we intended to attempt to separate out those visits made to the emergency department for treatment toxicity, but did not result in an inpatient stay. These data were also only available for patients treated in the hospital outpatient setting, and therefore could not be included for the same reasons as the setting of care factors.

Claims data is limited by nature, and does not offer the same opportunities to capture factors critical to clinical outcomes such as performance or psychosocial status, nor inform subtleties of the clinical situation that would be available in the narrative or other clinician documentation in an electronic health record. It is hoped that over time, rapid learning systems will incorporate electronically generated clinical data and be available to enrich the pool of secondary data for analysis.

CHAPTER VI. SUMMARY, CONCLUSIONS, IMPLICATIONS, RECOMMENDATIONS

This retrospective analysis conducted within the SEER-Medicare linked dataset in the lung and colorectal cancer populations illustrated predictors related to the likelihood of initial unplanned hospitalization, as well as those related to the number of hospitalizations experienced. The tumor types and research setting were selected to allow study among the two most commonly admitted cancers identified in the literature, from a nationally validated, population-based dataset comprised of patients over age 65, a group that is typically underrepresented in clinical trials.

Utilizing Brant's Symptom Management Model with the intention to identify meaningful Demographic, Physiologic and Situational antecedents, factors including patient age, sex, race, marital status, geographic area by SEER registry, census tract median income, educational level, cancer type, stage, receipt of radiation therapy and comorbidities were explored. Raw data from the SEER-Medicare database, derived from four file types with varied units of measurement and formatting were carefully reviewed and cultivated to produce two parallel tumor-based cohorts. A major area of skill building during the project involved efforts by the dissertation candidate to design work processes and SAS programming techniques to ensure valid, reliable and reproducible file management and analysis methods.

Two separate tumor-based cohorts, lung (n = 2457) and colorectal cancer (n = 1485), were constructed and analyzed in parallel. Despite the starting size of each population at over 100,000, conservative eligibility criteria to select patient cases constricted the final cohort size significantly. Patient eligibility included those who were

over 66 years of age at the time of diagnosis, had non-metastatic lung or colorectal cancer as their first malignant primary tumor, uninterrupted Medicare Part A and B coverage with no HMO usage, and who received intravenous chemotherapy at least one time prior to experiencing a cancer-related, non-surgical hospitalization.

The cohorts were analyzed using GEE models that accounted for the within-region effects of geography at the SEER registry level to identify factors associated with initial unplanned hospitalization as well as the number of hospitalizations. For lung cancer, decreasing age, non-white race, lower levels of education, higher median income, receipt of radiation therapy and absence of a comorbidity were significant predictors of the likelihood of initial unplanned hospitalizations. Non-white race, receipt of radiation therapy, and presence of a comorbidity were factors associated with the number of hospitalizations experienced. It should again be noted that there was an unexpected distribution of comorbidity scores between the hospitalized and non-hospitalized groups in this cohort that may have impacted these results.

For colorectal cancer, female sex, decreasing age, higher levels of education and lower median income were significant predictors of the likelihood of initial unplanned hospitalizations. Non-white race, receipt of radiation therapy and increasing comorbidity were factors associated with the number of hospitalizations experienced.

Conclusions

This work established that it is possible to identify predictors of unplanned hospitalizations among Medicare patients receiving outpatient chemotherapy through the use of a population-based, nationally validated claims dataset. Demographic and clinical factors were identified that can be utilized upon a patient's initial presentation to a

clinical practice or chemotherapy infusion center to select patients at an elevated risk for hospitalization, and nurses can proactively target additional patient education and clinical monitoring efforts to this group.

Implications for Nursing

This work represents a first step in a program of research to identify predictors for severe treatment-related toxicity and unplanned hospitalization. With the implementation of the Hospital Readmission Reductions Program by CMS in 2012, there are significant financial penalties to those hospitals with excessive readmissions for common issues such as heart failure, pneumonia and acute myocardial infarction. While these diagnoses are not cancer-specific, patients undergoing chemotherapy and other treatments may certainly experience these problems, and nurses of all specialties will be called upon to identify methods to optimize care practices.

The development of prospective risk factor profiles for early identification of those patients most likely to develop severe toxicity will guide nurses to provide targeted, proactive interventions early in the course of care where the effect will be most pronounced, including patient and caregiver education with special instruction on important clinical signs and symptoms that should trigger contact with the oncology service to obtain early outpatient management. Special considerations related to learning strategies reported to be most effective among older adults, such as self-paced learning materials or bulletin boards that allow absorption of material over time (John, 1988; Rigdon, 2010) .

Care protocols utilized by nurses in generalist and advanced practice roles may also be targeted by patient risk level. For example, a clinical pathway protocol for

patients with colorectal cancer about to start therapy on a regimen that includes 5-FU could include assessment for female sex, number of comorbidities, history of or plan for radiation therapy and socioeconomic status. In addition to the standard pre-chemotherapy teaching session and printed materials that all patients and their caregivers receive, those with several positive predictors would also undergo personalized education regarding the signs and symptoms of clinically significant nausea, vomiting, diarrhea, stomatitis or impending sepsis that warrant an urgent call to the oncology service for additional evaluation. The pathway would also specify any additional supportive medications and scheduling of extra phone or in-person nursing contacts to evaluate symptoms escalating beyond the patient's ability to self-manage.

In practice, nurses frequently use assessment scales incorporating predictors for adverse events to identify patients at risk of falls and pressure ulcers, and these tools assist nurses to improve outcomes (Oliver, Daly, Martin, & McMurdo, 2004; Pancorbo-Hidalgo, Garcia-Fernandez, Lopez-Medina, & Alvarez-Nieto, 2006). With further work, the predictors identified in this study, along with others to be determined, such as functional status and specific genomic markers influencing anticancer and supportive care drug selection can be incorporated into such a screening tool in the ambulatory oncology setting.

Recommendations

As is fitting for a dissertation project intended to begin a long-term research program, many new research questions have emerged during the conduct of this study. With the addition of additional analytic support, it will be possible to address issues such as trends in the relationship of chemotherapy administration date and time to unplanned

hospitalization, as well as a more sophisticated analysis of the frequency of the adverse events instigating the admission. Additionally, subgroup analyses exploring the relationships between patients with specific organ system comorbidities and risk of unplanned hospitalizations for the most frequently observed toxicities are warranted.

To build on the results of this work, data from additional sources would add value, such as electronic health records thoroughly integrated into hospital systems that provide multidisciplinary in- and outpatient oncology care. The ability to capture more extensive clinical data to complement or explain the context of the claims data utilized in this study would provide a more complete picture of the factors impacting outcomes over time as patients interact with the health care system. Several NCI designated comprehensive cancer centers have undertaken efforts in the last decade to develop clinical registries that link genomic data to de-identified clinical information, which may allow expanded exploration of predictors associated with severe adverse events and hospitalizations. This type of inquiry would also facilitate clarification of the interplay among genomic, race/ethnicity and the socioeconomic status variables that appeared to be related in this study.

The research questions in the current study centered on identification of predictors related to unplanned and potentially avoidable hospitalizations. During the conduct of the study, unexpected findings within the cohort data indicated several areas that bear further investigation. In the lung cohort, 29% of the cancer-related hospitalizations were longer than 7 days, and 11% were longer than 14 days. A better understanding of the characteristics of patients with extended, as well as unplanned hospitalizations may improve utilization of inpatient services. Additionally, on first examination,

approximately 5% of the hospitalizations in the first colorectal cohort were for 48 hour 5-FU chemotherapy infusions every two weeks (these hospitalizations were later excluded from this study's analysis). This therapy is usually provided on an ambulatory basis with a low volume, wearable infusion pump. Considering the much higher cost per day to provide this care as an inpatient, as well as the increased exposure to the risk of iatrogenic harm, exploration of the characteristics of the patients selected to receive care through this method is important.

In conclusion, nurses are well-positioned to promote high-quality, coordinated and compassionate supportive care to patients throughout the cancer experience. In addition to other valuable methods of research inquiry, we can increase our knowledge of how to identify and protect these patients from harm and avoidable adverse events through work within large, population-based datasets.

Appendix I

Proposed Variables		
Outcome	Unplanned Hospitalizations	
Predictors	Demographic	Chronologic Age
		Sex
		Race
		Marital Status
		Geography
	Clinical	Cancer Type
		Disease Stage
		Comorbidity
		Surgery
		Radiation Therapy
		Chemotherapy
Initially Planned for Inclusion		
	Setting of Care	Hospital Teaching Status
		NCI-Cancer Center Designation
		Participation in Cooperative Group Trials

Appendix II

Staging for Lung and Colorectal Cancer

http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/healthprofessional/page3#Section_510

http://www.cancer.gov/cancertopics/pdq/treatment/small-cell-lung/healthprofessional/page3

http://www.cancer.gov/cancertopics/pdq/treatment/colon/HealthProfessional/page3

http://www.cancer.gov/cancertopics/pdq/treatment/rectal/HealthProfessional/page3

Appendix III

ICD-9-CM Codes Commonly Used to Describe Comorbidities

Chronic pulmonary disease	416.9, 491.21, 493.2, 496
Diabetes with and without complications	249, 250
Peripheral vascular disease	443, 443.8, 443.9, 440.20-440.22, 747.60, 747.69
Congestive heart failure	428.0, 398.91, 428, 428.1-428.9
Cerebrovascular disease	430-438
Moderate or severe renal disease	585.6, 585.9, 593.9, 403, 404
Myocardial infarct (old or acute)	410-412, 414.2, 429.1, 429.7
Dementia	290-290.9, 294.1
Rheumatologic disease	714, v82.1
Ulcer disease	533, 707.9
Paralysis	344.9, 359.2, 332.0, 780.72
Mild liver disease	571, 571.8, 571.9, 573
AIDS	042, v08, 795.71

(Klabunde et al., 2007; Wang et al., 2012)

Appendix IV

Common Treatment Regimens Prescribed for Lung and Colorectal Cancer.

http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/healthprofessional/page4

http://www.cancer.gov/cancertopics/pdq/treatment/small-cell-lung/healthprofessional/page4

http://www.cancer.gov/cancertopics/pdq/treatment/colon/HealthProfessional/page4

http://www.cancer.gov/cancertopics/pdq/treatment/rectal/HealthProfessional/page4#Section_427

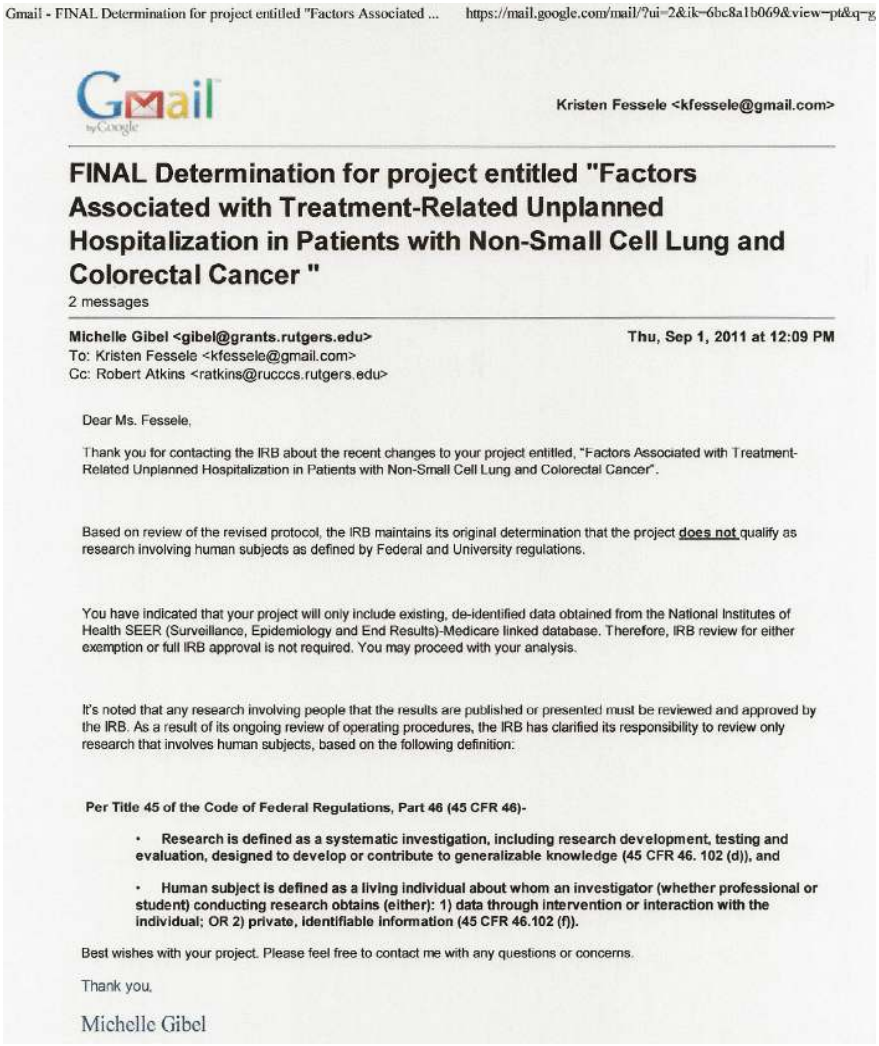
Appendix V

ICD-9-CM Codes Commonly Used to Describe Adverse Events

Abscess of lung/mediastinum 513
Acute cystitis 595.0
Adverse effects of systemic therapy E933.1
Anemia (284.0-285.9)
Anemia 395
Anorexia 783.0
Any dislocation 830 – 839
Aplastic anemia 284
Asthma 493
Chronic bronchitis with or without acute exacerbation 491
Bacteremia 790.7
Blood transfusion without reported diagnosis V58.2
Cachexia 799.4
Cellulitis 681 – 682
Chronic obstructive pulmonary disease exacerbation 491.21
Chronic renal failure 585
Complications of treatment with or without chief complaint 452 – 453
Congenital hypothyroidism 243
Dehydration (276.5)
Dehydration/hypovolemia 276.5
Delirium (780.x)
Diarrhea 787.91
Dizziness 780.4
DVT or PE Thrombophlebitis 451
Electrolyte disorder 276.9
Emphysema 492
Empyema 510
Failure to thrive — adult 783.7
Fever 780.6
Fracture femur, hip, or pelvis 235, 236
Fractures or dislocations 800 – 829
Functional diarrhea 564.5
Goiter 240, 241
Headache Migraine 784.0
Hip fracture (820.x)
Hypokalemia 276.8
Hyponatremia 276.1
Hypothroid — other reasons 244
Bronchitis 490
Injection/infusion of electrolytes 99.18
Iron deficiency anemias 280
Kidney infection 590
Kidney/urinary tract infection 320 – 321
Long-term current use of antibiotics V58.62
Malaise/fatigue 780.79
Malnutrition 263.9
Malnutrition Abnormal weight loss 783.21
Myocardial infarction (410.x or 412.x)
Nausea/emesis 787.0
Neutropenia (288.0)
Nutritional/metabolic disorder 296 – 297
Other and unspecified anemias 285
Other deficiency anemias 281
Other infection and parasitic disease 423
Other specifi ed diseases of white blood cells 288.8
Pneumonia 480 – 486
Pulmonary embolism 415.11
Renal failure 316
Acute renal failure 584
Renal failure unspecifi ed 586
Septicemia 038.0-038.9
Shock/septicemia — other 785.59
Shock/septicemia — septic 785.52
Shock/septicemia — unspecified 785.50
Signs/symptoms with or without chief complaint 463 – 464
Syncope 141 – 142
Syncope 780.2
Thrombocytopenia 287.4
Thyroiditis 245
Thyrotoxicosis 242
Transfusion — 99.04- 99.03
Transfusion of platelets 99.05
Unspecified diseases of white blood cells 288.9

(Du et al., 2002; Hassett et al., 2006)

Appendix VI



Gmail - FINAL Determination for project entitled "Factors Associated ... https://mail.google.com/mail/?ui=2&ik=6bc8a1b069&view=pt&q=g

Gmail by Google

Kristen Fessele <kfessele@gmail.com>

FINAL Determination for project entitled "Factors Associated with Treatment-Related Unplanned Hospitalization in Patients with Non-Small Cell Lung and Colorectal Cancer "

2 messages

Michelle Gibel <gibel@grants.rutgers.edu> **Thu, Sep 1, 2011 at 12:09 PM**
To: Kristen Fessele <kfessele@gmail.com>
Cc: Robert Atkins <ratkins@rucccs.rutgers.edu>

Dear Ms. Fessele,

Thank you for contacting the IRB about the recent changes to your project entitled, "Factors Associated with Treatment-Related Unplanned Hospitalization in Patients with Non-Small Cell Lung and Colorectal Cancer".

Based on review of the revised protocol, the IRB maintains its original determination that the project **does not** qualify as research involving human subjects as defined by Federal and University regulations.

You have indicated that your project will only include existing, de-identified data obtained from the National Institutes of Health SEER (Surveillance, Epidemiology and End Results)-Medicare linked database. Therefore, IRB review for either exemption or full IRB approval is not required. You may proceed with your analysis.

It's noted that any research involving people that the results are published or presented must be reviewed and approved by the IRB. As a result of its ongoing review of operating procedures, the IRB has clarified its responsibility to review only research that involves human subjects, based on the following definition:

Per Title 45 of the Code of Federal Regulations, Part 46 (45 CFR 46)-

- **Research is defined as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge (45 CFR 46. 102 (d)), and**
- **Human subject is defined as a living individual about whom an investigator (whether professional or student) conducting research obtains (either): 1) data through intervention or interaction with the individual; OR 2) private, identifiable information (45 CFR 46.102 (f)).**

Best wishes with your project. Please feel free to contact me with any questions or concerns.

Thank you,

Michelle Gibel

Michelle Gibel
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Appendix VII

SEER Registry Code and Name

01 = San Francisco

02 = Connecticut

20 = Detroit

21 = Hawaii

22 = Iowa

23 = New Mexico

25 = Seattle

26 = Utah

27 = Atlanta

31 = San Jose

35 = Los Angeles

37 = Rural Georgia

41 = Greater California

42 = Kentucky

43 = Louisiana

44 = New Jersey

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Principal Positions/Occupations

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1994-1995: Patient Care Coordinator, Montefiore Medical Center, Bronx, New York

1995-2002: Oncology Clinical Specialist, Amgen, Inc., Thousand Oaks, California

2002-2008: Advanced Practice Nurse and Associate Director, Clinical Research, The Cancer Institute of New Jersey, New Brunswick, New Jersey

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Publications

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