Effects of Primary Prophylaxis of Neutropenia on Outcomes, Utilization and Expenditures for Elderly Breast Cancer Patients Receiving Chemotherapy

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ABSTRACT

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Breast Cancer Patients Receiving Chemotherapy
(Under the direction of Sally C. Stearns)

Systemic chemotherapy is a well-established primary as well as adjuvant therapy for breast cancer, and is highly successful in ensuring recurrence free survival among patients. However, toxicity due to chemotherapy, specifically an early onset hematologic toxicity called neutropenia, restricts the use and therefore the efficacy of chemotherapy in breast cancer patients, especially in the elderly. The prophylactic use of granulocyte-colony stimulating factors (G-CSF), helps prevent neutropenia, improves the tolerance of chemotherapy in the elderly, and improves the prognosis of breast cancer. Nevertheless, evidence supporting the clinical and cost effectiveness of prophylactic G-CSF in the elderly is limited, and thus the American Society of Clinical Oncology (ASCO) guidelines for use of prophylactic G-CSF in the elderly are not explicit.

This study aims to assess the effect of primary prophylactic G-CSF on - the occurrence of chemotherapy-induced neutropenia hospitalization and length of stay; Medicare expenditures due to neutropenia management; overall expenditures in the first year after the start of chemotherapy; and successful administration of systemic cancer therapies that are otherwise hindered by the occurrence of neutropenia, in elderly breast cancer patients receiving chemotherapy.

The study found that primary prophylactic G-CSF reduced the probability of neutropenia hospitalization and improved the provision of systemic chemotherapy and radiation therapy during

the first course of the treatment in elderly breast cancer patients. The study also found that duration of primary prophylactic G-CSF administration was significantly associated with better outcomes, with lower rates of neutropenia hospitalization and better adherence to systemic cancer therapies. These findings have implications for ASCO guidelines and Medicare coverage policies for G-CSF administration and duration of administration in elderly breast cancer patients.

I dedicate this dissertation to my grandfather Dr.S.N. Sriramadesikan for being a constant source of inspiration since my childhood.

I would like to thank all my friends at Ohio State University and University of North Carolina, especially Sharath Kumar, for being my family in this foreign land. Finally, I would like to thank my family, my father for instilling the importance of independent thinking, my mother for her love and prayers, my brother for his faith and confidence in my abilities, and my husband, the man behind every achievement I have made since the last eight years. This dissertation is dedicated to my grandfather Dr. S.N.Sriramadesikan, one of India's most accomplished researchers.

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LIST OF ABBREVIATIONS

AIDS Acquired Immunodeficiency Syndrome

AJCC American Joint Committee on Cancer

ANC Absolute Neutrophil Count

ASCO American Society of Clinical Oncology

CSF Colony Stimulating Factors

EBCTCG Early Breast Cancer Trialists' Collaborative Group

EDB Enrollment Database

EPBR Equal Percentage Bias Reducing

ER Estrogen Receptor

ESRD End-Stage Renal Disease

FDA Food and Drug Administration

GA Genetic Algorithm

G-CSF Granulocyte Colony Stimulating Factor

GM-CSF Granulocyte Macrophage Colony Stimulating Factor

HIV Human immunodeficiency virus

HMO Health Maintenance Organization

KS Kolmogorov-Smirnov

ME Medicare Expenditures

MSI Medicaid Supplemental Insurance

NCCN National Comprehensive Cancer Network

NCI National Cancer Institute

NHE Neutropenia Hospitalization Expenditures

NSABP National Surgical Adjuvant Breast and Bowel Project

RDI Relative Dose Intensity

SBI State Buy-In

SEER Surveillance, Epidemiology and End Results

SES Socioeconomic Status

USCS United States Cancer Statistic

VA Veterans Affairs/ Veterans Administration

CHAPTER 1

Introduction

Breast cancer is the most common cancer among women in the United States and the second leading cause of cancer deaths among women (USCS, 2004). Systemic chemotherapy is a well-established primary as well as adjuvant therapy for breast cancer and is more commonly used in breast cancer compared to other cancers (EBCTCG, 2005; Jamul, 2005). However, toxicity due to chemotherapy, specifically an early onset hematologic toxicity called neutropenia, restricts the use and therefore the efficacy of chemotherapy in breast cancer patients (Webster, 1996). The rate of occurrence of the toxicity is especially high in the elderly ($\geq$ 65 years) since increasing age is one of the strongest risk factor for neutropenia and other chemotherapy-induced toxicities (Lyman, 2003a; Lyman, 2003c; Lyman, 2001). Neutropenia involves significant increase in expenditure due to the need for aggressive in-patient management, and a drop in treatment efficacy as a result of reduction and delay in both chemotherapy and radiation therapy, especially among the elderly. High risk of toxicity in the elderly is unfortunate because the incidence of breast cancer increases five times for women above the age of 65 years compared to younger women (Ries, 2008). The elderly also have a higher probability of detection at more advanced stages of breast cancer and a higher probability of metastasis, and therefore are more in need of a systemic therapy like chemotherapy and radiation therapy (Freyer, 2006; Gennari, 2004; Singh, 2004; Crivellari, 2007).

The use of hematopoietic growth factors, specifically granulocyte-colony stimulating factors (G-CSF), helps prevent neutropenia, thereby improving the tolerance of systemic therapy in the elderly and hence the prognosis of breast cancer (Osby, 2003; Lyman, 2003a; Lyman, 2002; Webster,

1996; Welte, 1996). However, evidence supporting the clinical and cost effectiveness of prophylactic G-CSF in the elderly is limited. As a result, the American Society of Clinical Oncology (ASCO) guidelines for use of prophylactic G-CSF in the elderly are not explicit (ASCO, 2006). The ASCO guidelines recommend the use of physician discretion in administering prophylactic G-CSF in "special circumstances" such as elderly >65 years, without explicitly stating whether or not to administer it to all elderly or specifying any high-risk sub-groups of elderly to whom it should be administered to (Gridelli, 2007). The lack of external validity and inadequacies of the clinical trials in the elderly call for nationally representative population based studies to establish the utility of prophylactic G-CSF use in the elderly (Hassett, 2006).

This study aims to assess the population level effects of primary prophylactic G-CSF on: the occurrence of chemotherapy-induced neutropenia hospitalization and length of stay; Medicare expenditures due to neutropenia management, and overall expenditure in the first year after the start of chemotherapy; and successful administration of systemic cancer therapy that could otherwise be hindered by occurrence of neutropenia. The study uses Surveillance, Epidemiology and End Results (SEER) data from 1994 to 2002 linked to Medicare claims through 2004 to examine primary prophylactic G-CSF administration and related outcomes. The target population consists of elderly (>65 years) female Medicare enrollees, newly diagnosed with stage I to III breast cancer between the years 1994 to 2002 and receiving chemotherapy.

The specific aims of the study are:

1. To explore the socio-demographic and clinical determinants of primary prophylactic G-CSF administration in the clinical setting.

2. To estimate the effect of primary prophylactic G-CSF administration on:

   a. Hospitalization and duration of hospitalization for neutropenia management in elderly female breast cancer patients receiving chemotherapy

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      b.   Neutropenia-related Medicare expenditures and overall Medicare expenditures in elderly female breast cancer patients receiving chemotherapy.

      c.   Successful administration of systemic cancer therapy, which could otherwise be hindered by occurrence of neutropenia.

3.   To explore the determinants and effects of duration of primary prophylactic G-CSF administration.

A population level study verifying the effect of primary prophylactic G-CSF on outcomes and costs in elderly patients is an important step in validating the use of the expensive G-CSF in the elderly. The results will contribute towards ASCO and Medicare policies.

The study found that the key determinants of primary prophylactic G-CSF administration in elderly patients receiving chemotherapy were – Race, SEER region, year of diagnosis/chemotherapy initiation and characteristics of the chemotherapy regimen, with SEER region and chemotherapy characteristics being the strongest predictors in terms of magnitude. Whites have a higher probability of receiving primary prophylactic G-CSF compared to other races. Women from SEER regions of California, Louisiana and Connecticut have a higher probability of receiving primary prophylactic G-CSF. Women diagnosed with breast cancer and receiving chemotherapy in later years (especially after the year 1999) were also more likely to receive primary prophylactic G-CSF. Women receiving a more intense chemotherapy regimen characterized by – administration of anthracycline, more drugs in the first cycle, and shorter duration between the first and second cycle, were more likely to receive primary prophylactic G-CSF. Unexplained and significant variations in primary prophylactic G-CSF administration based on race and region are a concern.

The study also found that primary prophylactic G-CSF reduced the probability of neutropenia hospitalization and improved the efficacy of systemic chemotherapy and radiation therapy during the

first course of the treatment. Primary prophylactic G-CSF was not found to be significantly associated with lower average length of stay and expenditure for neutropenia hospitalizations though the lack of significance may be due to small sample size; the direction of the effect did illustrate a lower average length of stay and hospitalization expenditures in women receiving primary prophylactic G-CSF. Patients receiving primary prophylactic G-CSF also had higher overall Medicare expenditures during the first year after the start of chemotherapy (which is the time when the bulk of the cancer-related therapies are provided). Duration of primary prophylactic G-CSF administration, and not just the administration itself, was significantly associated with better outcomes, with lower rates of neutropenia hospitalization and better adherence to systemic chemotherapy. These findings have implications for ASCO guidelines and Medicare coverage policies for provision of G-CSF and duration of provision in elderly breast cancer patients.

CHAPTER 2

Background and Significance

2.1 Burden of breast cancer

Breast cancer is the most common cancer among women in the United States and the second leading cause of cancer deaths among women (USCS, 2004). The probability of developing invasive breast cancer for women in the United States is 1 in 8, and the probability of death due to breast cancer is 1 in 33. In addition to the high prevalence of the disease compared to other cancer types, the incidence of breast cancer has also been increasing since the 1970s. The age-adjusted incidence of female breast cancer has increased since the last few decades from 105.0/100,000 in 1975 to 140.8/100,000 in 1998, and has stabilized in the last few years at 128.2/100,000 from 2003. Moreover, the mortality rates have decreased in the past few years from 31.4/100,000 in 1975 to 26.0/100,000 in 2002, thereby increasing the number of people needing post-diagnosis management and recurrence prevention (USCS, 2004; Ries, 2008). Every year $5.3 billion is spent nationally on the treatment of this disease, thus making breast cancer the second most expensive cancer in terms of treatment (Brown, 2002). Almost 50% of the overall national spending for breast cancer is covered by Medicare.

The US population is aging; the proportion of individuals, 65 years and older, is expected to double from 11.3% (25.5 million) in 1980 to 20.1% (70.2 million) in 2030 (Yancik, 1997). Since breast cancer occurrence is age-related, the absolute number of incident cases is predicted to increase in the nation (Statistical abstract of the United States, 1997). Also, epidemiological studies show that

by the end of the 20th century nearly 60% of all newly diagnosed breast cancers had occurred in women 65 years and older (Baranovsky, 1986) indicating an increase in the incidence of breast cancer in older individuals. The increase in breast cancer cases in the general population and among the elderly accentuates the need for cancer control and therapy in the aging population. One of the reasons for choice of the study population in this study is the cancer burden in United States, especially with respect to the elderly.

2.2 Stage, grade and corresponding treatment protocol for breast cancer

Protocols for treatment and management of breast cancer after diagnosis depend primarily on the American Joint Committee on Cancer (AJCC) staging of the tumor. Table 1 describes the stages and the relevant treatment for each stage. The staging has five categories, ranging from stage 0 to IV, based on the tumor size, the lymph node involvement, and the metastasis of the disease, all of which indicate the degree of spread of the disease. Stage 0 is called "carcinoma in situ", a non-invasive stage where abnormal cells are found in the affected breast tissue but have not developed into a tumor and have not spread outside the affected tissue. When an invasive cancer develops into a tumor of size less than 2 centimeters but does not spread outside the breast to the lymph nodes or other parts of the body then the cancer is classified as stage 1. Based on the size of the tumor (from 2 to 5 centimeters or more), and extent of cancer spread to lymph nodes and tissues around the breast like the chest muscles, the cancer is categorized into various subcategories of stages 2 and 3. Once the cancer metastasizes to other organs in the body, mostly the bones, lungs, liver, or brain, it is classified as stage 4.

The cancer grade, on the other hand, is determined by the histological examination of the cells. The grade is indicative of how aggressively the cells are multiplying and growing, and is an indicator for the spread of the cancer. The SEER classifies the cancer into four grades.

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The treatment protocol for breast cancer is determined by the stage at which the cancer is first diagnosed. Treatment is started immediately after diagnosis. Traditionally for stages I to III (the stages of interest in this study) the treatment starts after a Biopsy confirms the diagnosis and establishes the extent of spread. It involves surgery, followed by chemotherapy, radiation therapy and finally hormonal therapy (Figure 1). Since chemotherapy is administered in multiple cycles for a couple of months, radiation therapy can be started soon after surgery while the patient is still receiving chemotherapy.

In advanced cases, where the tumor is large and needs to be shrunk before surgery is performed, chemotherapy is administered immediately after Biopsy. Chemotherapy is followed by surgery, radiation therapy and hormonal therapy in that case (Figure 2). Additional chemotherapy can also be administered after surgery for a second time.

In the traditional scenario, surgery involves either lumpectomy or mastectomy, and is typically performed within a few days after diagnosis - often within the first month after diagnosis. Even if the surgery is delayed due to patient preference or any other constraint, it is performed within the first three months at most.

Chemotherapy is begun three to six weeks after surgery, once the surgical wound heals. This first regimen of chemotherapy administration is called the first course and it is administered over multiple days (cycles). Patients typically receive the first course chemotherapy within 3 months of breast cancer diagnosis. A delay in chemotherapy administration might occur if the patient suffers from surgical complications like infection. Chemotherapy could also be delayed if the patient is initially reluctant to receive it due to its associated toxicities but later decides to receive the therapy.

However, the vast majority of the patients scheduled to receive chemotherapy will have the process initiated within the first 6 months of diagnosis.

A single course of chemotherapy comprises of multiple cycles of administration interspersed with brief recovery period. Multiple administrations ensure that the chemotherapy is able to destroy more cancer cells, and at the same time provides rest periods in between to help the body recoup from the toxic side effects of chemotherapy. Normal cells usually repair the damage from chemotherapy more effectively than cancer cells, so in the rest periods the normal cells recoup but there is no danger of the cancer cells recovering. The number of administrations (cycles) usually range from 4 to 8. The period between each cycle ranges from 2 to 3 weeks. Thus the entire course lasts for 3 to 6 months. A chemotherapy cycle can be administered within one or a few days.

Radiation therapy usually lasts for six to seven weeks and is administered almost daily Monday to Friday. Finally hormonal therapy may be started after all radiation and chemotherapy are completed and administered for up to five years.

In cases where the tumor is very large and spreads aggressively, chemotherapy is begun first, within a week or two of diagnosis. Chemotherapy is administered for up to 3 to 6 months and then the patient is scheduled for surgery. Radiation therapy and hormonal therapy follow as mentioned before.

When employed, primary prophylactic G-CSF is typically administered at least 24 hours after the first chemotherapy cycle, but mostly within 2-3 days of completing the first cycle of chemotherapy. One course is administered for 5-10 consecutive days. A G-CSF course can be administered after every cycle of chemotherapy.

2.3 Significance of chemotherapy in female breast cancer patients

Chemotherapy is an established treatment for many types of cancer, and breast cancer is the most common indication for chemotherapy among women (Jemal, 2005, NCCN, 2000; Shifflett, 1999). Chemotherapy involves the use of cytotoxic drugs for controlling the growth and spread of cancer cells. Chemotherapy has been proved to be effective and efficacious in treating and containing breast cancer, irrespective of age, nodal status, estrogen receptor status, and administration with or without other systemic therapies like radiation and hormonal therapy (EBCTCG, 1988; EBCTCG, 1992; EBCTCG, 1998; EBCTCG, 2005; Fisher, 1999; Hortobagyi, 1998; Fisher, 1990). Chemotherapy is utilized following the initial diagnosis in an effort to reduce the risk of recurrence and eventual death from cancer.

As can be seen from Table 1, chemotherapy plays a pivotal role in most stages of breast cancer. Chemotherapy is recommended in women with breast cancer as an adjuvant therapy after surgery in early breast cancer stages of I to III; as primary therapy in inoperable cases of stage 3; and as palliative therapy after metastasis of breast cancer (NCCN, 2000; Shifflett, 1999). Even in the absence of breast cancer metastasis (in stages I to III), adjuvant systemic chemotherapy after surgery is recommended because in spite of early detection and treatment, undetected micro-metastasis might exist thereby increasing the possibility of recurrence and death (EBCTCG, 1998). The primary role of chemotherapy in early stages of I to III is to prevent breast cancer recurrence and breast cancer related mortality (EBCTCG, 2005).

2.4 Impediments for chemotherapy administration in breast cancer patients

In spite of its success in breast cancer treatment and management, the use of chemotherapy is restricted due to the toxicity associated with the therapy (Webster, 1996; Perry, 1984). Given the

pivotal role of chemotherapy in the treatment and management of this high burden disease, impediments for the effective administration of chemotherapy are a matter of concern. Chemotherapy drugs are the leading cause of therapeutic adverse effects among female breast cancer patients (Hassett, 2006). These toxicities are a result of the cytotoxic properties of the therapy; the therapy is geared towards hindering the rapid division and formation of new cancer cells. However, as a side-effect the therapy interferes with the growth of other healthy cells that are dividing and growing in the adults, such as bone marrow cells, skin, hair follicles, reproductive cells and gastrointestinal lining cells. Thus, some of the observed symptoms of chemotherapy-induced toxicity are hair loss, anemia, hemorrhage, infection, fever, nausea, emesis, diarrhea, dehydration, electrolyte abnormality, malnutrition, malaise, fatigue, delirium, and infertility (Perry, 1984).

Hematologic toxicity, caused by suppression of the hematopoietic processes (the process of bone marrow cells producing blood cells), is one of the most serious toxicities of chemotherapy at the early stage of the therapy. It begins within a week after chemotherapy administration and peaks after two weeks (Perry, 1984; Shapiro, 2001; Chrischilles, 2003a). Among the various manifestations of hematologic toxicity, neutropenia, which is marked by a drop in the neutrophil count in the blood below 2000/microL, is of major a concern (Du, 2005; Shapiro, 2001; Perry, 1984). The drop in the neutrophils in the blood reduces the body's capacity to resist infections, which might lead to neutropenic fever (febrile neutropenia), and a sequel of life threatening systemic infections or sepsis. Unfortunately neutropenia is specifically higher among breast cancer patients receiving chemotherapy compared to other cancer patients receiving chemotherapy (Shayne, 2007).

Infection and fever associated with a drop in the neutrophil count are the most common presenting symptoms of neutropenia (Hassett, 2006; Perry, 1984). Fever $\geq$ 100.6F associated with neutropenia involving a neutrophil count of < 1000 cells/microL is termed as febrile neutropenia (Chrischilles 2002). The increase in the risk of infection and mortality increases proportionately with

the severity and duration of neutropenia in a patient (Lyman, 1998). Chemotherapy patients face high risk of death if not treated aggressively for systemic infections and febrile neutropenia (Perry, 1984).

Standard practices to control chemotherapy-induced neutropenia, especially in the presence of infections and fever, are immediate hospitalization for evaluation of neutropenia and aggressive administration of empiric broad-spectrum antibiotics to control any infections (Perry, 1984; Baquiran, 2001). This is followed by dose modification/reduction or dose delay of the chemotherapy, and delaying or cancelling the required radiation therapy. The largest share of direct medical costs for cancer patients suffering from neutropenia are expensive hospitalization costs including diagnostic tests and antibiotic administration for treating life threatening systemic infections and febrile neutropenia (Eldar-Lissai, 2007; Kuderer, 2006; Lyman, 1993; Lyman, 1998; Weycker 2007). Hospitalization especially accounts for 62% to 82% of direct healthcare cost of febrile neutropenia management (Leese, 1993; Dranitsaris, 1995), and most of the hospitalization cost is associated with length of stay and level of neutropenia complications (Eldar-Lissai, 2007).

Dose reduction and dose delay to control neutropenia hinder the effective administration of a planned treatment regimen, diminish the efficacy of chemotherapy and radiation therapy, harm patient health outcomes and prognosis, increase the probability of recurrence and mortality, and might also increase the overall treatment costs due to lose of efficacy of the chemotherapy regimen (Shayne, 2006; Hershman, 2007; Weycker, 2006; Ozer 2000; Baquiran, 2001; Webster, 1996; Welte, 1996; Ziegler, 2006). Adjuvant chemotherapy for breast cancer loses its clinical benefit when dose intensity is reduced (Ziegler, 2006; Budman, 1998). Reducing the dose or increasing the duration between each chemotherapy administration cycle makes it difficult to prevent tumor re-growth. Hence dose reduction to control toxicity is referred to as "killing with kindness" (Hryniuk, 1988). Neutropenia-related adverse effects are the main dose-limiting toxicities for systemic chemotherapy (Lyman,

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1998), leading to increased healthcare costs of managing recurrence and worse prognosis, and compromising quality of life.

Radiation therapy could worsen neutropenia as it is also a systemic therapy that impedes the production of any new cells in the body. Thus, in an event of neutropenia, radiation therapy is also reduced until the patient recovers.

2.5 Chemotherapy for female breast cancer patients who are elderly

Breast cancer is an age-related tumor. Epidemiological studies show that by the end of 20th century nearly 60% of all newly diagnosed breast cancers had occurred in women 65 years and older (Baranovsky, 1986). Older individuals are also the ones who have a higher incidence of breast cancer and metastasis, larger tumors (Landis, 1998; Diab, 2000), higher node involvement (Molino, 2006; Daidone, 2003; Gennari, 2004) worse survival rate after metastasis (Yancik, 1989), higher probability of detection at more advanced stages (Molino, 2006; Shayne, 2007), and higher risk of disease recurrence after surgery (Gennari, 2004), necessitating systemic chemotherapy (Freyer, 2006; Gennari, 2004; Singh, 2004; Crivellari, 2007). Increase in the risk of breast cancer with age is attributed to higher duration of carcinogenic exposure over time during the lifetime of a person, and to breast tissue aging (Franceschi, 2001; Pike 1983). The higher incidence of metastasis, larger tumors, and late detection could be attributed to fewer breast examinations and screening mammograms (Worden, 1983; Zapka, 1989; NCI, 1990), reduced screening compliance with age (Beghe, 1994), reduced breast awareness among older women (Coates, 1999; Siahpush, 1995) and overall reduction in preventive services received with age (Earle, 2003). Higher risk of breast cancer and later stage of detection make systemic therapy like chemotherapy a very essential part of disease management in the elderly.

Increase in age is the strongest risk factor for chemotherapy-induced side-effects making elderly more vulnerable to chemotherapy-induced toxicities such as neutropenia (Lyman, 1998; Balducci, 2000; Lyman, 2003a; Armitage, 1984). Numerous studies examining the risk of neutropenia and neutropenic complications identify age (particularly >70 years) as an independent and significant risk factor (Lyman 2003a; Lyman 2001). Older individuals also have a higher risk of neutropenia-related mortality and morbidity, requiring hospitalization and aggressive treatment with antibiotics (Balducci, 2000). The higher risk is probably because of their lower marrow reserve, presence of co-morbidities, changes in liver and kidney functions, and lower baseline health (Hassett, 2006; Lyman 2003a; Chrischilles, 2002). Given the essential role of chemotherapy in breast cancer treatment and management, toxicity prevention is critical in elderly who have both higher risk of breast cancer and higher risk of chemotherapy induced toxicity.

The benefit of chemotherapy for elderly as compared to the younger patients could be questioned on the basis of the higher risk of toxicity due to the aging process and possible reduction in effectiveness of chemotherapy in the elderly. Due to the higher risk of toxicity and possible lower effectiveness, receipt of chemotherapy is often shown to decrease with age (Allen, 1986; Silliman, 1989; Busch, 1996). There are three reasons for possible lower effectiveness of chemotherapy in the elderly.

1. Elderly are often less responsive to chemotherapy (Lyman, 2003a).

2. Reduced metabolism of drugs with age make it very difficult to determine if standard drug dose is ideal for older patients. In order for chemotherapy to be effective specific blood concentration of the chemotherapeutic drugs should be maintained. Changes in intestinal absorption, reduced serum albumin, and reduced hepatic and renal functions make it difficult

to estimate the appropriate dosage in elderly (Chrischilles, 2002). If the dose administered is inadequate, then the therapy's effectiveness reduces.

3. A significant proportion of physicians believe breast cancer to be biologically indolent in elderly and thereby not requiring chemotherapy (Carey, 2006; Diadone, 2003).

Nevertheless, chemotherapy is essential in breast cancer patients of all ages. First, older women in good health tolerate standard doses of chemotherapy as well as the younger women (Muss, 1994). Second, for a breast cancer event with less aggressive biological characteristics, the baseline prognosis (when no chemotherapy is administered) of breast cancer is always better and the marginal change due to chemotherapy is lesser in magnitude, on average, than a faster spreading more aggressive event. Thus, the marginal benefit of chemotherapy is lesser on average for older individuals compared to younger individuals. Nonetheless, the marginal benefit exists and the improvement is still clinically efficacious and cost effective (EBCTCG, 1998). Third, although the elderly tend to be estrogen receptor (ER) positive with a higher probability, thus giving them the option of receiving hormonal therapy for a systemic treatment, it has been shown that in case of recurrence prevention, hormonal therapy cannot be a complete substitute to chemotherapy (EBCTCG, 1998). Administration of chemotherapy significantly increases recurrence free survival in ER positive patients receiving hormonal therapy, irrespective of the nodal and menopausal status. Thus, chemotherapy and hormonal therapy seem to be complementary in their actions, and not duplicative (EBCTCG, 1998). Fourth, there are elderly with early breast cancer and ER-ve status who only have the option of chemotherapy for preventing recurrence. Fifth, the belief that breast cancer is biologically indolent has proven to be controversial by many studies, which have demonstrated that breast cancer could be as aggressive in the elderly as in the younger population (Gennari, 2004; Mueller, 1978; Singh 2004). Thus, improving chemotherapy tolerance in elderly is important.

2.6 The role of Colony Stimulating Factors in sustaining chemotherapy and reducing healthcare costs

The introduction of hematopoietic growth factors, also known as Colony Stimulating Factors (CSF), as prophylactic or therapeutic drugs for chemotherapy-induced toxicity, has provided a method to prevent neutropenia and has improved the dose tolerance and outcomes of chemotherapy in cancer patients (Table 2). The CSFs, used for prevention and management of neutropenia, stimulate the production of neutrophils. They are called Granulocyte-Colony Stimulating Factors (G-CSFs) because neutrophils are a type of granulocytes. G-CSFs are glycoproteins that aid the reproduction and maturation of neutrophils, and this maintains the body's ability to fight infections (Welte, 1996). G-CSFs could be used as a primary prophylactic measure to prevent neutropenia after chemotherapy in patients with no prior documentation of neutropenia, as a secondary prophylactic measure after a cycle of chemotherapy with documentation of neutropenia in prior cycles, or as a therapeutic agent after neutropenia occurs, to aid the recovery of neutrophil production (Bennett, 1999).

The most noteworthy contribution of prophylactic G-CSF has been in sustaining dose intensity, especially in chemotherapy patients receiving high dose regimens (Lyman, 1998; Webster, 1996; Shayne, 2006). Maintaining the planned schedule of chemotherapy has been shown to increase recurrence free and overall survival in non-Hodgkin's Lymphoma patients (Chrischilles, 2003). Increasing dose intensity has now become quite popular for breast cancer due to better prognosis of high intensity treatment especially among node-positive patients (Ziegler, 2006; Citron, 2003). Dose intensity can be increased by either increasing the dose, or by increasing the frequency with which chemotherapy cycles are administered. Dose intensity is often expressed as Relative dose intensity (RDI), which is defined as the amount of drug administered per unit of time, expressed as the fraction of the amount recommended in the standard, evidence-based regimen. Studies show that increasing RDI by increasing dose frequency is more effective than increasing the amount of dose administered in preventing recurrence and breast cancer related mortality, as increasing the frequency is better able

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to prevent tumor re-growth before the next dose is administered (Norton, 1997; Citron, 2003; Ziegler, 2006). Increasing the frequency of the hematotoxic chemotherapeutic drugs however, does not allow sufficient time between the chemotherapy cycles for the neutrophil production and blood count to recover. The rate of neutropenia and febrile neutropenia is very high among patients receiving both standard and higher RDI. The febrile neutropenia incidence are reported to be between 57%-98% in case of higher RDI therapy (Baldini, 1997; O'Shaughnessy, 1994) and 23% in case of standard RDI therapy (Rahman, 1997). Neutropenia incidence is 60% in case of standardized RDI therapy (Rahman, 1997).

Prophylactic G-CSF enables the frequency increase of chemotherapy by shortening the time to neutrophil recovery and decreasing neutropenia-related toxicity (Ziegler, 2006). One particular study also showed that the chemotherapy dose tolerance and ability to keep up the dose intensity according to the planned chemotherapy regimen was higher for older patients receiving primary prophylactic G-CSF (Osby, 2003).

There is a need for scientific evidence documenting the value of primary prophylactic G-CSF in chemotherapy dose sustenance for patients with curable early stage (stage I to III) breast cancer (Webster, 1996). Past studies demonstrate the importance of chemotherapy in recurrence free and overall survival in early stage breast cancer patients (EBCTCG, 1992; EBCTCG, 1998; EBCTCG, 2005). Hence, these women have more to lose in terms of quality of life and survival, if the highly effective systemic chemotherapy is stopped or reduced due to toxicity (Budman, 1998; Bonneterre, 2005). Nevertheless, nearly 30% to 50% of these early stage breast cancer patients experience dose reduction below RDI <85% thereby jeopardizing their chance of complete cure and recurrence free survival (Shayne, 2006; Lyman, 2003b). One study showed that neutropenia hospitalization was the primary determinant of early termination of chemotherapy, in not only women who were at a early stage of breast cancer, but who were clinically proven to be responsive to chemotherapy (Chrischilles,

2003). RDI was especially lower in patients receiving a 28-day chemotherapy schedule compared to a 21-day chemotherapy schedule (Shyane, 2006).

In addition to chemotherapy dose sustenance primary prophylactic G-CSF can also reduce costs related to neutropenia management. Cancer care accounts for nearly 10% of the healthcare expenditure in the US, and currently stands at about $100 billion per annum, with the hospital care of cancer patients amounting to 50% of the total cancer-related expenditure. More than 60,000 neutropenia hospitalizations occur each year in the United States (Caggiano, 2005), and each neutropenia hospitalization could cost $10,000 to $30,000 on average (Eldar-Lissai, 2007; Kuderer, 2006; Weycker, 2007; Weycker 2006a). The disease burden and healthcare expenditures of neutropenia can hardly be overlooked.

The CSFs are also expensive and hence their administration should be justified both clinically and economically. Primary prophylactic G-CSF's clinical and cost effectiveness in older adults has been established in clinical trials and other studies (Table 2). Most of these studies involved lung cancer and Non-Hodgkin's lymphoma studies (Crawford, 1991; Chrichilles 2002; Scott, 2003; Weycker 2006). Primary prophylactic G-CSF is effective in reducing the incidence of neutropenia, neutropenia-related serious infections, and reducing number of hospitalization days and intravenous antibiotic use in patients receiving chemotherapy (Zagonel, 1994; Heil, 1997; Moore, 1997; Lyman, 2002; Weycker, 2004; Kuderer, 2007). Neutropenia hospitalization is the largest component of neutropenia-related direct medical expenditures (Eldar-Lissai, 2007; Kuderer, 2006; Lyman, 1993; Lyman, 1998; Weycker 2007). The administration of primary prophylactic G-CSF offsets the cost of neutropenia hospitalization by reducing both the probability of hospitalization (Lyman, 1993; Lyman, 1998; Crawford, 1991; Weycker, 2004) and the duration of hospitalization (Eldar-Lissai, 2007; Chrischilles, 2002). However, cost-effectiveness of primary prophylactic G-CSF in the general

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population has not been ambiguously established (Glaspy, 1993; Zagonel, 1994; Dranitsaris, 1995; Bassan, 1997; Eldar-Lissai, 2007; Uyl-de Groot, 1996; Lyman 2004; Lyman, 1993).

The use of G-CSF grew substantially in the last decade, after its approval by the U.S. Food and Drug Administration (FDA) in 1991. It is important to realize that G-CSFs do have side effects, including musuloskelatal complications like bone and muscle pain (Kuderer, 2005). Some researcher believe that the risk of acute myeloid leukemia or myelodysplastic syndrome may be increased due to G-CSF administration (Hershman, 2007). Chemotherapy often causes mutation in blood cells at an early stage of their development. Typically these mutated cells destroy themselves, but the G-CSF administration saves them from destruction leading to their developing into blood cancer cells. G-CSF also, has some direct mutant effects on the blood cells. Nevertheless the benefits of G-CSF outweigh the side effects (Hershman, 2007).

It is important to understand that primary prophylactic G-CSF is more effective in reducing neutropenia and neutropenia-related hospitalization occurrence than secondary prophylaxis, and even more so than therapeutic use of G-CSF. Neutropenia, neutropenia hospitalization occurrence and neutropenia-related mortality are highest in the first two cycles of chemotherapy (Chen-Hardee, 2006; Chrischilles, 2002; Armitage 1984; Gomez, 1998; Shayne, 2007); also, occurrence of neutropenia during the first cycle of chemotherapy increases neutropenic events in later cycles (Timmer-Bonte, 2006). Thus primary prevention in the very first cycle has a synergistic effect on future preventions. Studies also show that primary prophylactic G-CSF reduces repeat neutropenia hospitalization, and secondary and therapeutic prophylaxis have a lesser effect on recurrent neutropenia incidence and hospitalization (Chrischilles, 2002; Scott, 2003). Secondary prophylaxis is often too late to prevent and reduce neutropenia and related outcomes, and evidence for the clinical and cost effectiveness of secondary prophylaxis are low (Gridelli, 2007). Therapeutic G-CSF benefits have also not been consistently established in previous literature (Gridelli, 2007; Berghmans, 2002; Clark, 2005;

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Hartmann, 1997; Garcia-Carbonero, 2001; Lyman, 1998; Lyman 2004a). Moreover, treatment costs of G-CSF use as therapeutic agent are much higher than treatment cost of G-CSF use as a prophylactic agent, thereby reducing the cost-effectiveness of therapeutic use (Lyman, 1993).

2.7 Need for evidence of primary prophylactic G-CSF effectiveness in the elderly female breast cancer patients

Several clinical trials have been conducted on the efficacy of primary prophylactic G-CSF in reducing neutropenia occurrence, neutropenia hospitalization, frequency of infections, febrile neutropenia, early mortality and infection related-mortality (Table 2). Although a few of these studies show no effect on infection related mortality and early mortality (Crawford, 1991; Pettengell, 1992; Zinzani, 1997; Bui, 1995; Gatzemeier, 2000; Gisselbrecht, 1997), most studies demonstrate a statistically significant reduction in the occurrence of neutropenia, infections due to neutropenia, and febrile neutropenia (Kurderer, 2007; Crawford, 1991; Trillet-Lenoir, 1993; Fossa, 1998; Lyman, 2001). However, these studies lack external validity as their sample participants were selected from local healthcare facilities. Also these studies do not focus on elderly female breast cancer patients as they predominantly involve patients suffering from other solid cancers and lymphomas, such as small cell lung cancer and Non-Hodgkins Lymphoma (Kurderer, 2007).

From an economic perspective the cost-effectiveness of primary prophylactic G-CSF administration has also not been unambiguously established in clinical trials, and the studies have determined that the treatment is cost effective only for patients with a greater than 20% risk of febrile neutropenia occurrence after chemotherapy (Lyman, 2004; Lyman, 1998). Hence the American Society of Clinical Oncology (ASCO) established clinical guidelines (Table 3), with recommendations for use of primary prophylactic G-CSF for only those patient groups that benefited from primary prophylactic G-CSF use (risk of febrile neutropenia >20%), based on the finding of these clinical trials (Gridelli, 2007).

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Nevertheless, some recent studies established that the incidence and costs of adverse effects of chemotherapy for breast cancer patients are under-reported in clinical trials, thereby casting doubt on the toxicity-related costs estimated by these trials (Hassett, 2006; Russo, 2006; Du, 2002). A study estimated that younger (<65 years) female breast cancer patients receiving chemotherapy incurred $1,271 more per year in costs for medical expenses and $17,617 more per year in costs for ambulatory care than female breast cancer patients not receiving chemotherapy, due to chemotherapy-induced toxicity, and that predicted incremental expenditure due to chemotherapy toxicity could reach $45 million per year (Hassett, 2006). Chemotherapy-induced toxicity might lead to higher costs than predicted by the clinical trials because rates of chemotherapy-induced toxicity could be different at the population level versus in the clinical trials due to the following reasons:

1. Patient socio-demographic characteristics like education, income and age are different between clinical trial participants and the general population, often due to strict enrollment criteria for clinical trials, thus limiting the external validity of the trials. The restrictions due to age and comorbidities lead to the exclusion of the older individuals from the clinical trials (Holmes, 2003; Muss, 1994). Under-representation of elderly is a problem for estimating toxicity-related costs for elderly patients (Aapro, 2005; Britton, 1999; Bugeja, 1997; Adams-Campbell, 2004; Gross, 2005; Murthy, 2004; Simon, 2004; Talarico, 2004; Goodwin, 1988), more so in case of age-related tumors like breast cancer (Hutchins, 1999) requiring cytotoxic systemic treatments (Balducci, 1997).

2. The adherence and behavior of the patients in clinical trials are different from the general population, thus modifying the treatment effect (Braunholtz, 2001).

3. Provider behavior is also different during a clinical trial with better adherence to close monitoring and follow-up of patients (Du, 2002).

4. Clinical trials have, on average, longer duration of primary prophylactic G-CSF administration than the duration in practice - 10 to 11 days versus 4 to 7 days respectively (Weycker, 2006; Scott, 2003; Chrischilles 2003). Since duration of administration has a significant impact on neutropenia occurrence and hospitalization, it is essential to study the outcomes of primary prophylactic G-CSF administration outside of trials.

5. Most providers participating in clinical trials participate at or are affiliated with cancer centers, and thus do not necessarily represent all community practice (Chen-Hardee, 2006).

6. Inadequate reporting of adverse events like chemotherapy toxicities and incomplete documentation of reasons for patient discontinuation in case of adverse events affect the sensitivity of the trials in detecting the occurrence of these toxicities (Fromme, 2004; Ioannidis, 2001; Erban, 2006; Trotti, 2004). Moreover, some clinical trials are not designed with the aim to detect toxicities, but have other prognostic outcomes and survival as the endpoints of interest, thereby further increasing the inadequate reporting of toxicities (Erban, 2006).

7. Given the much smaller sample size in a clinical trial as compared to a nationally representative population level data, rare events of toxicity might be inaccurately detected (Ladewski, 2003; Hampson, 2002). Also, clinical trials often have insufficient statistical power to estimate treatment effects among subgroups of patients with certain demographic and clinical characteristics (Chen-Hardee, 2006).

Apart from looking at clinical effectiveness and cost issues it is also important to evaluate the effect of primary prophylactic G-CSF administration on sustaining systemic therapy in the elderly. Older patients (>65 years) and individuals with higher number of comorbidities are more at risk of substantial planned and unplanned dose reductions due to fear of toxicities (Lyman, 2005; Shayne, 2006; Shayne, 2007). Planned dose reductions before the start of chemotherapy for patients above 65 years were higher than younger patients, irrespective of an occurrence of toxicity, indicating the

physician attitude about administering chemotherapy to older patients (Shayne, 2006). Increase in age is significantly positively correlated with early termination of chemotherapy and lower RDI (Chrischilles, 2003; Shayne 2006; Shayne 2007; Lyman, 2003b) due to fear of toxicity, which hinders recurrence free and overall survival. Thus there is a need for evidence supporting the benefits of sustenance of standard RDI chemotherapy administration in the elderly by means of prophylactic agents like G-CSF.

Due to under-representation of older women in breast cancer clinical trials (Hutchins, 1999), and the unresolved challenges associated with including the elderly with comorbidities in clinical trials (Wild, 2003), treatment decisions for elderly women are often based on extrapolations from the results of trials on younger individuals, and also on subjective physician opinions with respect to the tolerance or suitability of the treatment among the elderly (Bergman, 1992; Yancik, 1989; Fentiman, 1990). Given the improvement in life expectancy and the aging population in the US, it is important that the medical decisions for the older women are made based on direct scientific evidence, thereby requiring a careful evaluation of primary prophylactic G-CSF use among older women receiving chemotherapy. There are studies using population level and nationally representative data that demonstrate a beneficial effect of primary prophylactic G-CSF on neutropenia, febrile neutropenia, and neutropenia hospitalization in both elderly and younger patients (Shayne, 2007; Shayne , 2006; Chrichilles, 2003; Scott, 2003; Weycker 2006; Chrichilles, 2002). Only one of these studies specifically looks at female breast cancer patients, and even that study does not specifically look at elderly patients (Shayne, 2006). Thus there is a dearth of studies on primary prophylactic G-CSF use in elderly female breast cancer patients receiving chemotherapy.

The more recent ASCO guideline (2006) made special recommendations with respect to primary prophylactic G-CSF use in patients above 65 years of age (Table 3) (Gridelli, 2007). The guidelines indicate that primary prophylactic G-CSF should be administered when the risk of febrile

neutropenia is greater than 20% in a patient or when dose dense therapy is required. Elderly >65 years

fall in the category of "special circumstances", and physicians are advised to consider patients with

these special circumstances (like age >65 years) when making a decision to administer primary

prophylactic G-CSF even if the risk of febrile neutropenia is lower than 20%. Yet the guideline also

stated that age alone cannot be an indication for primary prophylactic G-CSF administration due to

the lack of studies validating the clinical effectiveness of primary prophylactic G-CSF for older

individuals, thus clinicians should consider other patient risk factors as well. There are no explicit

recommendations about whether or not primary prophylactic G-CSF can be administered purely on

the basis of age >65 years even if the risk of febrile neutropenia is less than 20%.   The administration

of primary prophylactic G-CSF in the elderly is clearly indicated in only one clinical setting (diffuse

large cell lymphoma receiving relatively intensive chemotherapy) according to the guidelines.

Due to the limited recommendations of the ASCO guidelines (Table 3), and lack of studies

ascertaining the actual patient characteristics and risk factors associated with incidence of

neutropenia, many physicians still consider "watchful waiting" to be a viable option during the first

cycle of chemotherapy (Lyman, 2003b, Du, 2005). Thus, a population level study verifying the effect

of primary prophylactic G-CSF on outcomes and costs in elderly patients is an important first step in

validating the use of the expensive G-CSF in the elderly, and contributing towards ASCO and

Medicare policies.

**2.8 Importance of using population level data for understanding the effect of primary
prophylactic G-CSF administration**

There is a gap in the literature with regards to the effect of primary prophylactic G-CSF

administration on the occurrence, cost and treatment of neutropenia in elderly female breast cancer

patients. Thus in order to understand the significance of primary prophylactic G-CSF administration

for the elderly female breast cancer patients, it is important to use an externally valid, nationally

representative, population-based data to estimate the effect of primary prophylactic G-CSF on: (1) reducing chemotherapy-induced neutropenia; (2) reducing utilization of neutropenia therapy and management such as hospitalization; (3) reducing Medicare expenditure of neutropenia management, and overall healthcare expenditure; (4) successful administration of systemic chemotherapy soon after breast cancer diagnosis. Population based data can provide externally valid and nationally representative estimates of hematologic toxicity rates as compared to clinical trials. Since a methodology to accurately identify chemotherapy toxicity is yet to be developed (Wu, 2000), and clinical trials under-report the toxicities (Hassett, 2006), claims data offer an inexpensive way with better external validity (Du, 2002).

2.9 Conceptual framework

This study looks at the effect of primary prophylaxis on neutropenia related outcomes and expenditures. The conceptual framework used in this study is displayed in Figure 3. The use of chemotherapy could result in the occurrence of numerous toxicities based on the intensity and type of dose administered (Webster, 1996; Perry, 1984; Erban, 2006; Shapiro, 2001; Du 2002). Among these toxicities the dose limiting acute hematological toxicity called neutropenia is of a major concern due to cost and clinical implications associated with it (Bodey, 1996; Lyman, 2004; Gandhi, 2001). As depicted by arrow 1, chemotherapy induces neutropenia occurrence in breast cancer patients, which in turn leads to increased health services utilization for neutropenia management and increased cost of patient care. Occurrence of neutropenia results in reduction of chemotherapy cycles administered after incidence of neutropenia, and change in administration of radiation therapy to prevent further worsening of the condition (Shayne, 2006; Chrischilles, 2003; Lyamn, 2004) as depicted by arrow 2. This change affects future chemotherapy and radiation therapy outcomes, as reduction in treatment intensity adversely affects the prevention of breast cancer recurrence and mortality as depicted by

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arrow 3 (Chrischilles, 2003; Bouchardy, 2003; Budman, 1998; Bonneterre, 2005; Shayne, 2006; Lyman, 2003b; Weycker, 2006; Ozer, 2000).

Neutropenia occurrence, related healthcare utilization and cost could be reduced by the use of primary prophylactic G-CSF. G-CSF can be used for primary (arrow 4a) and secondary prevention (arrow 4c), and treatment of neutropenia (arrow 4b), and can thus sustain future chemotherapy dose intensities (Table 2).

Baseline characteristics like patient socio-demographic characteristics, clinical characteristics including tumor characteristics, and other therapies administered to the patient affect:

1. The administration and dose intensity of chemotherapy (Hassett, 2006; Shayne, 2006; Shayne, 2007; Voelker, 2004; Berrios-Rivera, 2007; Lyman, 2004; Du, 2001; Du 2005a) – arrow 5.

2. Administration of G-CSF (Hershman, 2007; Du, 2005; Chrischilles, 2003) – arrows 6a and 6b.

3. Neutropenia related outcomes like neutropenia hospitalization, length of stay for neutropenia hospitalization and hospitalization costs (Chrischilles, 2002; Shayne, 2007; Lyman, 2003a; Weycker, 2006; Chen-Hardee, 2006; Brooks, 2003; Lyman, 2004; Chrischilles, 2005; Du 2002) – arrow 7.

4. Future chemotherapy dose modifications (Chrischilles, 2003; Shayne, 2006; Chrischilles, 2004; Lyman, 2004; Lyman, 2005) – arrow 8.

5. Chemotherapy outcomes (Chrischilles, 2003) – arrow 9.

CHAPTER 3

Methods

3.1 Dataset and rationale for the choice of the dataset

Accomplishing the specific aims and ensuring external validity at the national level requires a nationally representative dataset that enables the identification of primary prophylactic G-CSF administration, along with the identification of chemotherapy administration, neutropenia occurrence, level of healthcare service utilization, Medicare expenditures, administration of other therapies, and patient socio-demographic and clinical characteristics. Population data improve the identification of chemotherapy-related toxicities, like neutropenia, by overcoming the under-reporting issues of clinical trials. The data also facilitate the estimation of actual healthcare utilization and Medicare expenditures at the population level. The population-based SEER linked to Medicare claims meets these requirements.

This study uses the SEER-Medicare data containing newly diagnosed breast cancer cases from 1994 to 2002, linked to Medicare claims through 2003. The linkage of SEER and Medicare files are a collaborative effort between the National Cancer Institute (NCI), the SEER registries and the Centers for Medicare & Medicaid Services (Warren, 2002).

The 17 geographic areas from which the SEER data are collected account for 25% of the US population. The data have been collected by NCI annually since 1973. Comparisons of SEER cancer mortality rates with those of the entire US population suggest that the SEER data are predominantly

representative of the national population (Warren, 2002). SEER data are very similar to the US population in terms of socio-demographic variables like age and gender, but the data have a higher proportion of non-whites, and more urban and affluent individuals. The data are valid, high quality and complete in terms of cancer incidence and diagnosis reporting in the United States (Warren, 2002). The data contain information on the patient's demographic characteristics (age, race, gender, marital status, education, income, geographic location), date of diagnosis, tumor characteristics (stage, grade, histology, size, lymph node positivity and hormone receptor status), presence of other malignancies, whether the cancer of interest is the first or a later malignancy, type of surgical treatment and radiation therapy recommended or provided within four months of diagnosis, follow-up of vital status, and cause of death. Thus, they provide sufficient information about variables known to influence primary prophylactic G-CSF administration and its clinical and cost effectiveness. Also, since the date of diagnosis is available in the SEER data it is easy to distinguish between prevalent versus incident cases, which is not possible with just the claims data.

Medicare claims data are available for 97% of the US population 65 years and above, and include health service claims for care provided by physicians, inpatient hospital stays, hospital outpatient clinics, home health care agencies, skilled nursing facilities, hospice programs, and durable medical equipment suppliers. The inpatient (part A) claims are available from the year 1986. The part B physician service claims and outpatient services are only available from the year 1991. Also, since it was made mandatory under the National Claims History System from 1991 to include the diagnosis codes in the physician claims, diagnosis codes are present in all physician claims only from that year. Medicare claims can be used to construct co-morbidity indices for the patients, to identify any service utilization, and costs (Charlson, 1987; Romano, 1993; Deyo, 1992; Klabunde, 2000; Klabunde, 2007).

Linking the Medicare claims to the SEER data provides a unique database to study cancer control, prevention, treatment, healthcare service utilization, and Medicare expenditures for patients above the age of 65 years. The SEER-Medicare data are an efficient and cost effective source of information on large heterogeneous, patient populations, unlike the geographically limited clinical trials (Potosky, 1993). These observational data include all women residing in a community setting, and biases such as volunteer bias in clinical trials and recall bias are also reduced. Also, since SEER data have been collected from medical charts and pathology reports, they contain a wealth of information on cancer histology, type, stage and extent of spread. Medicare data have the advantage of being longitudinal, and also provide the ability to identify tests and procedures more accurately; claims data have higher sensitivity for tests and procedures than chart audits (Nattinger, 2002). The two datasets complement each other as they combine the details during initial diagnosis from chart review, with a lifetime of utilization and cost data from claims.

Since the SEER Medicare database is large, it provides an opportunity to study the occurrence of neutropenia in breast cancer patients receiving chemotherapy with higher statistical power. It has been established that chemotherapy use in women above 65 years of age, rates of hospitalization for chemotherapy-induced toxicity (including neutropenia), and administration of G-CSF can be identified using SEER Medicare data (Du, 2002; Earle, 2001; Schrag, 2001, Du, 2001a; Du, 2001b). Chemotherapy and G-CSF are covered by Medicare and thus can be identified using the claims. Also, the validity and reliability of Medicare claims to identify chemotherapy administration has been successfully documented by previous studies (Warren, 2002; Du, 2005). Medicare has a high sensitivity for detecting the receipt of chemotherapy, which is around 88% for breast cancer. The claims code for the actual chemotherapy drug delivered, if present, is in high agreement with the drug as reported by comparative chart reviews in case of breast cancer.

One limitation of the data is that the chemotherapy drug is often not indicated in the claims in case of breast cancer. The sensitivity to identify specific chemo agents for breast cancer are 52.5% (Methotrexate), 76.2% (Cyclophosphamide) and 79.2% (5-FU). The sensitivity of other agents has not been verified (Warren, 2002). If the administrative data cannot be used to identify the specific agent, then it is difficult to identify the agent as breast cancer chemotherapy involves numerous agents. Also, frequency of the claims do not necessarily determine the frequency or duration of the chemotherapy since some providers bill Medicare for multiple administrations using just one claim. However, this is an issue only if we want to identify the actual chemotherapy drug, and we do not aim to accomplish that in this study. Claims data are very sensitive in identifying the chemotherapy administration itself.

3.2 Characteristics of the population of interest

The following criteria were used to select observations for the analysis sample:

1. Age – Only those individuals with age at diagnosis of 66 years or above were included in order to obtain observations with at least one year of Medicare claims prior to diagnosis. The complete Medicare claims for a person start at the age of 65 years and at least one year of claims prior to diagnosis is required to construct the Charlson comorbidity index.

2. Gender - Male breast cancer patients were excluded because on an average only .8% of new breast cancer cases every year occur in men in the US and their patho-physiology and treatment protocols are different from women (American Cancer Society, 2005).

3. Time period – Only patients with date of diagnosis of the first primary breast cancer between the years 1994 to 2002 were included. The G-CSF HCPCS codes were introduced only in 1994, hence G-CSF administration before that year cannot be identified. Thus, years prior to 1994 were excluded.

4. Insurance - Individuals who are not enrolled in both Medicare part A and B, or who are enrolled in an HMO one year before and one year after the breast cancer diagnosis, were excluded as their claims records are usually incomplete. The time window for a year before is chosen because the modified Charlson comorbidity index is created for a year before diagnosis/chemotherapy administration. The upper limit is a year after because all breast cancer patients who received chemotherapy within six months of diagnosis were included, and any health outcome following the chemotherapy administration for at least up to six months was looked into. Hence insurance status one year after diagnosis is crucial for the analyses.

5. Chemotherapy receipt – Breast cancer patients who receive the first cycle of the chemotherapy course within 6 months of diagnosis were included. Patients who do not get chemotherapy in the first 6 months but receive it after 6 months of diagnosis might be individuals who have had a recurrence of the disease. Chemotherapy in that case is not administered for the primary tumor but for the recurrence, and treatment protocol and prognosis are different for recurrence as compared to that for the primary tumor. Hence, patients who do not receive any chemotherapy or receive it after the first six months were excluded.

6. Stages of cancer – Breast cancer therapy predominantly depends on the stage of breast cancer (Table 1). Hence the stages were narrowed down to I to III in this study to focus on patients who receive chemotherapy as a curative therapy with the aim of reducing recurrence and mortality. For stage I to III breast cancer patients, adequate dose intensity has the highest benefit in terms of disease free survival. In stage IV breast cancer, chemotherapy is used just as a form of palliation to prolong and improve life. Physician attitude towards adherence and prescription of standard dose intensity is very different when treatment is used as palliation in stage IV cases. Delays and dose reductions are more common among stage IV cancer patients compared to patients at earlier cancer stages (Shayne, 2007), and extent of adherence to

standard chemotherapy dose is often a subjective decision between patients and physicians (Gridelli, 2007). Stage 0 cancer patients typically do not receive chemotherapy.

7. Neutropenia diagnosis - All patients with a neutropenia diagnosis code before the first date of chemotherapy administration were excluded. Neutropenia diagnosis before the administration of chemotherapy could be a coding error, or a true but uncommon occurrence of neutropenia from some other cause. In that case the neutropenia diagnosis confounds the analysis, as it is difficult to tease out whether or not the later occurrences of neutropenia are chemotherapy-induced. Since it is impossible to differentiate a coding error from a true occurrence of neutropenia before chemotherapy, these cases were excluded.

8. End-stage renal disease - Individuals above 65 years of age with end-stage renal disease (ESRD) were excluded.

9. Other Cancers - All patients with other cancers before the diagnosis of the first breast cancer were included. An indicator was developed to capture any prior occurrence of other cancers before the first breast cancer diagnosis.

10. HIV/AIDS - Individuals diagnosed with HIV/AIDS were excluded as the physiological condition of their bone marrow is much different, and their complications are predominantly due to immuno-suppression as a result of HIV.

11. Bone marrow and stem cell transplantation - All patients with bone marrow and stem cell transplantation one year before and after the first chemotherapy administration were excluded. Stem cell or bone marrow transplantation is often performed to enhance the hematopoietic process of the patient. A successful transplantation restores the blood cell production thereby preventing neutropenia irrespective of the administration of primary prophylactic G-CSF. On the other hand, stem cell or bone marrow transplantation is often performed in patients with a predisposition to leukopenia problems. Thus such a procedure could be indicative of a higher possibility of neutropenia in the patients until the transplantation becomes effective.

The result of these inclusions/exclusions and the remaining observations in the analytic data are shown in figure 4. The individuals of interest in the SEER-Medicare data based on these demographic and clinical characteristics were 10524 (337 treated individuals). Exclusion of missing variables leads to a sample size of 10441 (337 treated individuals), which is 99.21% of 10524. Matching based on all characteristics reduced the analytical sample size to 1760 (337 treated individuals). Matching in this study selects untreated observations closest to the treated observations and discards untreated observations that do not have appropriate matches among the treated. Treated observations are not discarded in this study.

The decrease in the sample size from 10441 to 1760 after matching raises concerns about the statistical power of the study. However, it is important to remember that the decrease in the sample size is due to the small number of treated observations (337). There is diminishing gain in power if more untreated observations are added to the sample keeping the treated observations constant. On the other hand retaining untreated observations that do not have comparable matches will reduce the balance after matching and decrease the benefits of the matching process.

3.3 Matching technique to account for non-random treatment assignment in primary prophylactic G-CSF administration

Estimation of the treatment effects of primary prophylactic G-CSF ideally aims to estimate the difference in the occurrence of outcomes if there is a primary prophylactic G-CSF administration versus if there isn't a primary prophylactic G-CSF administration for the same individual, at a given point in time. In the equation (A) below, y_{i1} denotes the outcome for a person if she obtains the primary prophylactic G-CSF at time t, and y_{i0} denotes the outcome for the same person if she does not obtain the primary prophylactic G-CSF at the same time t. The most commonly used estimator to

compute the effect of primary prophylactic G-CSF (treatment) on the outcome is the mean difference in y_{i1} and y_{i0} also known as the average treatment effect (ATE).

$$ATE = E(y_{i1} - y_{i0}) \qquad\qquad (A)$$

Here subscript i denotes each individual in the sample/population. In case of a randomized controlled trial this mean difference can be estimated by computing the mean difference in the groups having received primary prophylactic G-CSF and not having received primary prophylactic G-CSF. However, due to lack of randomization and selection into receiving the treatment, average treatment effect in observational studies are not simple to estimate.

In case of observational studies, one is able to observe only y_{i0} or y_{i1} for an individual at a particular time t, because an individual observed at a point in time has either obtained the treatment or not obtained the treatment. The unobserved outcome for each individual is called the counterfactual outcome. As a result, the estimation faces the problem of missing data in terms of one missing outcome variable for each individual. If the treatment assignment is indicated by variable d_i, such that $d_i=1$ when the individual is administered primary prophylactic G-CSF and $d_i=0$ when the individual is not, then one observes y_{i0} for individual with $d_i=0$ and y_{i1} for individuals with $d_i=1$. Thus the outcome variable observed in the sample is:

$$y_i = (1-d_i)y_{i0} + d_i\, y_{i1} \qquad\qquad (B)$$

One way to find the difference in effect, or the ATE is by using:

$$ATE' = E(y_i|d_i=1) - E(y_i|d_i=0) = E(y_{i1}\,|d_i=1) - E(y_{i0}|d_i=0) \qquad (C)$$

where y_i is the observed outcome of the individuals in the sample. ATE is equal to ATE' only when the act of administering the treatment is independent of the outcome (Rosenbaum, 1983), and there is no selection involved in treatment administration, which is the case in randomized control trials. In other words when:

$$\text{ATE'} = E(y_{i1}\,|d_i=1) - E(y_{i0}|d_i=0) = E(y_{i1}) - E(y_{i0}) = \text{ATE} \qquad \text{(D)}$$

where the second equality is true only when $d_i \perp\!\!\!\perp (y_{i1}, y_{i0})$. However, this independence does not exist in observational data because the administration of primary prophylactic G-CSF is not random. The administration depends on the physician's judgment about the patient's need for neutropenia prevention and baseline patient characteristics. Individuals who receive the treatment might be inherently different from individuals who do not, and hence their neutropenia related and chemotherapy related outcomes might be different even at the baseline. For instance individuals clinically at a higher risk of neutropenia, like individuals with higher co-morbidity indices, might have a higher likelihood of primary prophylactic G-CSF administration. In such cases, randomization of the treatment to patients is ideal because it balances all variables (observed and unobserved) except the outcome (y_i) and treatment (d_i) across the two groups of treated and untreated patients.

This problem could be partially solved by conditioning on observed variables X_i, where X_i are patient characteristics that determine the selection of the treatment by the physician as well as the outcome. Once these are controlled for, the outcome may become independent of the treatment. In other words $d_i \perp\!\!\!\perp (y_{i1}, y_{i0}) \mid X_i$. The conditional independence assumption is also called the ignorability of treatment assumption or no omitted variable bias assumption. The ignorability assumption implies that even if $E(y_i|d_i) =\!\!= E(y_i)$, $E(y_i|d_i, X_i) = E(y_i|X_i)$, and that the bias in treatment effect is predominantly contributed by observed variables 'X_i' (overt bias). The ignorability

assumption does not hold if there are unobservable variables (hidden bias) affecting the treatment assignment and outcomes.

3.3.1 The implication of (y_{i1}, y_{i0}) ⊥⊥ d_i | $p(X_i)$

It is important to understand that (y_{i1}, y_{i0}) ⊥⊥ d_i | $p(X_i)$ or (y_{i1}, y_{i0}) ⊥⊥ d_i | X_i, implies that the correlation between the outcome y_{ij} (where j =1 for treated and 0 for untreated patients) and treatment administration d_i is zero given X_i (The reverse is also true if $0 < P(d=1) < 1$ – Lee, 2005). However, COR $(y_{ij}, d_i | X_i) = 0$ does not imply COR $(y_i, d_i | X_i) = 0$, because the later means that the average treatment effect is zero (or primary prophylactic G-CSF has no effect on the outcome in case of this study) once the covariates are controlled for. Even if COR $(y_{ij}, d_i | X_i) = 0$, $E(y_i d_i | X_i)$ is not equal to $E(y_i | X_i) E(d_i | X_i)$:

$$E(y_i d_i | X_i) = E\{[d_i (d_i y_{i1} + (1- d_i) y_{i0})] | X_i\} = E(y_{i1} d_i | X_i)$$

$$E(y_{i1} d_i | X_i) = E(y_{i1} | X_i) E(d_i | X_i) \text{ (because COR } (y_{ij}, d_i | X_i) = 0)$$

However $E(y_{i1} | X_i) E(d_i | X_i) \neq E(y_i | X_i) E(d_i | X_i)$

In other words the ignorability of the treatment assumption given the X_i does not imply that the average effect of the treatment on the outcome is zero give the X_i. It only means the selection of treatment assignment based on expected outcomes disappears conditional on X_i. On the other hand, the absence of a treatment effect on the outcome after controlling for the covariates does not imply that the ignorability assumption is true (Lee, 2005).

3.3.2 Preprocessing using matching to better control for X_i

Most social science research uses different parametric or semi-parametric methods to control for covariates X_i that influence both the treatment and the outcome. Controlling for these observed covariates could make the assignment of treatment independent of the outcome, and hence make the observational data as close to a randomized control trial as possible. This independence holds only if two conditions are true – all variables affecting both outcome and treatment assignment are controlled for (no omitted variable bias), and the parametric or semi-parametric model/specification used to estimate the treatment effect is an unbiased estimator. Thus, the estimator used should not only be robust to the omitted variable bias, but also robust to the model dependence. Analysis of observational data is often not robust to model dependence because of lack of common support between the treated and untreated units with regards to the covaraites (X_i). There are untreated units far outside the range of treated units and vice versa, and this requires extrapolations in ranges where there are no treated or untreated observations in order to compute the average treatment effects. These extrapolations in the sample are dependent on the model specifications and might not be true for the population (King, 2006). Imai, King and Stuart also demonstrate mathematically that in a randomly collected sample representative of the population, the source of errors is mostly due to the imbalance in the covariates between the treated and the untreated group (Imai, 2008).

Preprocessing data by matching on the observed covariates, before using any model/specification to estimate a treatment effect, reduces the model dependence as illustrated by Ho (2007). Preprocessing data by matching brings the treated observations as close as possible to the untreated observations with regards to X_i, such that comparisons in the outcome are only made in the area of common support of X_i. It also breaks the link between the treatment variable and other covariates, and thus renders any parametric adjustment of X_i irrelevant or less important. Moreover, preprocessing using matching is a nonparametric method and hence the preprocessing itself is not

model/specification dependent. Preprocessing could also partially control for omitted variable bias. If unobserved heterogeneity between the treated and untreated observations are correlated with the observed variables, matching on the observed variables balances the unobserved variables to a certain extent.

Preprocessing should however be followed by the parametric analysis in our case, since the matching performed is not exact, and residual imbalance remains. The subsequent parametric analysis will not be model dependent in theory due to the preprocessing, and also be doubly robust in terms of the treatment effect estimation (Robins, 2001). Although preprocessing involves dropping observations Ho and colleagues (2007) demonstrate how the process does not compromise the efficiency of the estimates and improves mean squared error. Matching not only reduces bias in the estimated treatment effect by ensuring that only two (or more) similar individuals are compared for computing treatment effects, it also reduces the variance of the treatment effect estimates in many situations. This reduction occurs because the variance of the coefficient on the treatment variable is directly proportional to the size of the correlation between the treatment variable and other covariates in the model. Since matching reduces this correlation, the variance drops. However, there is a trade-off and dropping too many observations to improve the balance can offset this reduction in variance as the power of the analysis reduces. This is discussed in section 3.3.6.

3.3.3 Matching based on a single propensity score versus the entire covariate vector

Matching the patients on the observed characteristics is one way of conditioning on X_i. A completely non-parametric method of matching is covariate matching, and matching based on Mahalanobis distance is the most common method of covariate matching. The Mahalanobis distance is defined as:

$$md(X_i, X_j) = \{(X_i - X_j)' \ S^{-1} \ (X_i - X_j)\}^{1/2} \qquad\qquad (E)$$

S is the sample variance-covariance matrix of vector X. Untreated observations falling within a certain md() (in equation E) of the treated are matched with the treated. The difference between Mahalanobis matching and a simple covariate matching (that minimizes the Euclidian distance) is that the distance measure used to maximize the balance in covariates is standardized using the variance-covariance matrix in case of the Mahalanobis matching. As a result of the standardization the scale of each variable becomes irrelevant. The Mahalanobis technique also takes into consideration the distribution of each variable and this is very essential for a statistically significant balance.

Covariate matching poses a dimensionality problem especially if the vector of covariates is large. This can be resolved by matching on just a one-dimensional function of X_i, called the propensity score, instead of the entire vector. The propensity score, as defined by Rosenbaum and Rubin, "is the conditional probability p(Xi) (of treatment receipt) assigned to each observation, given a vector of observed covariates X_i".

Theoretically, if Z_i are the factors that determine the choice of treatment d_i, along with some unobservable variables U_i, then based on the patient's utility function, $V_i = \gamma \ (Z_i, U_i)$, a physician chooses $d_i=1$ if $V_i > V^*$, where V^* is the reservation utility/benefit for the patient. Similarly, outcomes are determined by: $y_{i1} = \gamma_1 \ (W_i, U_{i1})$ and $y_{i0} = \gamma_0 \ (W_i, U_{i0})$. X_i denotes the set of variables that are common for both the Z_i and W_i.

The propensity score matching uses the assumption that controlling for a function of the X_i-vector (which is probability p(X_i) in case of the propensity score matching) makes y_{ij} and d_i independent (Rosenbaum, 1983). This implies:

$(y_{i1}, y_{i0}) \perp\!\!\!\perp d_i \mid p(X_i)$ (This is an extension of the ignorability of treatment assumption or no omitted variable bias assumption)

In addition to this, Rosenbaum and Rubin make an additional assumption for propensity score matching, which is: $0 < P(d_i=1|p(X_i)) < 1$. Thus the function $p(X_i)$ does not perfectly predict the choice of treatment. This assumption is required because if there is perfect prediction then the possibility of finding matches between the treated and untreated groups with similar propensity scores will not be possible and the ATE becomes incomputable by a matching technique. This condition $0 < P(d_i=1|p(X_i)) < 1$ can be ensured by not controlling for all variables in Z_i to avoid perfect prediction, and this is achieved by using only those variables that are common to Z_i and W_i (Heckman, 2004). Since covariates in Z_i not in present W_i do not affect y_i, there is no omitted variable bias. If the two assumptions (ignorability of treatment and $0 < P(d_i=1|p(X_i)) < 1$) are satisfied, then propensity score matching will account for the selection problem (overt bias) and aid in the estimation of unbiased treatment effects.

Using propensity score does have its cons. The propensity to receive treatment by an observation is never known and has to be estimated. The unbiased estimation of the propensity score depends on the model used to estimate it. Since estimation is not perfect in all cases, relying just on the propensity score for matching might not lead to the achievement of the best balance in covariates between treated and untreated observations.

3.3.4 Types of matching techniques and options

Multiple types of standard matching estimators exist:

1. Exact matching – A treated unit is matched to all possible untreated units that have the exact same value for each of the covariates as the treated unit itself. The downside to this type of matching is that most social science research involves multiple covariates, and exact matching on each one will lead to deletion of many treated (untreated) observations due to the lack of untreated (treated) observations with exact values for all the covariates.

2. Nearest neighbor matching – The nearest untreated observation(s) for each treated observation is chosen. The matching could be limited with the use of a caliper measure. The caliper defines the maximum difference between the characteristics (covariates) of the treated and untreated observations for them to be matched. If no matches within the caliper are found the observation is discarded. The difference in magnitude of the propensity score is a type of caliper. The matching could also be limited on the basis of number of untreated matches per treated. If only one of the nearest matches is chosen for each treated observation, then it is a one-on-one matching. Multiple untreated observations could also be matched with one treated observation.

3. Stratification or interval matching – The treated and untreated individuals are sorted into strata based on a function of the covariates, for example pre-specified ranges of the propensity score.

4. Kernel matching – A counterfactual is generated for each treated observation using all untreated observations but the untreated observations are weighted differently based on the similarity in the matching measure e.g. the propensity score. For instance the untreated observation with the closest propensity score value as the treated observation will receive the highest weight.

Typically the choice of the matching technique is not made ex-ante but is decided based on the degree of balance in X_i achieved by the matching technique (Ho, 2007; Lee, 2005). Balance looks at the similarity of distribution of X_i in the treated versus the untreated group. The matching

technique that balances the covariates the most is chosen to construct the matched data for further parametric analysis. The aim is to reduce the baseline difference between treated and untreated observations as much as possible and form pairs as close as possible.

Other choices have to be made in order to bring the treated group as close to the untreated group as possible (Lee, 2005; Morgan, 2007; Ho, 2007). These choices involve decisions based on number of matches of untreated patients per treated patient, whether or not the number of matched untreated patients should be same or different for each treated patient, selection of untreated matches for each treated patient with and without replacement, whether or not a limit should be imposed on the magnitude of similarity in the propensity score between the treated and untreated observation (e.g. caliper), and whether or not the treated (untreated) patient should be dropped from the analytical dataset if no close matches exist. These choices are also made based on the nature of the data. For instance if the data have a larger number of untreated observations as compared to treated observations, matching each treated observation with multiple untreated observations, provided the matching is close enough, will increase the efficiency of the estimates. On the other hand if very few untreated observations exist compared to the treated observations then matching with replacement is recommended (Morgan, 2007; Ho, 2007). The primary aim while choosing among these techniques should be to reduce any imbalance between the treated and untreated groups.

3.3.5 Automated algorithm for choosing the best matches and improving balance – Genetic Matching

Balance between treated and untreated observations can be improved manually by testing different types of matching techniques and selecting the technique that achieves the maximum balance. Given the variety of matching options available achieving the most optimal balance manually is a tedious process. An automated search algorithm has been developed by Diamond and Sekhon (2006) to optimize balance while matching and to replace manual trial and error methods for

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optimizing balance. The algorithm also combines the benefits of both propensity score matching and matching on the complete covariate vector (covariate matching).

In order to obtain optimal balance in each one of the variables in X, the matching should be equal percentage bias reducing (EPBR). Traditional matching methods, based on propensity scores or Mahalanobis distance covariate matching, are EPBR if the covariates have an ellipsoidal distribution (normal/t-dist) (Rubin, 2006). When matching is EPBR for X, then the percent reduction in the biases (discrepancy between treated and untreated observations) of each of the matching variables is the same (Rubin 1976). If EPBR property does not hold, matching could increase the bias or not reduce the bias in some covariates, while reducing the bias for some others. Therefore, one of the chief reasons why good balance is not always obtained by matching observational data is because, given the nature of the variables in the data and their relationship to the treatment variable, the matching is not equal percentage bias reducing.

EPBR rarely holds in real social science data, because even if a covariate is ellipsoidally distributed in the population, a given finite sample may have departures from the distribution. Moreover, binary/categorical variables are not ellipsoidally distributed. If pretreatment variables are not ellipsoidally distributed in a sample, then EPBR holds only if the true propensity score model is known. Also, traditional matching methods give equal weight to each coordinate/covariate of X while reducing bias (in case of covariate matching), or base the bias reduction on the specification of the propensity score (in case of propensity score matching). Thus, under traditional matching methods EPBR will only hold if the functional forms of the covariates used in covariate matching, or specification of the propensity score are correct.

To overcome this issue and to automate the tedious process of optimizing the balance in covariates between the treated and untreated observation, a new matching algorithm called Genetic

matching has been introduced (Diamond, 2006; Sekhon, 1998). Genetic matching has been shown to dominate other matching methods both when EPBR holds and when it doesn't (Sekhon, 2006; Diamond, 2005). This matching is non-parametric and is a mathematical generalization of the propensity score and Mahalanobis distance matching.

The basic intuition of the algorithm is to search over the entire space of distance metrics (which includes the Mahalanobis distance metric) and obtain a distance metric that achieves the best possible balance. A generalized distance metric is represented as:

$$d(X_i, X_j) = \{(X_i - X_j)' \ (S^{-1/2})' \ WS^{-1/2} \ (X_i - X_j)\}^{1/2} \qquad \text{(F)}$$

where W is a weight matrix with non-zero parameters only in the main diagonal, and $S^{1/2}$ is the Cholesky decomposition of the sample variance-covariance matrix S. Genetic matching estimates the appropriate weight for each coordinate of X by allowing the data to state the appropriate weight for each covariate while matching, without assuming equal weights for each X or matching based on a single parametrically estimated propensity score.

The estimated propensity score or the linear predictor of the propensity score estimator should be included along with other pretreatment variables in the X vector (Sekhon, 2008). The importance of including the estimated propensity score is that if the propensity estimation specification is correct, and if indeed the propensity score matching ensures the best balance between the treated and untreated observations, then the algorithm will assign all the weight to the propensity score coordinate of X, and other pretreatment variables will have a weight of zero. On the other hand, the algorithm will converge to the Mahalanobis covariate matching if that is the appropriate distance measure for the best balance; all parameters of W will be 'one' except the weight corresponding to the propensity score (which will be zero). This method eliminates the need to re-perform matching

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every time the post-matched data exhibits poor balance of X between treated and untreated observations by incorporating the balance optimization into the matching procedure.

The algorithm attains best optimal balance using the data by minimizing a measure of the maximum observed discrepancy in any coordinate of X between the treated and the untreated groups. The measure of discrepancy is in the form of p-values of paired t-tests for the covariates in the treated and untreated observations and Kolmogorov-Smirnov (KS) tests, or any other user defined measure. The KS test is equivalent to a t-test for binary variables. The statistics are just a measure of balance and are not used to conduct formal hypothesis testing, and the objective is to maximize balance between the two groups without bounds (Sekhon, 2008). Hence, the algorithm does not stop if the p-values for the difference between the covariates in the treated group and untreated group becomes statistically insignificant (>0.05), but continues to optimize without limit until the best possible balance is reached.

The balance in pretreatment variables between treated and untreated observations should be maximized without bounds because hypothesis testing to check balance between treated and untreated groups is theoretically incorrect. The aim is to achieve balance in the given data and not to test the expected balance in a super-population or population from which the sample is hypothetically or actually drawn. Balance in a sample is required to avoid extrapolation bias and should be tested directly in a sample without having to average over populations and super-populations. Moreover, hypothesis test between two groups are affected by other factors apart from balance, like the remaining sample size after discarding observations due to matching. Hence the test statistics are not monotone functions of balance. Ideally, the joint empirical distribution of all the pretreatment variables between the treated and untreated groups should be tested. Lower dimensional measures like t-test and KS test can be used, but they should be optimized without bounds as well.

The algorithm is based on the principles of population genetics (the criteria of "survival of the fittest") and hence called the genetic algorithm. The genetic algorithm (GA) begins with an arbitrary population of trial solutions. Each trial solution is a vector of numbers that serve as parameters of the function to be optimized. In this case, the algorithm is used to estimate weights for the model pretreatment variables in equation B and hence the trial solution is a vector of weights. The GA uses a collection of heuristic rules to change one or more of these trial solutions in the current population to produce one or more trial solutions for the next set of population with the goal to ultimately construct a weight vector (one trial solution in the population of solutions) which achieves the best balance in the data. The heuristic rules are genetic operators based on the genetic process of reproduction (selecting some trial solutions better satisfying the optimization function and including them in the next population), mutation (randomly changing numbers in a population), and crossover and inversion (mixing and matching current set of trial solutions to get new ones). The advantage of this algorithm is that the function to be optimized need not be continuous and need not have derivatives in order for the optimization to work (Sekhon, 1998).

Using a Markov chain method, Nix and Vos (1992) showed that if each population of trial solutions represents a state, and the heuristic rules determine the probability of changing from one state to the other in order to reach the global optimum, then the system is asymptotic in population size and converges to the global optimum with an increase in population size. Thus the algorithm benefits from its asymptotic properties.

3.3.6 Important issues and concerns to be considered

Certain points should be kept in mind before preprocessing the data. First, to make sure that matching does not introduce any bias in the treatment effect estimation, all post-treatment variables that could be affected by the treatment itself, or that could be affected by the outcome after treatment,

should be kept out of the matching equation. Thus, any variable measured after treatment administration should not be included. Second, the variance reduction mentioned in section 3.3.2 could be offset by dropping too many observations that do not have matches. If we desire bias reduction using as exact a matching as possible, it could mean lose of many observations (given the large size of the covariate vector X) and thus an increase in variance. Thus, exact matching is not a good option for our observational data. Third, variables that do not affect the treatment assignment should be kept out of the matching equation to avoid inefficiencies.

The data analyzed in this study have a very small treated group (337 observations) and a large untreated group. Matching was used to discard untreated observations that did not match treated observations. The convex hull criterion was used for this purpose and untreated observations outside the convex hull of the treated observations were discarded. The convex hull for data is the smallest convex set that contains all the k-dimension data points, where k is the number of covariates in the data. When treated and untreated observations fall within each other's convex hull they share a common support for all covariates; a technique to verify common convex hull between the treated and the untreated observations is a means of identifying common support (King, 2006). In case of one covariate, the common support can be identified by plotting a histogram of the covariate for the treated and untreated group and eliminating the areas that do not overlap between the two groups. This method is not possible if the covariate X vector is multidimensional. Thus the convex hull method provides conservative evaluation of common support when multiple variables are involved, and using the convex hull method in combination with the matching technique helps achieve the goal of reducing extrapolation and interpolation bias, and consequently reduces the model dependence. When estimating causal effects, the counterfactual used to estimate the effect should be within the convex hull of the observed data, otherwise the analysis leads to extrapolation bias and model dependence (King, 2006).

Since matching is performed before parametric analysis, it is important to determine the standard errors estimation for the average treatment effect estimates from parametric analysis. Researchers using non-parametric techniques to estimate ATE use elaborate procedure, to compute variance estimates after matching. However, in this analysis, matching is only used for pre-processing the data as a function of the observables. This is followed by the parametric estimation, which again treats the observables as fixed or exogenous. Thus, as Ho and colleagues have suggested, we use the variance and standard error estimates which are part of the parametric estimation (Ho, 2007) thereby treating the observables and the entire preprocessing procedure as fixed.

3.4 Estimations and Hypotheses

This study looks at the effect of primary prophylactic G-CSF administered within 5 days of chemotherapy initiation (Figure 1) on the occurrence of chemotherapy-induced neutropenia hospitalization and length of stay; Medicare expenditures due to neutropenia management, and overall expenditure in the first year after the start of chemotherapy; and successful administration of systemic cancer therapy that could otherwise be hindered by occurrence of neutropenia. The conceptual framework behind the hypotheses is illustrated in figure 3.

3.4.1 Determinants of primary prophylactic G-CSF administration

The likelihood of primary prophylactic G-CSF administration based on patient socio-demographic characteristics, clinical characteristics, and type of chemotherapy and other therapies administered, was estimated using a logistic regression model. The analysis aimed to identify the determinants of primary prophylactic G-CSF administration in elderly female breast cancer patients receiving chemotherapy. The predicted value of the dependent variable for each individual from this logistic model, denoted by $p(X_i)$, was used as the propensity score for that individual.

The following equation was analyzed for ascertaining the likelihood of primary prophylactic G-CSF administration:

$$P_1(d_i=1 | X_i) = F_1(\lambda_i, \varphi_i, \rho_i, \tau_i, \varepsilon_{1i}) \qquad (1)$$

- The treatment, d_i, is a variable indicating the administration of primary prophylactic G-CSF within the first five days of the first course chemotherapy initiation (the very first cycle). Administration of primary prophylactic G-CSF was identified by procedure codes for all the commercially available G-CSF drugs - Filgrastim, Pegfilgrastim, Lenograstim and Sargramostim, from the Medicare Claims. Since G-CSF is administered both as a prophylactic as well as a therapeutic drug for neutropenia, it is hard to distinguish if the G-CSF was administered prophylactically or in response to some neutropenic symptoms, using claims data. In order to prevent misclassification of therapeutic or secondary prophylactic use of G-CSF as primary prophylaxis, we have restricted the primary prophylactic G-CSF administration window to just 5 days after the first course chemotherapy initiation which is in line with other claims based studies (Weycker 2006; Chrischilles, 2002). Primary prophylactic G-CSF is administered at least 24 hours after the first chemotherapy cycle, but mostly within 2-3 days of administering a cycle of chemotherapy. Neutropenic symptoms begin within a week after chemotherapy administration and peak after two weeks (Perry, 1984; Shapiro, 2001). Thus, any administration of G-CSF within 5 days of chemotherapy initiation is not therapeutic. Moreover, studies also show that primary prophylactic administration of G-CSF after the first five days of chemotherapy initiation are less effective in preventing neutropenia (Crawford, 1997; Kuderer 2007), and hence a 5-day window following the first chemotherapy cycle for primary prophylactic G-CSF administration is a crucial period to analyze.

- λ_i denotes patient socio-demographic characteristics comprising of age, race, marital status, socio-economic status (primarily education and income), geographic area of residence and urbanicity. These patient socio-demographic characteristics are obtained from the SEER records.

- φ_i denotes patient clinical characteristics comprising of modified Charlson comorbidity index (Charlson, 1987; Klabunde, 2002), relevant clinical history one month prior to chemotherapy initiation (including occurrence of infection, administration of antibiotics, and hospitalization), presence of other primary cancers before the first breast cancer diagnosis, and tumor characteristics (stage, tumor grade, tumor size, lymph node involvement, and hormone receptor status). Patient clinical characteristics are obtained from the SEER records as well as the Medicare Claims.

- ρ_i denotes the group of variables representing breast cancer therapy administered to the patient, which includes chemotherapy characteristics, and administration of other therapies like surgery and radiation therapy before primary prophylactic G-CSF administration. Provision of other therapies like surgery and radiation therapy are obtained from both the SEER and Medicare databases. Chemotherapy characteristics include - whether or not the first chemotherapy cycle was anthracycline based, the number of drugs in the first cycle, and the duration between the first and second cycle. These indicators were obtained from the claims data. Anthracycline drug regimen has a higher probability of toxicity and hence needs to be controlled for (Lyman, 2003c; Lyman 2004). The number of drugs and the duration between the cycles are a measure of chemotherapy intensity. All characteristics for chemotherapy are measured only in the first cycle (not the entire first course). G-CSF is administered within five days after the first cycle (which is the start of the first course) and

hence the other chemotherapy characteristics after the first cycle are post-treatment variables, which could be influenced by the treatment itself, and so should not be controlled for.

- Time trends are controlled by using indicator variables for each year (τ_i). The indicator variables were based on year of chemotherapy administration and were obtained from the Medicare data containing chemotherapy claims.

- X_i denotes all the independent variables controlled for in the model, namely λ_i, φ_i, ρ_i, τ_i.

- ε_{1i} was the error term in this model.

The probability distribution F_1 was assumed to be logistic for equation (1), and hence a logistic regression was used to estimate the propensity score in this study. Once the propensity score was computed and the analytic dataset with matched treated and untreated patients was created using genetic matching, all the below-mentioned hypotheses (sections 3.4.2 to 3.4.5) are tested. Different specifications and higher order terms were evaluated before arriving at the final model estimating the probability of primary prophylactic G-CSF administration.

3.4.2 Effect of primary prophylactic G-CSF on neutropenia prevention

The initial aim of this study was to estimate the effect of primary prophylactic G-CSF administration on reducing the occurrence of neutropenia, for elderly female breast cancer patients receiving chemotherapy. The occurrence of clinical neutropenia (marked by a drop in the neutrophil count in the blood below 2000/microL) without hospitalization cannot be identified using claims data, since many cases of mild neutropenia go unreported. Also, in practice the ICD-9-CM diagnosis code used to identify neutropenia (288.0x) is used while filing claims for all G-CSF administrations, even

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if no neutropenia has occurred and G-CSF is administered as a preventive therapy for neutropenia. These practices compromise the sensitivity and specificity of using claims to identify neutropenia alone. However, if a patient is serious enough to be hospitalized due to very low neutrophil count or febrile neutropenia (fever with neutrophil drop) then the diagnosis code recoded as the cause of hospitalization is definitely indicative of a neutropenia occurrence. Thus, in order to measure the treatment effect of primary prophylactic G-CSF administration on neutropenia prevention, neutropenia hospitalization was used as the dependent variable of interest.

The following hypothesis was tested:

Hypothesis 1: Administration of primary prophylactic G-CSF reduces the occurrence of neutropenia hospitalization following initiation of chemotherapy for elderly female breast cancer patients.

Three indicators for the first neutropenia hospitalization were developed for three different time periods after the start of first course chemotherapy using the claims data. The first indicator captures whether or not a neutropenia hospitalization occurred during the first month after chemotherapy initiation. The other two indicators are used to capture the same indicator for a time window of three and six months after chemotherapy initiation, respectively. Neutropenic symptoms begin within a week after chemotherapy administration and peak after two weeks (Perry, 1984). Thus, the first month captures the immediate effect of primary prophylactic G-CSF administration on neutropenia occurrence. The time periods 3 and 6 months capture the entire period of first course chemotherapy, which lasts from about 3 to 6 months after chemotherapy initiation.

The following equation was analyzed for ascertaining the likelihood of neutropenia occurrence:

$$P_2(Y_i=1|d_i, X_i) = F_2(d_i, \lambda_i, \varphi_i, \rho_i, \tau_i, \varepsilon_{2i}) \qquad (2)$$

where the dependent variable Y_i is an indicator denoting the occurrence of the first neutropenia hospitalization (within one, three or six months) and d_i is the indicator for administration of primary prophylactic G-CSF. The other independent variables controlled for $(\lambda_i, \varphi_i, \rho_i, \tau_i)$ are the same as mentioned above. F_2 was assumed to be a logistic distribution and a logistic regression model was used to assess the occurrence of neutropenia hospitalization.

3.4.3 Effect of primary prophylactic G-CSF on neutropenia-related healthcare utilization

After a neutropenia hospitalization, a patient is not usually discharged until she recovers from fever and associated infections, and her neutrophil count improves. Thus, healthcare utilization (measured by length of stay due to neutropenia hospitalization) is an indicator for severity of the neutropenia. In order to estimate the effect of primary prophylactic G-CSF on the neutropenia-related healthcare utilization in elderly female breast cancer patients receiving chemotherapy, the following hypothesis was tested:

Hypothesis 2: Administration of primary prophylactic G-CSF reduces the duration of neutropenia hospitalization, for elderly female breast cancer patients receiving chemotherapy

The length of stay for the first neutropenia hospitalization was measured using the Medicare in-patient files. Since three different time-periods were observed to develop the indicator for the first neutropenia hospitalization, three corresponding variables with lengths of stay were developed.

The equation used for the analysis was:

$$E\ (LOS_i\mid Y_i = 1, d_i, X_i) = F_3(d_i, \lambda_i, \varphi_i, \rho_i, \tau_i, \varepsilon_{3i}) \qquad\qquad (3)$$

Here LOS_i represents the duration of hospitalization for neutropenia. An ordinary least square regression model was used to assess the effect of primary prophylactic G-CSF on the duration of hospitalization for the management of neutropenia. X_i 's comprised of the same independent variables referred to above $(\lambda_i, \varphi_i, \iota_i, \rho_i, \tau_i)$.

A logarithmic form for the lengths of stay variables was used during the least square regression because the lengths of stay were skewed to the right thereby creating a possibility that the error terms in the model are not normally distributed. A graphical examination of the lengths of stay demonstrated that the dependent variables have a lognormal distribution. However, since this is the distribution of the unconditional dependent variable, it is not indicative of the distribution of the error term that depends on the distribution of the dependent variable conditional on the covariates. In order to conclusively decide the model specification a Box-Cox test was performed which supported the use of a logged dependent variable for the lengths of stay.

3.4.4 Effect of primary prophylactic G-CSF on Medicare Expenditures

G-CSF is expensive, and thus it was interesting to see if cost savings are associated with primary prophylactic G-CSF administration. Neutropenia, especially in the presence of infections and fever, requires immediate hospitalization for evaluation and aggressive administration of empiric broad-spectrum antibiotics to control the infection. The largest share (62% to 82%) of direct healthcare costs for cancer patients suffering from neutropenia are expensive hospitalization costs

including diagnostic tests and antibiotic administration for treating life threatening systemic infections and febrile neutropenia (Kurderer, 2006; Leese, 1993; Dranitsaris, 1995). Most of the hospitalization cost is associated with length of stay and level of neutropenia complications. Thus, examining any reduction in expenditure of neutropenia hospitalization with primary prophylactic G-CSF administration was one important aspect of this cost.

Also, dose reduction and dose delay to control neutropenia hinder the effective administration of a planned treatment regimen, diminish the efficacy of chemotherapy and radiation therapy, harm patient health outcomes and prognosis, and increase the probability of recurrence and mortality (Baquiran, 2001; Webster, 1996; Welte, 1996; Lyman, 2002; Ziegler, 2006). Hence the overall treatment costs might increase due to lose of efficacy of the chemotherapy and radiation therapy regimen. Managing recurrence and worse prognosis could also increase the healthcare costs. Thus, overall treatment costs during the first year following the chemotherapy initiation (when bulk of the curative cancer treatment takes place in stages I to III) might be affected by primary prophylactic G-CSF. Possible second course chemotherapy administration in the first year due to ineffective first course administration, a more spread out but less intense first course chemotherapy, early recurrence in the first year, increased hospitalization due to neutropenia, and antibiotic administration for managing neutropenia symptoms even in the absence of neutropenia hospitalization could increase the costs for patients not receiving G-CSF.

In order to estimate the effect of primary prophylactic G-CSF use on neutropenia-related Medicare expenditures, and overall Medicare expenditures during the first year after chemotherapy initiation in elderly female breast cancer patients, the following hypothesis was tested:

Hypothesis 3: Administration of primary prophylactic G-CSF reduces the neutropenia hospitalization expenditure, and the first year's Medicare expenditures following the initiation of chemotherapy in elderly female breast cancer patients.

Two groups of variables for Medicare expenditures were developed:

1. Three expenditure variables corresponding to the three different time periods used for observing the first neutropenia hospitalization were developed. Neutropenia hospitalization expenditures in the Medicare inpatient files associated with the first neutropenia hospitalization were used to estimate these variables.
2. Overall healthcare expenditure for breast cancer patients in the first year after the initiation of chemotherapy.

The neutropenia hospitalization expenditure associated with the first neutropenia hospitalization was recorded from the Medicare inpatient files. Inpatient, outpatient and physician office claims are used to construct the overall healthcare expenditures during the first year after the start of primary prophylactic G-CSF.

The equation used for estimation of the difference in neutropenia hospitalization expenditures (NHE) with and without primary prophylactic G-CSF is:

$$E\,(NHE_i \mid Y_i = 1,\, d_i,\, X_i) = F_4(d_i,\, \lambda_i,\, \varphi_i,\, \rho_i,\, \tau_i,\, \varepsilon_{4i}) \qquad\qquad (4)$$

The equation used for estimation of the difference in overall Medicare expenditures (ME) in one year following chemotherapy initiation with and without primary prophylactic G-CSF is:

$$E(ME_i \mid d_i, X_i) = F_5(d_i, \lambda_i, \varphi_i, \rho_i, \tau_i, \varepsilon_{5i}) \qquad\qquad (5)$$

An ordinary least square regression was used to estimate the affect of primary prophylactic G-CSF on expenditures for female breast cancer patients receiving chemotherapy. A logarithmic form for the expenditure variables was used during the least square regression because the expenditures were skewed to the right thereby creating a possibility that the error terms in the model are not normally distributed. A graphical examination of the expenditures demonstrated that the dependent variables have a lognormal distribution. However, since this is the distribution of the unconditional dependent variable, it is not indicative of the distribution of the error term that depends on the distribution of the dependent variable conditional on the covariates. In order to conclusively decide the model specification a Box-Cox test was performed which supported the use of a logged dependent variable for the expenditures.

3.4.5 Effect of primary prophylactic G-CSF on systemic therapy

The most noteworthy contribution of primary prophylactic G-CSF has been in sustaining systemic therapy administration that are otherwise hindered due to neutropenia occurrence (Webster, 1996; Lyman, 1998; Shayne, 2006). Both chemotherapy and radiation therapy are aimed at inhibiting cancer cell growth. Since both therapies are systemic in nature they also have an effect on other normally dividing cells in the body, like the bone marrow cells. Thus, further chemotherapy and radiation therapy could worsen the drop in neutrophil count, and hence the systemic therapies are stopped, delayed or reduced in intensity to manage neutropenia. Prevention of neutropenia ensures adherence to standard treatment protocols, and continued administration of systemic therapy throughout the initial breast cancer treatment period.

The following hypotheses are tested in order to examine the effect of primary prophylactic G-CSF in sustaining systemic therapy:

Hypothesis 4: Administration of primary prophylactic G-CSF increases the probability of administering radiation therapy during the first course of chemotherapy.

Hypothesis 5: Administration of primary prophylactic G-CSF increases the number of chemotherapy cycles administered during the first course.

A logistic regression model was used to estimate the probability of administration of radiation therapy after initiation of chemotherapy, and probability of administering more than five cycles of chemotherapy during the first course using the following equation:

$$P_6(ST_i=1|d_i, X_i) = F_6(d_i, \lambda_i, \varphi_i, \rho_i, \tau_i, \varepsilon_{6i}) \qquad (6)$$

where ST_i represents the indicator for administration of radiation therapy after chemotherapy initiation and the indicator for administering more than five chemotherapy cycles during the first course.

Indicators were developed to measure the administration of chemotherapy and radiation therapy after the start of the first course chemotherapy. The two main indictors were:

1. Administration of any radiation therapy during the first course.
2. Administration of more than five cycles of chemotherapy during the first course.

The reason why more than five cycles during the first course was used as a marker for clinically adequate chemotherapy was because an average first course has around 6 cycles (or more).

3.5 Measures

The SEER-Medicare dataset provides good measures of most variables required for the analysis. Table 4 gives the variable name, the source (Medicare claims versus SEER data), the claims codes used and the time period for which the variable was constructed, if applicable.

3.5.1 Dependent Variables

3.5.1.1 Neutropenia Hospitalization

Three indicators for the first neutropenia hospitalization following the start of chemotherapy were developed for three different time periods after the start of chemotherapy using the claims data. The first indicator captures whether or not a neutropenia hospitalization occurred during the first month after first course chemotherapy initiation. The other two indicators are used to capture the same indicator for a time window of three and six months after chemotherapy initiation, respectively.

3.5.1.2 Neutropenia Hospitalization Length of Stay

Length of stay due to neutropenia hospitalization is an indicator for severity of the neutropenia, and was measured from the length of stay reported in the Medicare in-patient files after the first neutropenia hospitalization. Since three different time-periods were observed to develop the indicator for the first neutropenia hospitalization, three variables with corresponding lengths of stay were developed. A logarithmic form for the lengths of stay variables was used during the least square regression because the lengths of stay were skewed to the right thereby creating a possibility that the error terms in the model are not normally distributed. A graphical examination of the lengths of stay demonstrated that the dependent variables have a lognormal distribution. However, since this is the

distribution of the unconditional dependent variable, it is not indicative of the distribution of the error term that depends on the distribution of the dependent variable conditional on the covariates. In order to conclusively decide the model specification a Box-Cox test was performed which supported the use of a logged dependent variable for the lengths of stay.

3.5.1.3 Expenditures

Two groups of variables for Medicare expenditures were developed:

1. Three expenditure variables corresponding to the three different time periods used for observing the first neutropenia hospitalization were developed. Neutropenia hospitalization expenditures in the Medicare inpatient files associated with the first neutropenia hospitalization were used to estimate these variables.

2. Overall healthcare expenditure in the first year after the initiation of chemotherapy.

The neutropenia hospitalization expenditure was recorded from the Medicare inpatient files, associated with a neutropenia hospitalization. Inpatient, outpatient and physician office claims are used to construct the overall healthcare expenditures during the first year after the start of chemotherapy.

A logarithmic form for the expenditure variables was used during the least square regression because the expenditures were skewed to the right thereby creating a possibility that the error terms in the model are not normally distributed. A graphical examination of the expenditures demonstrated that the dependent variables have a lognormal distribution. However, since this is the distribution of the unconditional dependent variable, it is not indicative of the distribution of the error term that depends on the distribution of the dependent variable conditional on the covariates. In order to

conclusively decide the model specification a Box-Cox test was performed which supported the use of a logged dependent variable for the expenditures.

3.5.1.4 Systemic cancer therapy variables

Indicators were developed to measure the administration of chemotherapy and radiation therapy after the start of the first course chemotherapy. The two main indictors were:

1. Administration of any radiation therapy during the first course.
2. Administration of more than five cycles of chemotherapy during the first course.

The reason why more than five cycles during the first course was used as a marker for clinically adequate chemotherapy was because an average first course has around 6 cycles (or more).

3.5.2 Independent Variables

3.5.2.1 Primary prophylactic G-CSF administration and duration

Administration of primary prophylactic G-CSF was identified by procedure codes in the outpatient and physician claims for all the commercially available G-CSF drugs - Filgrastim, Pegfilgrastim, Lenograstim and Sargramostim. G-CSF begun within 5 days of the first chemotherapy administration was considered primary prophylaxis. Since primary prophylactic G-CSF is administered to prevent chemotherapy induced neutropenia occurrence, and chemotherapy induced neutropenia can occur from the very first week of chemotherapy initiation, primary prophylaxis should be started soon after the first course chemotherapy. As mentioned above, the earliest G-CSF can be given is after 24 hours of chemotherapy administration. Also, studies show that prophylactic

administration of G-CSF after the first five days of chemotherapy initiation are less effective in preventing neutropenia (Crawford, 1997; Kuderer 2007), and hence a 5-day window period is important for evaluating "primary" "prophylactic" G-CSF administration.

In order to understand the G-CSF administration claims, it is important to know the following facts.

1. Commercially available G-CSFs are Filgrastim, Pegfilgrastim, Lenograstim and Sargramostim, with Filgrastim being the most commonly used product (86% of primary prophylactic use in this study) (Welte, 1996). Lenograstim is rarely used in the United States and is not present in the Medicare files used in this study. Pegfilgrastim is not present for the time period examined in this study – 1994 to 2002.

2. Sargramostim is also referred to as granulocyte-macrophage colony stimulating factor (GM-CSF), and in this study both G-CSF and GM-CSF are referred to as G-CSF, as some other authors had done previously (Hershman, 2007).

3. Filgrastim is usually administered intravenously or subcutaneously at 5 micrograms per kilogram per day, 24-hours after chemotherapy administration, and continued for up to 2 weeks or till the neutrophil count exceeds the 10,000/microL (Package insert – Amgen; Ellis, 2002; Baquiran, 2001; Du, 2005).

4. Empirical studies show that if primary prophylactic G-CSF is administered, the first dose of G-CSF is given after 24-hours, and most often within three days of a chemotherapy cycle. The primary prophylaxis is definitely administered by the first five days of a chemotherapy cycle. The 24-hour wait period after a chemotherapy cycle administration is to prevent cytotoxic changes in the stem cells stimulated by G-CSF from the still active chemotherapeutic drugs. Rarely some physicians initiate primary prophylactic G-CSF after seven to 10 days following a chemotherapy cycle administration. Also, in practice the entire

prophylactic course is given for less than a week in breast cancer patients receiving chemotherapy (Weycker, 2006).

5. Pegfilgrastim (pegylated filgrastim) is a relatively new drug, and its use in community practice has just begun. It has been shown to be more cost effective and clinically efficacious than filgrastim or lenograstim in various clinical trials (Kuderer, 2007; Kuderer, 2005). Pegfilgrastim, due to the pegylation, is longer lasting and hence requires administration only once per chemotherapy cycle (2-3 weeks). Filgrastim, on the other hand, needs to be given every day for 1 to 2 weeks after its start. Therefore Pegfilgrastim is ideal for higher dose dense or more frequently administered chemotherapies (every 2 weeks; regular chemotherapy is every 3 weeks), as it can be injected into the patient whenever she comes for her chemotherapy cycle, and the patient need not visit the provider everyday just for receiving a shot of G-CSF.

Duration of the primary prophylactic G-CSF is the number of consecutive days the primary prophylactic G-CSF is administered. It is important to keep in mind that the duration is different for Pegfilgrastim, as it is not meant to be administered everyday. However, Filgrastim was the most common drug encountered in claims (86% of primary prophylactic use in this study). Pegfilgrastim was FDA approved only on January 2002 and did not appear in the claims for the years under study (1994-2002).

Claims data have some limitations in determining the duration of G-CSF administration. G-CSF is administered as an outpatient or in the physician's office. If the patient is admitted, then the inpatient claims do not indicate G-CSF administration. In most cases, if the G-CSF is started with chemotherapy and then the patient gets hospitalized, G-CSF administration is continued, but the duration cannot be established while the patient is an inpatient.

Another reason why G-CSF duration cannot be accurately measured is because G-CSF is reimbursed by Medicare only if patients obtain it under physician supervision; if G-CSF is self-administered then the patient has to pay for it out of pocket and the administration does not show up in Medicare claims. Most patients do obtain it at the physician's office or as outpatients, due to the high cost of G-CSF, which makes out of pocket payments unaffordable. However, if the patients have supplementary insurance or are located at a considerable distance from the nearest provider, they might choose to self-administer at least part of the G-CSF course. The patients might obtain the initial shots at the doctor's office, and once they are confident of the administration technique, they could self-administer it. In such cases claims data are inadequate to measure G-CSF duration.

However, the main variable of interest in this study was the dummy variable for whether or not primary prophylactic G-CSF was administered. Unlike its effect on measuring duration, the choice to self-administer G-CSF had very little effect on the sensitivity to identify a primary prophylactic G-CSF administration. Primary prophylactic G-CSF, as defined in this study, is administered for the first time to the patient soon after the first cycle of the first course. The first few administrations occur predominantly at the physician's office and are reimbursed by Medicare.

Three variables were developed to capture primary prophylactic G-CSF administration:

1. An indicator for whether or not G-CSF was administered within the first five days of the start of chemotherapy. This was the chief variable of interest.
2. A continuous variable for the number of days primary prophylactic G-CSF was administered.
3. An indicator variable for whether or not the number of days primary prophylactic G-CSF was administered for was greater than or equal to five. Empirical studies show that although G-CSF administration duration is recommended for 10-14 days, in practice prophylactic G-CSF

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is administered only for 4-7 days (Weycker, 2006). Thus, five days were considered to be the lower limit for a clinically adequate primary prophylactic G-CSF administration.

3.5.2.2 Patient socio-demographic characteristics

An increase in <u>age</u> is significantly correlated with early termination of chemotherapy, lower RDI, G-CSF administration and all other clinical outcomes (Chrischilles, 2003; Shayne 2006; Shayne 2007; Lyman, 2003b; Du, 2005; Chen-Hardee, 2006), thus it is important to control for this variable. Since the study period does not span more than 12 to 18 months after diagnosis, age at diagnosis was used in the analyses instead of current age. Age at diagnosis is present in both the SEER data and Medicare Enrollment Database (EDB). The study relies on Medicare EDB data for age because social security information on age is considered to be highly accurate (Bach, 2002).

<u>Race</u> has been shown to be correlated with chemotherapy administration, G-CSF administration, and other clinical outcomes (Du, 2001; Du, 2005; Lyman 2004). The race indicator present in the data is reliable for blacks and whites and has a high agreement between SEER and Medicare records. A recent validation of Medicare showed that Asians and native Americans have a very low sensitivity, though a high specificity (Arday, 2000). The indicator for Hispanics is inconsistent between the SEER and Medicare, since in the Medicare files it is classified as a type of race, which is identified by an individual's social security application, and in SEER it is a type of ethnicity identified using algorithms for Spanish last names. Thus the SEER algorithm often misclassifies Hispanic women. Nevertheless, the SEER ethnicity variable is more sensitive than the Medicare variable (Bach, 2002). The most commonly used Race/Ethnicity variable in statistical analysis is the Race Recode B variable in the SEER data, which combines the race and the Hispanic ethnicity information in the SEER-Medicare. The "Race Recode B" variable was used in this study.

Since the number of observations in the minority races was very low, a single indicator for white was used.

Marital status predicts both chemotherapy receipt and G-CSF administration (Du, 2001; Du, 2005); the presence of a spouse may encourage adherence to treatment protocols. An indicator for marital status is available in the SEER data. A single indicator for whether or not the person is married was used.

Socioeconomic status (SES) variables are important covariates in the analysis because they affect the administration of chemotherapy and G-CSF, and overall clinical outcomes (Du, 2005; Shayne 2006; Shayne 2007). The only individual level SES variable in the data is the state buy-in (SBI) variable, which indicates that the individual is low income as she receives Medicaid Supplemental Insurance (MSI). However, the MSI variable is specific but not sensitive to poverty as most poor individuals do not apply for SBI. Due to privacy concerns, education and income are aggregate measures at a census tract level or Zip code level. Some aggregations are further broken down by race and age group.

The aggregate measures, however, are that they are noisy at an individual level. They have construction validity issues as they often end up capturing neighborhood related health effects instead of SES related health effects. Studies comparing the aggregate measures with the original individual measures stated that the aggregate measures had much lower power and poorer predictive capacity compared to individual measures (Greenwald, 1994). A study showed that further stratifying SES variables based on race or rural and urban location increased the validity of the aggregate measure, but stratifying did not necessarily improve the aggregate measures in all cases (Bach, 2002).

The individual level income variable is highly correlated with the aggregate measure; it was found that a self-reported income variable was well correlated with aggregate income variable irrespective of the level of aggregation (Bach, 2002). On the other hand, for the education variable, the census tract level aggregation was believed to be more predictive than the ZIP code level aggregation.

The variables used to control for in this study are:

1. Four education variables, stratified by race, measuring percentage of adults above 25 years in the residential census tract for each of the four education categories – Less than high school, High school diploma, Some college, At least four years of college. The race specificity reduces the noise in the aggregate variable.

2. One variable measuring the median income in the residential census tract for the breast cancer patient.

Geographic variation in treatment administration, healthcare utilization, and healthcare expenditures have long been established in the literature (Wennberg 1975; Wennberg, 2005; Wennberg, 2008). A recent study also found that there is significant geographic variation in the administration of G-CSF (Du, 2005). Geographic variation was controlled for using the SEER registry area variable. Urban/rural area influences healthcare access for the patients and was controlled for using an indicator for urban residence.

3.5.2.3 Patient clinical characteristics

Comorbidities are very important predictors of treatment administration and outcome. Previous literature has established that comorbidities are important determinants of administration

and duration of both chemotherapy and G-CSF (Voelker, 2004; Du, 2001b; Hershman, 2007; Du, 2005; Berrios-Rivera, 2007; Shayne, 2006). Comorbidities also affect the occurrence of neutropenia and other chemotherapy-related outcomes (Scott, 2003; Chrischilles, 2002; Chrischilles, 2005; Lyman, 1998; EBCTCG, 1998) Comorbidities are a significant determinant of length of stay (Chrischilles, 2002) and so need to be controlled for in both length of stay and cost estimations. Older women with breast cancer are a very heterogeneous group with respect to their comorbidities. The number of comorbidities increases with age and comorbidities have a greater role in the prognosis of older patients with breast cancer (Diab, 2000; Satariano, 1994). If comorbidities are not captured in the analysis then the resultant confounding may make age appear to be correlated with worse prognosis (Chrichilles, 2003). Renal and heart disease, and anemia are specific comorbidities which need to be controlled for due to their direct association with chemotherapy effectiveness and neutropenia related outcomes (Chrischilles, 2005; Chrischilles, 2002; Voelker, 2004; Scott, 2003). The modified Charlson comorbidity index is one of the most commonly used measures in previous research (Chrischilles, 2002; Chrischilles, 2005; Du, 2001; Hershman, 2007; Du, 2005). This study uses the Romano and Deyo modified Charlson comorbidity index, which has been further modified for cancer patients by the SEER-Medicare research group. The algorithm for the modified comorbidity index is available in the official SEER-Medicare website.

Since we are considering the first primary occurrence of breast cancer without excluding patients who suffered from other cancers previously, it is important to take the presence of other cancers before the breast cancer diagnosis into account. This was captured by an indicator for absence of any cancer diagnosis before the breast cancer under study.

History of infection, antibiotics use and hospitalization one month before the start of chemotherapy are controlled for using an indicator variable each. Each of these clinical factors could

affect the susceptibility of a patient to neutropenia and hospitalization and also affect the probability of prophylactic G-CSF administration.

Tumor characteristics like stage, tumor grade, tumor size, lymph node involvement, and estrogen and progesterone receptor status are important determinants of chemotherapy and G-CSF administration, and also the occurrence of neutropenia and other clinical outcomes (Voelker, 2004; Du, 2001; Hershman, 2007; Du, 2005; Scott, 2003; Chrischilles, 2002; Chrischilles, 2005; Chrischilles, 2003). Thus these factors are controlled for.

3.5.2.4 Therapeutic characteristics

Surgery could be performed before or after chemotherapy administration as illustrated in Figures 1 and 2. Thus indicators are developed to capture whether or not the surgery was performed and if it was before or after the chemotherapy. Performance of Lymph node dissection before and after the chemotherapy was also controlled for. Administration of radiation therapy before the start of chemotherapy was also controlled for.

Chemotherapy in breast cancer is characterized by the types of drugs administered, the dose of these drugs, the number of drugs administered and the duration between cycles in a chemotherapy course. Since not all types of drugs can be identified for each administration, an indicator was developed for whether or not anthracycline was administered in the first cycle because anthracycline based drugs are known to have a higher probability of chemotherapy toxicity as compared to other drugs (Lyman, 2003c; Lyman 2004), and their administration can be identified using claims (Warren, 2002). Dosage cannot be measured from claims data. The other chemotherapy characteristics that are controlled for include the number of drugs administered in the first cycle, and the duration (in days) between the first and second cycle. Chemotherapy characteristics after the first cycle were not

controlled for because the treatment (primary prophylactic G-CSF) is administered immediately after the first cycle and controlling for post-treatment characteristics is inappropriate given that the treatment itself might influence the chemotherapy characteristics (like duration, and number of drugs).

3.5.2.6 Time trend

Controlling for <u>year of chemotherapy</u> dose administration and toxicity occurrence is essential. Studies show that the overall cost associated with neutropenia hospitalization and management has been reduced over time due to the shifting of care from in-patient setting to out patient setting (Lyman, 2003a). Also, the treatment protocols, the type of drugs used and their effectiveness have been changing, thereby making the year of chemotherapy and primary prophylactic G-CSF administration an important parameter. Time trends also control for, changes due to guideline updates, practice changes due to multiple G-CSF effectiveness studies published after the year 2002, and the increased use of dose dense chemotherapy regimen in the recent years.

Chapter 4

Results

The SEER incidence data from 1986 to 2002 had 310835 observations with breast cancer

diagnosis (Figure 4). Based on the inclusion and exclusion criteria discussed in section 3.2, 10524

were observations of interest. The insurance criteria (presence of both part A and B, and being a non-

HMO enrollee an year before and after diagnosis) led to the largest number of exclusions. After

dropping observations due to missing values and individuals residing in Rural Georgia who did not

receive any treatment, the total number of observations left was 10441. 337 patients out of 10441

received G-CSF as primary prophylaxis within five days of chemotherapy initiation.

4.1 Determinants of primary prophylactic G-CSF administration - Descriptive statistics

The data were divided into women who received primary prophylactic G-CSF (treated group)

and women who did not (untreated group), and differences in their socio-demographic characteristics,

clinical (including tumor) characteristics, and type of procedures performed were investigated. With

regards to socio-demographic characteristics it was found that younger women, whites, and women

from certain SEER regions (especially of California) were more likely to receive primary

prophylactic G-CSF (Table 5). Clinically, women who received primary prophylactic G-CSF were

more likely to have tumor stage III, have a larger sized tumor, be lymph node positive, have a history

of recent (one month before start of chemotherapy) antibiotic administration, and receive

anthracycline as part of the chemotherapy regimen during the first cycle. As expected primary

prophylactic G-CSF administration is more common in the recent years than earlier years.

The variables with the largest difference in the means for the treated and untreated group were SEER registry region and anthracycline administration during the first cycle (Figure 5 and 6). Figure 5 shows that the SEER registries in California, Louisiana, and Connecticut have the highest administration rates for primary prophylactic G-CSF, and Hawaii, Kentucky, Iowa, Atlanta and Utah have some of the lowest rates. Rural Georgia has no patient receiving prophylactic chemotherapy.

In summary younger women, whites, women living in SEER regions of California, Louisiana and Connecticut, and diagnosed at a later year were more likely to receive primary prophylactic G-CSF. Clinically, women with more advanced tumor stage, larger tumor size, and node positivity had a higher probability of receiving primary prophylactic G-CSF. History of antibiotic use in the recent past and anthracycline administration in the first cycle of chemotherapy were also significantly correlated with use of primary prophylactic G-CSF.

4.2 Determinants of primary prophylactic G-CSF administration – Parametric estimation of propensity score

In order to estimate the propensity of receiving primary prophylactic G-CSF for each observation a logistic regression was performed as depicted in equation 1, and the results are presented in table 6. The analysis revealed that SEER region and anthracycline based chemotherapy are the most significant predictors of receipt of chemotherapy, as demonstrated by the descriptive statistics previously. Since the SEER region with the highest proportion receiving primary prophylactic G-CSF, San Francisco, was used as the reference category for the region variables, all regional coefficients are negative in magnitude. The regional variables were jointly statistically significant.

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Race is another significant predictor with whites having a higher probability of primary prophylactic G-CSF receipt. The year variables were also jointly statistically significant, such that the individuals diagnosed in later years had a higher probability of getting primary prophylactic G-CSF. Chemotherapy characteristics like number of drugs administered during the first cycle, and shorter duration between the first and second cycle are also highly correlated with primary prophylactic G-CSF administration.

In summary, race, geographic region, year of diagnosis and chemotherapy characteristics are the primary variables which are statistically correlated with primary prophylactic G-CSF administration. After controlling for chemotherapy, age and most other clinical characteristics are not significantly correlated with primary prophylactic G-CSF administration in the multivariate analysis.

4.3 Comparison between longer duration versus shorter duration of primary prophylactic G-CSF administration

Studies in non-Hodgkin's Lymphoma patients show that "duration" of primary prophylactic G-CSF administration is an important factor in improving neutropenia-related outcomes (Weycker, 2006; Weycker 2004; Scott 2003; Chrichilles 2003). Thus, some descriptive statistics and parametric analysis were performed to understand the determinants as well as effects associated with duration of G-CSF administration in patients who received primary prophylactic G-CSF.

In this study the number of days of primary prophylactic G-CSF receipt ranged from 1 to 43. However 90% of the patients who received primary prophylactic G-CSF got it for 10 days or less, with both the mean and median days of administration being around 5 days. This study looked at the duration of primary prophylactic G-CSF administration both as a continuous variable, with one day as the unit of analysis, and as a categorical variables with two categories - less than five days of administration (inadequate duration) and five or more days of administration (adequate duration).

Scott and colleagues using medical records data classified shorter (inadequate) duration as less than seven days and longer (adequate) duration as seven or more days (Scott, 2003) for non-Hodgkin's Lymphoma patients, since the mean number of days of G-CSF administration was 9.5 days in their study. Weycker et al's study used claims data and a continuous measure for G-CSF duration (in days); the mean duration of G-CSF administration was 6 days for breast cancer patients in their study. Studies looking at the effectiveness of G-CSF in NHL and breast cancer patients are consistent in their finding about the mean duration of G-CSF administration, which is shorter (5-6 days) in breast cancer patients compared to NHL patients (7-10days) (Webster 1996; Scott, 2003; Weycker, 2006; Chrischilles, 2003). In this study the mean and the median duration of administration was 5 days and hence the categorical variable was constructed accordingly.

A descriptive look (table 5) at the differences between patients receiving adequate primary prophylactic G-CSF versus inadequate primary prophylactic G-CSF, among the 337 patients who receive primary prophylactic G-CSF, revealed that being white and more educated increased the probability of receiving adequate primary prophylactic G-CSF. Race (being black versus white) had one of the largest differences in terms of proportion of patients receiving adequate primary prophylactic G-CSF (Figure 7). Unlike administration of primary prophylactic G-CSF the duration is not influenced by geographic variation.

Past history of other cancers, recent infections, larger tumor size and lymph node positivity increase the probability of adequate primary prophylactic G-CSF administration. Chemotherapy characteristics like anthracycline regimen (Figure 6), more number of drugs administered in the first cycle and shorter duration between first and second cycle are also highly correlated with adequate primary prophylactic G-CSF administration. In summary, based on the univariate analysis the chief determinants of duration of primary prophylactic G-CSF administration are race, education, diagnosis

of another cancer before the first primary breast cancer diagnosis, recent history of infections, larger tumor size, lymph node positivity, and all chemotherapy characteristics.

A logistic regression on the indicator for adequate primary prophylactic G-CSF administration, and an ordinary least square on the actual number of days primary prophylactic G-CSF was administered, indicated that chemotherapy characteristics like anthracycline regimen, more number of drugs administered in the first cycle and shorter duration between first and second cycle were significant predictors for a longer duration of primary prophylactic G-CSF administration (Table 6). Past history of other cancers and recent infections also increase the duration of primary prophylactic G-CSF administration. Recent antibiotic use reduced the duration of primary prophylactic G-CSF administration. In summary, chemotherapy characteristics and patient's recent clinical history are the chief predictors of duration of primary prophylactic G-CSF administration.

4.4 Outcomes – Descriptive analysis

Outcome variables such as – Neutropenia hospitalization, length of stay and expenditure associated with Neutropenia Hospitalization, overall Medicare expenditure, and provision of systemic therapy during the first course – were compared for women who received primary prophylactic G-CSF and those who did not. Comparisons were also made for women who received adequate ($\geq$5 days) primary prophylactic G-CSF versus women who received less than five days of primary prophylactic G-CSF.

4.4.1 Neutropenia Hospitalization

The descriptive analysis showed that neutropenia hospitalization was more common among individuals who received primary prophylactic G-CSF compared to individuals who did not (Table

7). This result was statistically significant for hospitalization within a month of chemotherapy initiation. However, patients with longer duration of primary prophylactic G-CSF administration had lower mean hospitalization compared to patients with shorter (inadequate) duration and this was statistically significant for both hospitalizations after 1 month and 3 months of chemotherapy initiation (Table 7). Figure 8 illustrates this effect, where irrespective of the time window used to measure the first neutropenia hospitalization after chemotherapy initiation, individuals receiving primary prophylactic G-CSF had higher hospitalization rates than individuals not receiving primary prophylactic G-CSF. On the other hand as shown in figure 9 individuals receiving a longer duration of primary prophylactic G-CSF (>=5 days) consistently have lower rates of hospitalization as compared to individuals receiving a shorter/inadequate duration of primary prophylactic G-CSF, irrespective of the time window used to measure neutropenia hospitalization.

On further analyzing the affect of longer duration of primary prophylactic G-CSF on neutropenia hospitalization, a very interesting trend was observed. The longer duration seemed to matter more in cases of more advanced and severe cancer, than a less severe one. Figure 10 illustrates the rate of neutropenia hospitalization with respect to the three breast cancer stages under study for individuals with and without primary prophylactic G-CSF administration. Here the stage of cancer does not really make a difference in the rate of hospitalization with and without primary prophylactic G-CSF, and people receiving primary prophylactic G-CSF have a higher neutropenia hospitalization rate. However, as illustrated by figure 11 the longer duration of primary prophylactic G-CSF administration has lower hospitalization rates in patients with higher stages of breast cancer (stage II and III). As shown in figures 12 to 15, this trend repeats itself when the cancer is classified based on grade (such that grades 3 and 4 have lower hospitalization rates for individuals receiving longer duration of primary prophylactic G-CSF versus shorter duration of primary prophylactic G-CSF) and size (patients with tumor size above 2 cms have lower hospitalization rates with higher G-CSF duration). In summary, duration of primary prophylactic G-CSF seems to have a positive correlation

with lower probability of neutropenia hospitalization based on simple descriptive statistics, and more so in case of more advanced cancer.

4.4.2 Neutropenia Hospitalization – Length of stay

Patients receiving primary prophylactic G-CSF have a lower length of stay due to neutropenia hospitalization on an average (Table 7 and Figure 16). However, the difference was not statistically significant. The duration of primary prophylactic G-CSF administration does not seem to have an effect on the length of stay once hospitalized (Table 7 and Figure 17), although it was associated with lower neutropenia hospitalization rates as described above. The means of logarithmic length of stay are also presented in table 7 since the parametric analysis is performed on logarithm of length of stay.

4.4.3 Neutropenia Hospitalization – Expenditure

Patients receiving primary prophylactic G-CSF have a lower expenditure due to neutropenia hospitalization on an average (Table 7 and Figure 18). Longer duration of primary prophylactic G-CSF administration was also associated with lower expenditure due to neutropenia hospitalization (Table 7 and Figure 19). However, neither of these differences was statistically significant. The means of logarithm of the expenditure are also presented in table 7.

4.4.4 Overall Medicare Expenditure for a year after chemotherapy initiation

The descriptive analysis of the overall Medicare expenditure for a year after initiation of chemotherapy showed that for patients receiving primary prophylactic G-CSF the expenditures were on an average higher than patients not receiving primary prophylactic G-CSF (Table 7 and Figure 20). This trend continued among patients receiving a longer duration of primary prophylactic G-CSF

(Table 7 and Figure 21), such that the patients receiving 5 days or more of primary prophylactic G-CSF had a higher overall Medicare expenditure for a year after chemotherapy initiation compared to patients receiving less than 5 days of primary prophylactic G-CSF. These differences were statistically significant.

4.4.5 Systemic therapy administration

Both the administration of primary prophylactic G-CSF and longer duration of primary prophylactic G-CSF administration increase the average number of chemotherapy cycles administered during the first course (Table 7, Figure 22 and 23). The probability of any administration of radiation therapy during the first course is higher in patients receiving primary prophylactic G-CSF versus patients not receiving primary prophylactic G-CSF (Figure 23). However, duration does not seem to be associated with radiation therapy administration (Figure 23). This seems to suggest that appropriate primary prophylaxis might actually improve systemic therapy administration in breast cancer patients.

4.5 A closer look at primary prophylactic G-CSF duration and outcomes

Parametric analysis was done to examine the effect of "duration" of primary prophylactic G-CSF administration on neutropenia hospitalization, expenditure and systemic chemotherapy administration. The covariates controlled for in these analyses were the same as those used for other parametric analysis examining the effect of primary prophylactic G-CSF on these outcomes, namely – age, race, marital status, education, income, urban residence, SEER region, relevant clinical history, tumor characteristics, chemotherapy characteristics and other therapies administered. This analysis was not preceded by any form of matching, but was performed using the 337 observations who received primary prophylactic G-CSF. The analysis was done using the continuous variable for

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number of primary prophylactic G-CSF days as well as the categorical variable for primary prophylactic G-CSF administration for 5 or more days.

Performing two analyses using two different dependent variable specifications (a continuous and a categorical variable) showed that higher duration of primary prophylactic G-CSF administration reduced the rate of neutropenia hospitalization after chemotherapy initiation, and improved the rates of systemic therapy administration (Table 10). Table 12 shows the marginal effects computed by the average of probabilities method. The average of probability method was used in this study because it is easy to interpret for binary variables like administration of primary prophylactic G-CSF and does not ignore the distribution of the marginal effects in the data (Norton, 2004).

The adequate administration of primary prophylactic G-CSF for five or more days reduces the probability of neutropenia hospitalization by seven percentage points, nine percentage points, and four percentage points in the first month, first three months, and the first six months after chemotherapy initiation respectively. Each additional day of primary prophylactic G-CSF administration reduces the probability of neutropenia hospitalization by one percentage point in the first month and first three months respectively. The adequate administration of primary prophylactic G-CSF for five or more days, versus less than five days, increases the probability of radiation therapy administration and adequate (more than 5 cycles) chemotherapy administration during the first course by one percentage point each (Table 12).

The overall Medicare expenditure for a year after chemotherapy initiation were higher for patients receiving primary prophylactic G-CSF for a longer duration. Receiving 5 or more days of primary prophylactic G-CSF administration increased the overall expenditure by 19.62%, and increase in primary prophylactic G-CSF administration by one day increased the overall expenditure by 1.74% (table 12). Analyses on neutropenia length of stay and neutropenia related hospitalization

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expenditures could not be performed as the number of patients hospitalized for neutropenia, among those who received primary prophylactic G-CSF, were too low to perform any parametric analyses. Among the 337 patients who received primary prophylactic G-CSF, 15 were hospitalized within the first month of chemotherapy initiation, 20 were hospitalized within the first 3 months, and 25 were hospitalized within the first 6 months of chemotherapy initiation. A sample size of 15-25 observations was not an adequate for the parametric analysis.

Since the decision to develop a categorical variable for 5 or more days (versus less than five days) was based on clinical practice patterns in the claims data (since five days was the mean and median duration in this study and other similar studies), and did not have any scientific basis, similar analyses were also performed by creating categorical variables for 7 or more days of administration, and 10 or more days of administration. It was interesting to note that both 7 or more days and 10 or more of administration did not have a statistically significant benefit in reducing neutropenia hospitalization rates, though there were some effects on improving adherence to systemic therapies.

4.6 Parametric analysis after genetic matching

Before performing the parametric analysis to determine the effect of primary prophylactic G-CSF on probability of neutropenia hospitalization, length of stay, expenditures, and provision of systemic therapy, the 337 treated individuals were matched with untreated individuals closest to them in terms of the covariates. Genetic matching technique was used for selecting the appropriate matches. The propensity score was included as one of the variable to be matched on, as discussed in section 3.3.5.

In order to make the matching process as flexible as possible to ensure optimal matching and also abiding by the choice limitations of the software, several choices were made. Since there were

only 337 treated observations among the 10441 observations, discarding treated observations while matching might compromise the power of the study. Given that there were 10104 untreated observations finding appropriate matches for all the 337 treated observations will not be challenging. On the other hand all the10104 untreated observations might not have an appropriate match among the 337 treated observations. Thus, **discard** options were set to remove untreated observations that did not match with the treated observations and at the same time preserve all the 337 treated observations.

Matching was performed with **replacement** so that the treated observations matched later are not forced to match with untreated observations which are not optimal matches; this often happens when the matching is done without replacement and the pools of untreated and treated observations shrink in size as each pair is formed. Since treated observations are not discarded the treated observations matched later will have to be paired with leftover untreated observations even if the match is poor. Thus, matching with replacement was preferred.

There are concerns about variance estimation in the case of matching with replacement because the assumption of independent and identically distributed observations is violated as the same observation is matched multiple times. However, in case of this analysis this assumption is not violated because matching is used to construct the analytic data but is not directly used to estimate the treatment effects. Once the analytic data are constructed the parametric estimation is performed as it would be with any other data. The untreated units matched with replacement are not counted twice during the analysis. Thus matching with replacement does not have any implications on variance estimation in case of this analysis.

Since the **ratio of untreated to treated** was very high, each treated observation could potentially have more than one match. The software requires that the user specify the number of

matches for each treated. The number of untreated to be matched with treated was set at six. The number of untreated observations to be matched should not be too low, especially in this sample, since only 337 observations were treated. Having only one to two untreated matches for each treated might severely compromise the power of the sample. On the other hand increasing the untreated matches, keeping the treated observations constant, has diminishing returns for the power, and might also lead to poor forced matches. Multiple matches were performed by specifying 4 to 8 untreated matches with each treated observation. It was found that, due to the matching with replacement option the untreated observations in the matched sample did not increase much when more than six untreated were matched with treated. Moreover, the descriptive statistics showed that the matches became poorer with more statistical difference in the control variables of the treated versus untreated observations as the number of matches were increased beyond six. Thus, the number of untreated matches per treated were specified as six. It is important to note that the final matched sample will not have a 1:6 ratio of treated to untreated due matching with replacement; some untreated observations will be matched with more than one treated observation.

Options were also set for specific genetic matching parameters. The population size for the number of solution sets (number of sets of weights in this case) was set at 5000. This implies that the algorithm begins with 5000 sets of 57 weights required in this optimization (there are 56 control variables and one propensity score), tries them out on the sample, and accordingly performs the genetic operations of reproduction, mutation, crossover and inversion to come up with the next set of trial solutions of 5000 weights vectors. This process is continued till the most optimal set of weights are selected such that they cannot be further improved. The higher the population size the better the optimization. In order to decide when the optimal solution is achieved the "wait.generation" option is set, which is the maximum number of generations of population until which, if the solution is not improved by the genetic operations, the algorithm stop. The wait.generation was set to 25 in this optimization. If the genetic operations are unable to improve the solution within 25 generations, then

the last best solution is considered optimal. Another important option used was the memory matrix option. This option preserves all the previously tried solution vectors and ensures that the newly generated solutions are not redundant. This option however compromised the speed of the algorithm. The optimization was aimed at minimizing the statistical difference in control variables between the treated and untreated by maximizing the p-values associated with each variable.

After discarding untreated observations which did not match treatment observations 1760 observations were left. The treated to untreated ration was 1:4.223 approximately.

The descriptive statistics of means and statistical differences of control variables between the treated and untreated group for the final matched sample is presented in table 8. The descriptive statistics before matching are also presented for the purpose of comparison. The statistically significant differences in covariates that existed before matching were no longer present after matching. However, three variables, past history of cancer, history of infection a month before chemotherapy initiation, and receipt of radiation therapy before chemotherapy initiation, became significantly different, which was not the case previously. These variables were not statistically correlated with administration of primary prophylactic G-CSF before – both based on descriptive statistics and the logistic regression – hence the algorithm assigned smaller weights to these variables during the matching process. Thus their balance was compromised while ensuring good balance in variables which were significant determinants of primary prophylactic G-CSF administration. Performing the matching multiple times with different specifications did not make any difference and imbalances still remained. Since parametric analysis will be performed to control for the remaining imbalances, further analysis was performed on this matched pool even though minor differences in the treated and untreated existed.

Table 9 shows the comparative statistics for the dependent variables, and the results illustrate that the statistically significant differences between women who received primary prophylactic G-CSF and who did not remained the same after matching. This is because the matching process did not involve any balancing of the dependent variables. Although there were few statistically significant changes in the dependent variables after matching some new trends emerged. The proportion of individuals hospitalized due to neutropenia during the first three and six months after the start of chemotherapy was higher in the untreated individuals than the treated individuals after matching. This was a reverse trend as compared to the trend before matching, although not statistically significant both before and after matching. The mean difference in the length of stay and expenditures due to neutropenia hospitalization increased, such that they were higher in the untreated individuals as compared to the treated individuals. The trends were same as before but just more pronounced in magnitude. However, they were not statistically significant. Most other differences remained similar.

Table 10 presents the regression coefficients with standard deviations in the parenthesis after parametric analysis. Post-matching primary prophylactic G-CSF administration seems to have a statically significant affect in lowering the probability of neutropenia hospitalization, for the first neutropenia hospitalization within three and six months of chemotherapy initiation. Women receiving primary prophylactic G-CSF have a one percentage-point lower risk of being hospitalized as compared to women who did not receive primary prophylactic G-CSF, both during the three month as well as the six month window (Table 11). This trend did not exit before matching. For the first month after chemotherapy initiation, however, primary prophylactic G-CSF did not have any statistically significant effect on neutropenia hospitalizations post-matching.

The average length of stay and neutropenia hospitalization expenditures were lower in magnitude for women receiving primary prophylactic G-CSF both before and after matching. These effects are not statistically significant. However, it is interesting to note that the magnitude of

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difference in length of stay and neutropenia hospitalization expenditures become more prominent after matching such that the average length of stay and neutropenia hospitalization expenditures are higher in women not receiving primary prophylactic G-CSF as compared to those receiving it. The lack of statistical significance in spite of an increase in magnitude of the effect of primary prophylactic G-CSF on length of stay and expenditures is probably because of the reduction in sample size of hospitalized individuals post-matching.

The analysis for the reduction in hospitalization length of stay and expenditure during the first month after the initiation of chemotherapy could not be performed as the number of observations was far too low post-matching (48 patients hospitalized during the first month in both treated and untreated women put together). Since logarithm of length of stay and expenditure was used the marginal effects are computed using the Kennedy transformation method (Kennedy, 1981).

Overall expenditures within one year of chemotherapy initiation were consistently higher for women who received primary prophylactic G-CSF versus who did not both before and after matching (Table 11). In the analysis post-matching the overall expenditures were 57.25 percent higher in women receiving primary prophylactic G-CSF (Table 11). G-CSF prophylaxis also significantly increased the probability of radiation therapy administration and administration of chemotherapy for more than 5 cycles during the first course by 8%-points and 6%-points respectively (Table 11).

4.7 Analysis without controlling for therapeutic modalities

The previous analysis controlled for all the breast cancer therapies provided before and at the start of chemotherapy first course (the first cycle). Primary prophylactic G-CSF administration occurs two to five days after the administration of first cycle of chemotherapy first course and hence the therapy variables were pretreatment and were included in the analyses.

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However, physicians often plan the short-term treatment protocol for a breast cancer patient soon after her diagnosis based on the tumor characteristics and other clinical characteristics. Type of surgery to be performed and type of radiation therapy and chemotherapy to be administered might be decided simultaneously. In addition, primary prophylactic G-CSF administration is often decided based on the type of chemotherapy regimen planned. Thus, treatment administered during the first few months after diagnosis could be a joint decision along with the decision to administer primary prophylactic G-CSF, and the treatment variables controlled in this study, although administered before primary prophylactic G-CSF (pre-treatment variables), might be correlated to the decision to administer G-CSF. A sensitivity analysis was performed by excluding all the treatment variables to see if the treatment protocols associated with the decision to administer primary prophylactic G-CSF (and not just the primary prophylaxis itself) were associated with better health outcomes overall.

The descriptive statistics after matching on only the socio-demographic, clinical and tumor characteristics are provided in table A1. The sample size after matching was 2046 with ratio of treated to untreated being 1:5.07. The balance in control variables between treated and untreated observations was well achieved, with statistically significant differences only in anthracycline use in the first cycle of the first course chemotherapy. The descriptive statistics for the outcome variables post-matching, and the results of the parametric analysis are presented in tables A2 and A3 respectively. It is important to remember that the results before matching in table A3 are different from results before matching in table 10 because the analysis in table A3 does not control for the therapy variables before matching even though the observations used are the same as in table 10.

An important difference in the results in table 10 versus table A3 was the lack of effect of primary prophylactic G-CSF on probability of neutropenia hospitalization when treatment variables are not controlled for. Primary prophylactic G-CSF reduced the probability of neutropenia

hospitalizations in the first three and six months after the start of chemotherapy in the analysis controlling for pre-treatment therapies (table 10 and 11). However, as can be seen in table A3 and A4 there was no statistically significant effect of primary prophylactic G-CSF on neutropenia hospitalizations if the analysis did not control for pre-treatment therapies. Similar to the analysis controlling for treatment variables, G-CSF prophylaxis significantly increased the probability of radiation therapy administration and administration of chemotherapy for more than 5 cycles during the first course by 4%-points and 8%-points respectively (Table A4). The overall expenditures were 70.47 percent higher in women receiving primary prophylactic G-CSF (Table A4). The trends in the effect of primary prophylactic G-CSF duration on the key outcome variables were mostly not statistically significant when pre-treatment variables were not controlled for (Table A5). The positive effect of primary prophylactic G-CSF duration on adequate chemotherapy administration during the first course was the only effect significant at the 5% level.

Since neutropenia occurrence is associated more with systemic therapy administration, the surgery performed might not be endogenous to the administration of G-CSF but the type of chemotherapy and radiation therapy administered before the start of G-CSF might be associated with the plan to start primary prophylactic G-CSF administration. Hence the analysis was re-performed by just excluding the chemotherapy and radiation therapy variables instead of all the treatment variables.

The sample size after matching on all socio-demographic, clinical and tumor characteristics, and surgery performed was 2090 with the ratio of treated to untreated being 1:5.2. The balance in the covariates was well achieved, with statistically significant differences only in the history of antibiotic use before start of G-CSF and anthracyline use as part of the first cycle in chemotherapy (Table A6). The trends were similar to the previous analysis performed without controlling for any treatment variable (table A8). Both administration of primary prophylaxis and adequate duration of

administration were positively correlated with the expenditures in the first year and improved

systemic therapy provision (Table A9 to A10). No other effects were statistically significant.

Chapter 5

Discussion

5.1 Determinants of primary prophylactic G-CSF administration

One of the chief aims of this study was to establish the clinical and socio-demographic determinants of primary prophylactic G-CSF administration and to better understand the factors underlying a physician's decision to administer G-CSF prophylactically in an actual clinical setting. The study found that race, geographic region, year of diagnosis and chemotherapy characteristics are the primary variables which are statistically correlated with primary prophylactic G-CSF administration; SEER region and anthracycline based chemotherapy are the major predictors of receipt of primary prophylactic G-CSF.

5.1.1 Chemotherapy characteristics as predictors of a physician's decision to administer primary prophylactic G-CSF

Past studies show that younger age, and numerous clinical characteristics like extent of breast cancer disease spread, advanced tumor stage, tumor size, node positivity and lower comorbidity index are significant clinical predictors of G-CSF administration in Non-Hodgkin's Lymphoma patients (Chrischilles, 2003) and breast cancer patients (Hershman, 2007; Du, 2005). One study expressed concern that physicians should administer primary prophylactic G-CSF to younger women and women with lower comorbidity index even though older and sicker women are more vulnerable to chemotherapy toxicity (Du, 2005).

Initial univariate comparisons in this study did indicate similar trends in age and clinical characteristics, but the trends disappeared in multivariate analysis. Further sensitivity analysis with different multivariate specifications revealed that including chemotherapy characteristics in the multivariate analysis made the correlation of age and other clinical characteristics with primary prophylactic G-CSF administration insignificant. The past studies did not control for chemotherapy characteristics.

This finding suggests that physicians first decide the chemotherapy regimen (type of drugs, doses, frequency and intensity) based on patient clinical characteristics, and then decide the need for primary prophylactic G-CSF administration based on the risk of toxicity of the chemotherapy regimen. Younger and healthier patients (with lower co-morbidity index) are more tolerant of intense chemotherapy, and patients with higher extent of cancer spread (measured by advanced stage, larger size and node positivity) require a more intense chemotherapy. Hence, these patients receive a more intense chemotherapy and are also administered primary prophylactic G-CSF to counter the high risk of chemotherapy induced neutropenia. Thus, it is not the cancer characteristics and patient demographics, but the risk associated with chosen chemotherapy regimen that directly determines the physician's decision to administer primary prophylactic G-CSF.

Since anthracycline-based chemotherapy regimen, more number of drugs used in the first cycle, and more frequent cycles have a higher risk of toxicity, it is not surprising that these individuals are more likely to receive primary prophylactic G-CSF (Lyman, 2003c; Lyman 2004).

5.1.2 Temporal Variation in the use of a new drug

Temporal variation in the probability of primary prophylactic G-CSF administration is similar to variation in a previous study which looked at general hematopoietic factors administration (Du,

2005). Significant temporal variation is not surprising given that primary prophylactic G-CSF was introduced in 1991 and the data include administrations from 1994 to 2002. G-CSF administration as prophylaxis is often a provider's decision; hence, awareness and beliefs of the providers are important determinants of whether or not the patient gets the drug. Since the drug was introduced relatively recently, it will take some time for the physicians to become aware of the drug, and the awareness will steadily increase with time, therefore patients diagnosed in the later years are more probable of receiving the drug. Practice guidelines also have an effect on how soon the physicians come to know about the drug and adopt it in their practice. Incorporation of recommendations for primary prophylactic administration of G-CSF in the ASCO guidelines since 1994 definitely contributed towards the awareness and use of the drug in clinical practice. The use of G-CSF in the general population experienced the maximum increase after the year 1999.

5.1.3 Unexplained racial and regional disparities

Racial and regional disparities in the administration of primary prophylactic G-CSF are a concern. Regional differences chiefly indicate geographic variations in practice patterns. Many studies have been published since early 1970s documenting significant geographic variations in different treatment modalities especially by the research group at The Dartmouth Institute (Wennberg 1975; Wennberg, 2005; Wennberg, 2008). These variations are attributed primarily to variations in practice styles and provider beliefs about treatment effectiveness. Given that G-CSF is a recently introduced preventive agent, geographic variations might be more pronounced as it will take physicians some time to incorporate the use of G-CSF in their practice. Different physicians will adopt the drug at a different rate, and the adoption will also be heavily influenced by practices of colleagues, thereby making the difference appear very regional. Also, since no strict guidelines exist for the administration of G-CSF as a prophylactic agent in the elderly breast cancer patients, the

administration often depends on the discretion of the provider thereby increasing the variations in practice patterns.

Figure 5 shows that the SEER registries in California, Louisiana and Connecticut have the highest administration rates for primary prophylactic G-CSF, and Hawaii, Kentucky, Iowa, Atlanta, and Utah have some of the lowest rates. Rural Georgia has no patient receiving prophylactic chemotherapy. Past studies using the SEER-Medicare data demonstrate that Los Angeles, Connecticut and Utah have higher rates of G-CSF administration, and Hawaii, New Mexico, Seattle and Detroit had the lowest in Non-Hodgkin's Lymphoma patients (Chrischilles, 2003). For breast cancer patients in the SEER data California, Detroit and Atlanta had a higher probability of receiving general G-CSF (not just primary prophylaxis) (Du, 2005).

Since regional variations are one of the most significant in determining the probability of G-CSF administration, a more detailed descriptive analysis was performed to understand the possible factors that might be driving the trend. Table 13 illustrates the number of women who received G-CSF in each region, sample size in each region, the total number of unique physician identifier associated with the chemotherapy claims in each region (indicating the total number of physician in the data for that region), the number of physicians who administered G-CSF to all their patients, and the number of physicians who never administered G-CSF to their patients. The regions are arranged in a descending order of the rate of primary prophylactic G-CSF administration.

Certain regions could have higher rates either because few physicians who believe in the merits of the drug drive its use in that region, or because the proportion of physicians administering the drug in that region is higher. Table 13 illustrates that only about 10% of physicians on an average administer the drug prophylactically. Clearly a higher proportion of physicians administer the drug in regions with higher rates of G-CSF administration. Physicians in the regions with higher rates of G-

CSF administration do administer G-CSF to a higher proportion of the patients on an average, but this trend is not consistent. The trends suggest that higher percentage of physicians administering the drug in each region is probably driving the overall rates more than the higher rates of drug administration per physician. A higher proportion of providers seem to be aware of G-CSF and support its use in areas with higher rates of administration. There was no evidence that certain physicians were involved with unusually high rates of G-CSF administration or overuse in regions of high rates. Moreover, there are very few patients under each physician in a region and so physician specific statistical trends are not easy to interpret using the SEER data for these years.

Change in regional trends with time was also descriptively examined, but no significant temporal differences between regions were observed in the rate of administration of the drug.

5.2 Determinants of duration of primary prophylactic G-CSF administration

Few studies look at the determinants of duration of primary prophylactic G-CSF. The study looking at NHL patients showed that previous radiation therapy use, older age (>75 years) and later years of cancer diagnosis (after 1997) were associated with lower duration of primary prophylactic G-CSF administration (<7 days) (Chrischilles, 2003). These findings were very different from our study looking at breast cancer patients. This study found that past history of cancer, recent infections, and chemotherapy characteristics influence the duration of primary prophylactic G-CSF administration. History of recent antibiotics administration reduced the duration of primary prophylactic G-CSF administration.

Interestingly, regional differences that were statistically significant in predicting the administration did not play any role in predicting the duration of primary prophylactic G-CSF. This could be because the decision to administer primary prophylactic G-CSF is predominantly provider

dependent and once the providers decide to administer primary prophylactic G-CSF, they intend to administer it for at least a week, which is the typical standard practice. However, the duration of administration is dependent on patient's convenience and treatment adherence. Thus the duration is affected more by patient characteristics and clinical needs, and not significantly affected by provider practice styles that are captured as regional trends.

Past history of other cancers and recent infections increase the probability of adequate (≥ 5 days) primary prophylactic G-CSF administration. These correlations are indicative of higher compliance among patients with previous bad health experiences, and provider's insistence on better adherence due to patient's susceptibility to infections. Chemotherapy characteristics are, as discussed before, an important determinant of both primary prophylactic G-CSF administration and its duration. This significant effect of chemotherapy is due to the direct impact of the chemotherapy regimen on the severity of neutropenia occurrence.

An interesting finding is that antibiotics use reduces primary prophylactic G-CSF duration. Some physicians use antibiotics as partial substitutes for the expensive G-CSF prophylaxis to prevent febrile neutropenia and other neutropenia related infections, although the substitution is not clinically recommended (Dr. Gary Lyman, personal communication). These physicians, anticipating a higher risk of neutropenia occurrence, start their patients on prophylactic antibiotics a few days before the administration of chemotherapy, and might not be administering primary prophylactic G-CSF long enough due to the intended substitution.

5.3 Effect on neutropenia hospitalization probability

The beneficial effect of prophylactic G-CSF in the form of reduction in the risk of hospitalization has been demonstrated by other clinical trials and studies as well (Chrischilles, 2002;

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Glaspy, 1993; Engelhard, 1994; Dranitsaris, 1995; Heil, 1997; Moore, 1997; Weycker, 2004). However, none of these studies involved breast cancer patients or focused on the elderly patient population. This study found a reduction in risk of hospitalization among elderly breast cancer patients receiving primary prophylactic G-CSF. Women receiving primary prophylactic G-CSF have a one percentage-point lower risk of being hospitalized as compared to women who did not receive primary prophylactic G-CSF, both during the three month [95%CI: -1.2 to -0.5%-points] as well as the six month [95%CI: -1.8 to -0.6%-points] window post-matching (Table 11). The effect of primary prophylactic G-CSF for the first month was not statistically significant. These findings support the first hypothesis that primary prophylactic G-CSF reduces the occurrence of neutropenia hospitalization in elderly female breast cancer patients receiving chemotherapy.

The lack of any beneficial effect of primary prophylactic G-CSF in the first month might be due to two reasons. First, in the first month neutropenia occurrence might not be severe enough to require hospitalization. Since we are looking only at neutropenia hospitalization and not the incidence of neutropenia, it might be hard to detect the benefits. Second, the benefits of primary prophylactic G-CSF could be additive because occurrence of neutropenia in the first month increases the probability of neutropenia occurrence and severity in the later months (Timmer-Bonte, 2006). Also, the women who receive primary prophylactic G-CSF might be more likely to receive the drug at a later date during the course of chemotherapy (along with the later cycles) thereby further improving better toxicity tolerance throughout the first course (which lasts for three to six months after the start of chemotherapy).

It is important to note that positive correlation of primary prophylactic G-CSF and neutropenia hospitalization rates before matching is strongly suggestive of endogeneity; primary prophylactic G-CSF is often administered to women who have a higher risk of neutropenia. Post-matching, this trend reverses possibly because matching ensures comparison between women with

very similar clinical characteristics and risk of neutropenia. Thus, in women with similar neutropenia risk, administering primary prophylactic G-CSF reduces neutropenia hospitalization risk.

Some clinical trials have also looked at the effect of G-CSF on occurrence of neutropenia and febrile neutropenia and find a beneficial effect of G-CSF, especially the drug Filgrastim (Gridelli, 2007; Oyama, 1990; Crawford, 1991; Pettengell, 1992; Anderson, 1991; Havemann, 1991; Kotake, 1991; Trillet-Lenoir, 1993; Gerhartz, 1993; Kaku, 1993; Gebbia, 1993; Gebbia, 1994; Eguchi, 1994; Rampling, 1994; Bui, 1995; Bergmann, 1995; Muhonen, 1996; Jones, 1996; Zinzani, 1997; Gisselbrecht, 1997; Moore, 1997; Bassan, 1997; Fossa, 1998; Feng, 1998; Hidalgo, 1998; Lyman, 2002; Osby, 2003; Scott, 2003; Kuderer, 2005; Timmer-Bonte, 2005; Vogel, 2005; Shayne, 2007; Kuderer, 2007).

Other studies find no effect of primary prophylactic G-CSF on neutropenia occurrence or hospitalization (Shaffer, 1993; Bunn, 1995; Woll, 1995; Weiss, 1996; Fridrik, 1997; Dunlop, 1998; Steward, 1998; Doorduijn, 2003). These studies predominantly looked at Sargramostim (GM-CSF) and Lenograstim administration. Filgrastim, which is the most commonly used G-CSF in the Medicare patients (86% of primary prophylactic use in this study), is usually found to be very clinically effective by most of the clinical trials and meta-analyses (Kuderer, 2007).

Adequate duration of primary prophylactic G-CSF administration has been found to be effective in reducing neutropenia incidence and neutropenia hospitalizations in non-Hodgkin's lymphoma patients (Weycker, 2004; Chrischilles, 2003; Scott, 2003). These studies show that longer duration was associated with lower incidence of febrile neutropenia (Scott, 2003), and lower risk of hospitalization and infection (Weycker, 2006; Weycker 2004). Weycker (2004) found significant differences between patients receiving primary prophylactic G-CSF for less than five days, and for

five or more days. Chrischilles and colleagues also show that lower duration of prophylactic G-CSF is associated with higher risk of neutropenia hospitalization (Chrischilles, 2003).

This study, which for the first time looked at elderly breast cancer patients, found that adequate (or longer) duration of primary prophylactic G-CSF reduced the probability of neutropenia hospitalization. The adequate administration of primary prophylactic G-CSF for five or more days reduces the probability of neutropenia hospitalization by 7 %-points [95%CI: -15 to -1 %-points], 9%-points [95%CI: -15 to -3 %-points], and 4%-points [95%CI: -8 to -0.3 %-points] in the first month, first three months, and the first six months after chemotherapy initiation respectively (Table 12).

It was interesting to note that adequate duration of primary prophylactic G-CSF administration particularly lowered the probability of neutropenia hospitalization in women suffering from more severe cancer like – higher stages, higher grade, and larger size (Figures 11, 13 and 15), and these reductions were statistically significant. One reason why adequate duration lowered neutropenia hospitalization in more severe cases, but did not have much effect in the less serious cases, could be because the severe cases are more likely to receive intense chemotherapy with a higher risk of neutropenia, thus neutropenia prophylaxis is more beneficial in such cases. This trend of better effectiveness of adequate primary prophylactic G-CSF (versus less than 5 days of G-CSF) in severe cases is not observed in patients who receive any primary prophylactic G-CSF (versus those who do not) (Figures 10, 12 and 14).

5.4 Effect on neutropenia hospitalization length of stay

A reduction in the length of stay due to G-CSF has been documented by many studies previously (Kaplan, 1991; Glaspy, 1993; Moore, 1997; Chrischilles, 2002; Maher, 1994; Gerhatz, 1993; Zagonel, 1994; Dranitsaris, 1995). There have also been studies in which the beneficial effects of G-CSF on length of stay have been statistically insignificant (Bunn, 1995; Woll, 1995; Dunlop, 1998). In this study there is no statistically significant effect of primary prophylactic G-CSF on the length of stay once patient is hospitalized probably due to the small sample size of women who were hospitalized. Thus, the second hypothesis could not be corroborated. In addition, the effect of duration of primary prophylactic G-CSF administration on neutropenia hospitalization length of stay could not be assessed due to the small sample size of the women receiving primary prophylactic G-CSF as well as getting hospitalized.

5.5 Effect on Medicare expenditures

In order to test hypothesis three the expenditures associated with the first neutropenia hospitalization within the first, third and sixth month after the start of chemotherapy were examined. The trends in magnitude were very similar to the findings from length of stay, which further emphasizes the fact that length of stay is one of the chief determinants of Medicare costs associated with a hospitalization (Lyman, 2004). None of the effects were statistically significant, probably because of the small sample size of women who get hospitalized, hence the first part of the hypothesis three could not be corroborated as well. The effect of duration of primary prophylactic G-CSF administration on neutropenia hospitalization expenditures could not be assessed due to the small sample size of the women receiving any primary prophylactic G-CSF as well as getting hospitalized.

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The second part of hypothesis three looks at the effect of primary prophylactic G-CSF on overall Medicare Expenditures for one year after the start of chemotherapy. The initial aim was to see if primary prophylactic G-CSF administration prevented early recurrence and other worse outcomes, and hence lowered the cost of breast cancer management and treatment in the first year after the start of chemotherapy. The study, however, found reverse trends. Women who received primary prophylactic G-CSF had higher mean overall expenditure and this effect was statistically significant. In the post-matching analysis the overall expenditures were 57.25% higher in women receiving primary prophylactic G-CSF (Table 11). Women receiving a higher duration of primary prophylactic G-CSF also had higher overall Medicare expenditure during the first year after start of chemotherapy. Receiving 5 or more days of primary prophylactic G-CSF increased the overall expenditure by 19.62%, and increase in primary prophylactic G-CSF by one day increased the overall expenditure by 1.74% (Table 12).

There could be multiple reasons for higher overall expenditure in spite of effective primary prophylaxis. The administration of primary prophylactic G-CSF increased the successful administration of the first course of chemotherapy and radiation therapy (as discussed in the next section). Since the bulk of these therapies are administered in the first year, increased adherence to these therapies will increase the Medicare expenditure in the first year. It is also important to understand that G-CSF is expensive, and the costs for prophylactic G-CSF administration during the entire first course chemotherapy could range between $5,000 to $30,000. This considerable cost could offset cost reductions due to reduced neutropenia management and hospitalization costs. In order to understand the main driving factors behind higher first year expenditure in women receiving primary prophylactic G-CSF a descriptive analysis was performed to identify different components of these overall costs (Table 14).

In the matched data the average G-CSF expenditure in the first year for women who received the drug as primary prophylaxis was $7914 versus $1369 for women who did not receive the drug as primary prophylaxis (but received it later). The maximum expenditure of G-CSF for women who received primary prophylaxis was $44204 and was below $20,000 for 95% of the women receiving primary prophylaxis. On the other hand the expenditure was below $8,000 for 95% of the women not having received primary prophylaxis, with the maximum expenditure being $24927. Seventy percent of women who did not receive primary prophylactic G-CSF had no G-CSF expenditure in the first year.

Chemotherapy expenditures were twice as high for women receiving primary prophylactic G-CSF. Fifty percent of women who did not receive primary prophylaxis had less than $4,000 of chemotherapy expenses in the first year, and 50% of the women having received G-CSF had more than $10,000 of chemotherapy expenses in the first year with a maximum of $61,705. Given both the difference in the expenditure due to G-CSF and chemotherapy, it is not surprising that women having received primary prophylactic G-CSF have high expenditures in the first year in spite of any cost reductions due to reduced neutropenia management and hospitalization costs. It is also important to note that in women receiving primary prophylactic G-CSF, G-CSF accounts for nearly 30% of the overall costs in the first year and is almost as big a contributor to overall costs as chemotherapy (at 40%).

Previous studies predominantly look at neutropenia hospitalization and immediate care costs and have ambiguous findings in terms of the cost reduction due to G-CSF. These past studies are broadly of three types - some directly estimate the expenditures associated with neutropenia hospitalization; some develop cost models to estimate the threshold above which prophylaxis of neutropenia becomes cost-effective; and some estimate the reduction in hospitalization costs and other neutropenia related costs due to G-CSF administration.

Studies that just look at the cost of neutropenia hospitalization have found that cost of care and inpatient care is around 1.5 to 2 times higher in women experiencing neutropenia (Weycker, 2006; Gandhi, 2001) and the neutropenia hospitalization cost could range from $10,000 to $30,000 (Eldar-Lissai, 2007; Kuderer, 2006; Weycker, 2007; Weycker 2006; Brooks, 2003). Studies also find that the cost of care for neutropenia predominantly depends on the patient's baseline clinical status like cancer stage and existence of other comorbidities (Chrischilles, 2005).

Studies looking at cost-effectiveness of G-CSF using cost-models have demonstrated that primary prophylactic G-CSF is cost-reducing and cost effective in patients with high risk of developing neutropenia, febrile neutropenia or neutropenia hospitalization (>20% risk according to the currently accepted model by ASCO) (Eldar-Lissai, 2007; Uyl-de Groot, 1996; Lyman 2004; Lyman, 1993). Uyl-de Groot and colleagues show that G-CSF is cost effective in terms of reducing hospitalization and antibiotic administration costs in patients receiving chemotherapy, especially for patients with higher risk of infections (Uyl-de Groot, 1996). These cost-effectiveness models only include direct healthcare costs and do not include out-of-pocket costs, indirect costs (due to caregiver's time and any other form of loss of pay), intangible costs and quality of life considerations. Lyman and colleagues suggest that prophylactic G-CSF should be administered even if the risk is less than 20% in patients with possibly complicated or prolonged course of management such as the elderly patients (Lyman, 1998).

Studies looking at reductions in costs due to neutropenia are mostly clinical trials and retrospective chart reviews with low external validity (Glaspy, 1993; Zagonel, 1994; Dranitsaris, 1995; Bassan, 1997). These studies have mixed findings. Some studies reveal a drop in costs, on average, in patients receiving primary prophylactic G-CSF compared to those not receiving the prophylaxis (Glaspy, 1993; Zagonel, 1994), while some reveal no change in costs (Dranitsaris, 1995;

Bassan, 1997). Two studies found that although the neutropenia hospitalization length of stay was reduced in patients receiving G-CSF, the cost reduction was offset by the initial cost of G-CSF administration (Dranitsaris, 1995; Bassan, 1997).

5.6 Effect on systemic therapy provision

This study found that primary prophylactic G-CSF administration was associated with higher probability of radiation therapy administration during the first course and higher probability of administration of more than 5 cycles of chemotherapy during the first course, thereby supporting hypotheses four and five. Primary prophylactic G-CSF increased the probability of radiation therapy administration and administration of chemotherapy for more than 5 cycles during the first course by 8%-points [95%CI: 1 to 14 %-points] and 6%-points respectively [95%CI: 0.1 to 12 %-points] (Table 11). Also, women receiving a higher duration of primary prophylactic G-CSF also had higher probability of radiation therapy administration during the first course and higher probability of administration of more than 5 cycles of chemotherapy during the first course. The adequate administration of primary prophylactic G-CSF for five or more days leads to a 1%-point increase in both the probability of radiation therapy administration [95%CI: 0.1 to 1.6 %-points] and the probability of adequate chemotherapy administration (more than 5 cycles) [95%CI: 0.1 to 2.0 %-points] during the first course (Table 12).

These findings are crucial from the point of view of the providers. Not reducing systemic therapy intensities ensures complete cure from breast cancer, prevents recurrence and reduces mortality. One of the prime incentives for physicians to administer primary prophylactic G-CSF is to sustain dose intensity, adhere to preplanned chemotherapy regimen, and avoid reduction or stopping of systemic chemotherapy which might lead to worse future prognosis (Bonneterre, 2005; Budman, 1998; Webster, 1996; Shayne, 2007).

Past clinical trials and other studies do find that primary prophylactic G-CSF administration increased adherence to preplanned chemotherapy regimens without reductions, successful administration of adequate chemotherapy dose intensities, or ability to increase the dose intensity based on patient needs (Jost, 1990; Kaplan, 1991; Kotake, 1991; Ardizzoni, 1994; Engelhard, 1994; Miles, 1994; Zagonel, 1994; Hansen, 1995; Woll, 1995; Webster, 1996; Jones, 1996; Heil, 1997; Fridrik, 1997; Fukuoka, 1997; Hidalgo, 1998; Steward, 1998; Stoger, 1998; Pfreundschuh, 2001; Lyman, 2002; Kuderer, 2005; Shayne, 2006; Kuderer, 2007). Two clinical trials also found no beneficial effect of chemotherapy on sustaining chemotherapy does intensity (Shaffer, 1993; Logothetis, 1995), but these two studies looked only at Sargramostim (GM-CSF) and not the Filgrastim, the more commonly used G-CSF. To the best of the author's knowledge, none of the studies looked at the effect of primary prophylactic G-CSF on future radiation therapy administration; hence the positive effect of primary prophylactic G-CSF in sustaining radiation therapy during the first course is a new finding in this study.

5.7 Analysis without controlling for the type of treatment

Physicians often plan the short-term treatment protocol for a breast cancer patient soon after her diagnosis based on the tumor characteristics and other clinical characteristics. Type of surgery to be performed and type of radiation therapy and chemotherapy to be administered might be decided simultaneously. In addition, primary prophylactic G-CSF administration is often decided based on the type of chemotherapy regimen planned. Thus, treatment administered during the first few months after diagnosis could be a joint decision along with the decision to administer primary prophylactic G-CSF, and the treatment variables controlled in this study, although administered before primary prophylactic G-CSF (pre-treatment variables), might be correlated to the decision to administer G-CSF.

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A sensitivity analysis was performed by excluding all the treatment variables to see if the treatment protocols associated with the decision to administer primary prophylactic G-CSF (and not just the primary prophylaxis itself) were associated with better health outcomes overall. As can be seen from table A4, A5 and A6 most effects are similar to the previous parametric analysis performed after controlling for the type of pre-treatment therapies (table 10-12), except for hypothesis one. The important difference was that there was no effect of primary prophylactic G-CSF administration on neutropenia hospitalization probability. Since the reduction in neutropenia hospitalizations is the main finding of this study, the difference between analyses controlling for and not controlling for the type of treatments administered is interesting.

This lack of neutropenia hospitalization risk reduction could be because of the following factors:

1. The treatment variables are acting as indirect measures for unobserved heterogeneity in clinical characteristics that providers are aware of but are not reported in the observational data (like laboratory values for baseline blood cell counts and co-morbidities not recorded in the Medicare claims). Thus, patients receiving similar therapy are closer to each other in terms of their clinical characteristics and neutropenia susceptibility. Not controlling for these treatment characteristics increases the unobserved heterogeneity and makes unbiased estimation of treatment effect difficult.

2. The treatment (especially chemotherapy) variables are the main source of neutropenia risk. Since neutropenia and neutropenia hospitalization are induced by chemotherapy (and worsened by other systemic therapies like radiation therapy), not controlling for these leads to the comparison of patients with different risks of neutropenia occurrence. As established

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before in this study patients receiving primary prophylactic G-CSF receive more intense chemotherapy and hence are inherently at a higher risk of neutropenia occurrence. Thus, not controlling for difference in type of treatment increases the baseline risk of patients receiving G-CSF and biases the treatment effect estimate towards zero.

The same lack of effect on neutropenia hospitalization is observed when surgery variables are controlled for but chemotherapy and radiation therapy are not (since these are more directly related to neutropenia risk and G-CS administration) (Tables 9 to 11), emphasizing the fact that neutropenia risk is determined by systemic therapy and not controlling for the treatments makes the treated group different from the untreated group in terms of baseline neutropenia risk.

5.8 Policy Implications

5.8.1 Implications for Providers and ASCO policies

One of the main aims of the study is to provide evidence for the benefits of primary prophylactic G-CSF administration, address gaps in the literature, and contribute towards ASCO policies with regards to the appropriateness of the primary prophylaxis in elderly female breast cancer patients. The study found that primary prophylactic G-CSF is clinically beneficial in elderly breast cancer patients receiving chemotherapy as it reduces the probability of neutropenia hospitalizations and improves adherence to provision of systemic therapy (both radiation and chemotherapy).

Standardized and unambiguous ASCO guidelines for primary prophylactic G-CSF administration in the elderly could help reduce unexplained racial and regional disparities currently observed in the population. It is not surprising that unexplained regional disparities exist in the administration of a recently introduced drug since it takes time for providers to become aware of a

new drug. The extent to which they change their treatment protocols to incorporate the new drug depends on unambiguous standard medical guidelines supporting its use and the extent to which their colleagues adopt the drug successfully and realize its benefits. Clear ASCO guidelines for the primary prophylactic G-CSF use in the elderly patients, and publication of scientific evidence supporting primary prophylaxis, will help reduce subjective judgment and promote standardization of care.

ASCO recommendation for appropriate primary prophylactic G-CSF administration should address various aspects including successful identification of high risk patients, appropriate window for primary prophylaxis, duration of administration and concerns about any side effects or counter-indications.

1. Risk Identification:

Factors that increase the risk of neutropenia occurrence include older age, presence of comorbid conditions (especially those that impede the body's ability to maintain and excrete the chemotherapeutic agents like – renal disease, live disease, bone marrow disease), more advanced cancer stage, previous anemia, abnormal leukocyte counts, recent infection and chemotherapy characteristics (Chrischilles, 2002; Shayne, 2007; Lyman, 2003a; Weycker, 2006; Chen-Hardee, 2006; Brooks, 2003; Lyman, 2004; Chrischilles, 2005; Du 2002). Many of the comorbidities, and conditions like anemia and abnormal leukocyte counts are assessed by the providers using the latest blood tests. Since blood levels are not present in these data, the study could not verify if the providers were indeed using this information while deciding to administer primary prophylactic G-CSF. The study did establish that chemotherapy characteristics determined the administration of G-CSF. The providers use the clinical information to determine the intensity of the chemotherapy regimen and based on the risk of the chosen regimen they decide to administer prophylactic G-CSF.

In order to standardize the risk identification process ASCO guidelines should be more explicit and specific about comorbidities, blood tests and chemotherapy characteristics that increase the risk of neutropenia while making recommendations for administering prophylactic G-CSF. The guidelines state risk rates above which primary prophylaxis is recommended but do not explicitly state the clinical causes for these high-risk rates and the extent to which these causes affect the risk rates (ASCO, 2006). This ambiguity needs to be addressed. The guidelines do provide incidence rates for neutropenia with different chemotherapy regimen, which is probably why physicians decide G-CSF administration based on the regimen.

2. Appropriate window for primary prophylaxis:

This study establishes the benefits of primary prophylaxis administered within the first five days of the start of first course chemotherapy, i.e. within five days of the very first cycle. However, this study does not provide evidence for a broader definition of primary prophylactic G-CSF. According to the clinical definition, any administration after the start of chemotherapy but before the first incidence of neutropenia constitutes primary prophylaxis. Since neutropenia is an acute complication and can occur any time after a week of starting the chemotherapy, most providers suspecting a patient's higher susceptibility administer the drug within the first two to three days of starting chemotherapy. Sometimes, given the cost of the drug some providers might decide to wait for few days (or cycles) and administer the drug in case the blood counts worsen. For example if the patient had an Absolute Neutrophil Count (ANC) of 5000 cells/mm^3 before the start of chemotherapy and it dipped to 4000 cells/mm^3 after three cycles of the first course chemotherapy, the patient is still not neutropenic (normal ANC is 1500 to 8000 cells/mm^3 and neutropenia starts below 1500 cells/mm^3). If the provider starts the G-CSF soon after the third cycle, due to the drop in ANC, it will still be primary prophylaxis. This study does not account for such late but justifiable starts in primary prophylaxis.

On the other hand, it is important to emphasize that 50% of neutropenia cases occur soon after the first cycle, and the first occurrence significantly increases the likelihood of later occurrences (Chen-Hardee, 2006; Chrischilles, 2002; Armitage 1984; Gomez, 1998; Shayne, 2007; Timmer-Bonte, 2006). Thus the 5-day window following the first cycle for primary prophylactic G-CSF administration is an important time frame because administration during that time prevents the initial neutropenia after first cycle and reduces the probability of future neutropenia occurrences. ASCO recommends prophylactic administration within 24 to 72 hours of administration of chemotherapy but does not indicate if the patient should start receiving it with the very first cycle. Since primary prophylaxis started after 5 days is difficult to identify using claims data, it is hard to establish if an earlier start of primary prophylaxis is better than administrations at later dates/cycles in this study. However, an earlier start does seem to be beneficial in itself as per the findings in this study.

3. Duration of administration:

Given the findings in this study adequate administration of primary prophylactic G-CSF seems to be very important. Provider's awareness about the importance of duration and explicit guidelines about the duration are important to ensure consistent practices across all providers. ASCO guidelines recommend continuation of G-CSF until ANC returns to 2000 to 3000 cells/mm^3 but the guidelines do not state a minimum duration until which the drug should be administered. Thus, there is no guidance for primary prophylactic G-CSF administration where the ANC is normal at the start of the prophylactic administration.

A sensitivity analysis was done in this study to see if five or more days of administration was particularly beneficial in reducing neutropenia hospitalization compared to a different cut off for the duration – 7 or more days and 10 or more days. It was interesting to note both 7 or more days and 10 or more of administration did not have a statistically significant benefit in reducing neutropenia hospitalization rates, though there were some effects on improving adherence to systemic therapies.

This lack of effect probably suggests a diminishing return to increasing duration. If administering the drug for at least five days has better overall outcome in the population then it is important that ASCO recommend a minimum duration for G-CSF administration accordingly. More research with different cancers, age groups, and population subsets needs to be done in order to establish a scientifically valid minimum duration for primary prophylactic G-CSF administration in all cases.

4. Concerns about side effects:

Although none of the reported or hypothesized side effects have been scientifically evaluated through population based studies or clinical trials, long-term safety of G-CSF has not been established. The most common concern is occurrence of Acute Myeloid Leukemia or Myelodysplastic Syndrome (Hershman, 2007). Chemotherapy often causes mutation in blood cells at an early stage of their development. Typically, these mutated cells destroy themselves, but the G-CSF administration saves them from destruction, thereby leading to their developing into blood cancer cells. G-CSF also has some direct mutant effects on the blood cells. The National Surgical Adjuvant Breast and Bowel Project (NSABP) conducted a study by pooling data from six clinical trials in order to look at the possible occurrence of Acute Myeloid Leukemia or Myelodysplastic Syndrome due to G-CSF administration (Smith, 2003). Due to small sample sizes the study could not establish statistically significant correlations or causality but reported the findings as hypothesis generating. Another study using the SEER Medicare data reported statistically significant increase in the occurrence of Acute Myeloid Leukemia or Myelodysplastic Syndrome in patients receiving G-CSF, however causality could not be established.

Bone and muscle pain is another concern. Bone pain occurs due to rising pressure within bone marrow by increased granulocytes, edema within bone marrow by histamine release, and increased level of bradykinin due to the biochemical effect of G-CSF. Studies report the incidence to be about 1-5% in patients receiving G-CSF (Ogata, 2005; Kuderer, 2005). Most other symptoms are

related to the subcutaneous mode of administration of G-CSF leading to redness, irritation or other inflammatory symptoms of the injection.

The side effects are predominantly temporary discomforts and have very low incidence rates, and studies state that the benefits far outweigh these side effects (Hershman, 2007). However, these possible risks could deter some providers from using the drug. It is important that the ASCO guidelines explicitly outline the nature and incidents of these side effects in light of the benefits in order to alleviate any concerns about the use of this drug.

5.8.2 Implications for Payers and Medicare Policies

1. Implications for cost:

Cost effectiveness has not been unambiguously established for primary prophylactic G-CSF, and some studies show that any cost reduction due to reduction in neutropenia hospitalization are often offset by the initial cost of G-CSF administration (Dranitsaris, 1995; Bassan, 1997). However, these studies do not account for quality of life issues associated with reduction of neutropenia complications and indirect costs to the patient and family due to hospitalizations and neutropenia management.

The cost of G-CSF administration is not trivial. Each shot costs $250. Since one course of primary prophylaxis is administered for 5 to 10 days, a course costs $1,250 to $2,500. If G-CSF is administered after every cycle in the first course chemotherapy, and the first course has 4 to 12 cycles on an average, the costs could range from $5,000 to $30,000. This is almost the same as the cost of the first course chemotherapy itself. In this study neutropenia hospitalization costs are lower for patients receiving G-CSF but the difference is not statistically significant. Overall costs are

significantly higher for patients receiving G-CSF, hence cost saving is not apparent in this study and primary prophylaxis is justifiable only on the basis of clinical and therapeutic benefits.

2. Implications for coverage:

This study found adequate primary prophylactic G-CSF administration to be vital for improving the clinical benefits. The stipulations associated with Medicare coverage of G-CSF have a significant effect on the duration of G-CSF administration. Medicare only covers G-CSF administration if the drug is administered in the physician's office. Since the drug is very expensive if bought out-of-pocket for self-administration, and traveling to the physician's office everyday for a week or more might not be feasible for all patients, many patients find it hard to comply with the adequate duration. Expanding coverage to include self-administration as long as it is approved by the physician is an important step to ensure adequate drug administration.

5.8.3 Implications for patients

1. Awareness about the importance of duration:

The decision to administer G-CSF is clearly the provider's decision, but adequate uptake of G-CSF is also determined by patient's ability to comply with the recommended duration. The study found that the determinants of duration of administration are more patient specific instead of factors like geographic location that are associated with provider beliefs in the region. It is important to ensure that patients understand the significance of duration and improve their compliance.

2. Awareness about side effects:

Side effects could deter patients from complying with the adequate administration of G-CSF. Patient awareness about the side effects, especially possible bone and muscle pain, and other effects associated with subcutaneous administration will help the patient be mentally prepared and avoid

unnecessary panic. It is also important to explain the low occurrence and easy medical management

of these symptoms and precautions the patients can take to avoid or alleviate these symptoms.

5.9 Limitations

1. Non-Random treatment assignment:

Providers decide whether or not to administer primary prophylactic G-CSF based on patient

characteristics, thus the treatment assignment is not random in this study and estimation of unbiased

treatment effect is not straightforward. The physician administers primary prophylactic G-CSF to

patients at a higher neutropenia risk, hence the baseline outcomes for patients receiving G-CSF are

different from the baseline outcomes for patients not receiving G-CSF. This issue is partially

addressed by controlling for patient clinical characteristics and using a matching technique to reduce

bias. This technique, however, does not account for unobserved differences in patients who receive

G-CSF versus who don't.

2. Narrow primary prophylactic G-CSF window

Since G-CSF is administered both as prophylactic and therapeutic drug for neutropenia, it is

hard to distinguish using claims data if the G-CSF was administered prophylactically or in response

to some neutropenia symptom. In order to prevent misclassification of therapeutic use of G-CSF as

prophylaxis, we have restricted the primary prophylactic G-CSF administration window to just 5 days

after the first chemotherapy administration similar to other claims based studies (Weycker 2006;

Chrischilles, 2002). The sample size issues and small post-matching sample were due to the low

number of patients receiving primary prophylaxis within the first 5 days of the start of chemotherapy.

A descriptive analysis was done to look at the number of women receiving G-CSF at different

time periods after the start of chemotherapy. 475 (476 on including rural Georgia) women received

G-CSF within a week of the start of chemotherapy compared to 337 (none in rural Georgia) women who received it within the first five days. 1699 (1700 on including rural Georgia) women receive G-CSF within the first month after start of chemotherapy, 2719 (2723 on including rural Georgia) women receive it within three months and 3066 (3072 on including rural Georgia) women receive it within six months of the start of chemotherapy. Increasing the window after the start of chemotherapy considerably increases the number of patients receiving any G-CSF. Some of these administrations could be primary prophylactic and might have been misclassified due to the restrictive 5-day window. This leads to the estimation of the treatment effects of primary prophylaxis to be biased towards zero, thus the estimates would be more conservative than in the actual population.

The effects of primary prophylaxis administered during the 5 day window is however important to look at because 50% of neutropenia occur soon after the first cycle and the first occurrence significantly increases the later occurrences (Chen-Hardee, 2006; Chrischilles, 2002; Armitage 1984; Gomez, 1998; Shayne, 2007; Timmer-Bonte, 2006). The prophylaxis administered during the first five days of chemotherapy initiation prevents the initial neutropenia after first cycle and reduces the probability of future neutropenia occurrences.

3. Inability to estimate chemotherapy dose intensity:

Dose of chemotherapy cannot be observed in the claims data. Dose intensity of chemotherapy (amount of dose and frequency of the cycle) is the direct determinant of neutropenia risk (Shayne, 2007), but could not be controlled for in this study. This is partially addressed by controlling for the type and number of drugs administered in the first cycle, and the duration between the first and the second cycle.

4. External validity issues

Matching helps compare treated patients (receiving G-CSF) with untreated patients closest in their socio-demographic and clinical characteristics and helps reduce model dependence and baseline differences in observed characteristics. In this analysis many untreated observations were dropped due to the small size of the treated group and the inability to find an appropriate treated match for each of the untreated patients. This does not compromise the power of the study as there is very little improvement in power if the untreated group is increased keeping the treated group constant. Dropping these observations might reduce the generalizability of the study. However, it is important to understand that the untreated observations that were dropped do not have treated observations to compare against. Hence using them to estimate treatment effects requires extrapolating treated observations in areas were the common support is lacking, thus leading to model dependence. Any lose in generalizability due to dropping unmatched untreated observations is a limitation of the data and not the matching technique. It is also important to note that there were no covariate (observed variable) categories which were eliminated from the analysis (except rural Georgia) due to discarding observations while matching.

5.10 Future research and next steps

Future research is required to explore some areas which could not be examined in this study, and also to further corroborate the findings in this study:

1. Analysis with the more recent SEER-Medicare data with patients diagnosed after 2002:

Examining some of the trends revealed in this study using the more recent SEER Medicare data will be interesting. Since G-CSF has been around for a while it will be interesting to see if unexplained regional disparities reduce with time. Regional trends with time were examined in this data and it was observed that primary prophylactic administration rates were increasing with time in

all regions, but regional disparities existed even in the later years. However, due to the small number of patients receiving primary prophylactic G-CSF (337) in this sample, regional trends with time could not be statistically evaluated.

Addition of the recent SEER-Medicare data will provide more observations and statistical power to look at the effect of primary prophylactic G-CSF on neutropenia hospitalization length of stay and expenditures, and to examine the effects of duration of primary prophylactic G-CSF administration on these neutropenia related outcomes.

2. Evaluating the effects of primary prophylaxis in younger breast cancer patients:

It will be interesting to see if the beneficial effects of primary prophylactic G-CSF on neutropenia hospitalization rates and systemic treatment adherence exist in the younger population, as compared to the elderly patients, using the Market Scan data.

3. Evaluating the effects of primary prophylaxis in other cancer patients:

Since this study only looks at breast cancer patients receiving chemotherapy, it is important to assess these effects in other cancers requiring chemotherapy – like Pancreatic Cancer, Leukemia, and Non-Hodgkin's Lymphoma, in order to further contribute evidence towards the ASCO guidelines.

4. Comparing the effectiveness between different G-CSF drugs – Filgrastim versus Sargramostim:

Since Medicare patients predominately receive Filgrastim (86% in this analysis), and studies examining Sargramostim (used in VA patients) often reveal a lower effectiveness of G-CSF, it will be interesting to use VA claims to compare the effectiveness of Filgratsim with Sargramostim.

5. *Detailed cost-effectiveness study:*

This study could not establish any changes in cost due to administration of primary prophylactic G-CSF. However, a comprehensive cost study requires examination of all types of cost associated with neutropenia. It is also important to determine the perspective form which the cost analysis will be performed. This study evaluated costs from the payer's perspective and only looked at actual expenditure to Medicare. Given the quality of life, out of pocket and indirect cost issues involved with primary prophylaxis it is also important to conduct cost-effectiveness analyses from the patient's or societal perspective by incorporating direct, indirect and intangible costs to the subject.

6. *Analysis using other clinical data:*

One of the limitations of the study was the inability to control for relevant laboratory values used as markers by providers to decide the need for administration of primary prophylactic G-CSF (Blood cell counts, and markers for bone marrow, liver and renal functioning). Using clinical data that include these parameters might help develop better propensity models for determinants of G-CSF administration.

Chapter 6

Conclusion

Primary prophylactic G-CSF is aimed to prevent chemotherapy related toxicities and sustain

dose intensity in cancer patients requiring chemotherapy. This study looks at the effect of primary

prophylactic G-CSF in preventing neutropenia hospitalization, length of stay and expenditure

associated with neutropenia hospitalization, overall Medicare expenditures in the first year after start

of chemotherapy, and ability to administer adequate systemic therapies (chemotherapy and radiation

therapy) during the first course chemotherapy in elderly breast cancer women. The study also

examines the determinants of primary prophylactic G-CSF administration in these patients.

The study found that the key determinants of primary prophylactic G-CSF in the elderly

patients receiving chemotherapy were – Race, SEER region, Year of diagnosis/chemotherapy

initiation and Characteristics of the chemotherapy regimen. Unexplained and significant variations in

primary prophylactic G-CSF administration based on race and region are a concern. The study also

found that primary prophylactic G-CSF reduced the probability of neutropenia hospitalization and

improved the probability of adequate chemotherapy and radiation therapy provision during the first

course chemotherapy. Primary prophylactic G-CSF patients also had significantly higher overall

Medicare expenditures during the first year after the start of chemotherapy (which is the time when

bulk of the cancer related therapies are provided). The study also found that along with the

administration of primary prophylactic G-CSF the number of days G-CSF is administered was very

crucial for these outcomes. The study calls for changes in ASCO and Medicare policies and clear

guidelines for administration of primary prophylactic G-CSF and duration of G-CSF administration in the elderly.

TABLES

Table 1 Extent of disease spread and standard treatment protocol by breast cancer stage

Stage	Extent of disease spread	Standard Treatment Protocol
Stage 0	Carcinoma in situ. The precancerous stage with no tumor or disease spread.	• Observation with regular mammograms • In some cases surgery with or without radiation • In some adjuvant Hormonal therapy. • In some stand alone Hormonal therapy
Stage I	Tumor size < 2 cm, no axillary lymph nodes or other body parts involved.	• Surgery with or without radiation • Adjuvant Systemic Chemotherapy with or without Hormonal therapy • Adjuvant Radiation therapy • Adjuvant Hormonal therapy
Stage IIA	No tumor and axillary lymph nodes involved. Or Tumor size <2 cm and axillary lymph nodes involved. Or Tumor size 2-5 cm and no axillary lymph nodes involved.	• Surgery with or without radiation • Adjuvant Systemic Chemotherapy with or without Hormonal therapy • Adjuvant Radiation therapy • Adjuvant Hormonal therapy
Stage IIB	Tumor size 2-5 cm and axillary lymph nodes involved (< 4 axillary nodes) Or Tumor size > 5 cm and no axillary lymph nodes involved.	• Surgery with or without radiation • Adjuvant Systemic Chemotherapy with or without Hormonal therapy • Adjuvant Radiation therapy • Adjuvant Hormonal therapy
Stage IIIA	No tumor and cancer is found in the axillary lymph nodes that are attached to each other or to other structures. Or Tumor size 2-5 cm with 4 or more axillary nodes are attached to each other or to other structures Or Tumor size > 5 cm and axillary lymph nodes involved.	• Surgery with or without radiation • Adjuvant Systemic Chemotherapy with or without Hormonal therapy • Adjuvant Radiation therapy • Adjuvant Hormonal therapy
Stage IIIB	Tumor has penetrated chest wall or skin, and may have spread to < 10 (or no) axillary nodes	• Systemic chemotherapy • Systemic chemotherapy followed by surgery followed by radiation therapy followed by systemic chemotherapy
Stage IIIC	Any tumor size or no tumor with involvement of often more than 10 lymph nodes including the ones in the collarbone and neck, and internal breast lymph nodes.	• Surgery with or without radiation • Adjuvant Systemic Chemotherapy with or without Hormonal therapy • Adjuvant Radiation therapy • Adjuvant Hormonal therapy • In some cases just Systemic chemotherapy • In some cases Systemic chemotherapy followed by surgery followed by radiation therapy followed by systemic chemotherapy
Stage IV (metastasis)	The cancer has spread to other organs of the body, most often the bones, lungs, liver, or brain.	• Systemic chemotherapy • Systemic chemotherapy followed by surgery followed by radiation therapy followed by systemic chemotherapy

Table 2 Findings from previous research exploring the effects of G-CSF administration

	Study Reference	Type of tumor studied	Type of Study	Age Range	Treatment type	Outcome
1.	Oyama, 1990	Non-Hodgkin's Lymphoma	Clinical Trial	All Adults	Primary Prophylaxis – G-CSF	G-CSF reduced incidence and duration of neutropenia induced by intensive chemotherapy.
2.	Jost, 1990	Germ cell tumors	Clinical Trial	All Adults	Primary Prophylaxis – GM-CSF	GM-CSF resulted in a significant shortening of neutropenia and allowed for the timely administration of the subsequent cycle of chemotherapy.
3.	Crawford, 1991	Small Cell Lung Cancer	Clinical Trial	31-80	Primary Prophylaxis - Filgrastim	Reduces febrile neutropenia. No effect on infection-related mortality and early mortality.
4.	Pettengell, 1992	Non-Hodgkin's Lymphoma	Clinical Trial	16-71	Primary Prophylaxis – Filgrastim	Reduces febrile neutropenia. No effect on infection-related mortality and early mortality.
5.	Anderson, 1991	Small Cell Lung Cancer	Clinical Trial	All adults	Primary Prophylaxis – GM-CSF	GM-CSF prevents neutropenia.
6.	De Vries, 1991	Ovarian Cancer	Clinical Trial	31-66	Primary Prophylaxis – GM-CSF	GM-CSF reduces the severity of neutropenia and thrombocytopenia after chemotherapy
7.	Havemann, 1991	Small Cell Lung Cancer	Clinical Trial	All adults	Primary Prophylaxis – GM-CSF	GM-CSF does reduce neutropenia but has no effect on response rates and survival.
8.	Kaplan, 1991	Non-Hodgkin's Lymphoma	Clinical Trial	Adults	Primary Prophylaxis – GM-CSF	GM-CSF lead to higher mean nadirs of the absolute neutrophil count, shorter mean durations of neutropenia, fewer chemotherapy cycles complicated by neutropenia and fever, fewer days hospitalized for fever and neutropenia, fewer reductions in chemotherapy dosages, and less frequent delays in

	Study Reference	Type of tumor studied	Type of Study	Age Range	Treatment type	Outcome
						chemotherapy administration.
9.	Kotake, 1991	Urogenital cancer	Clinical Trial	All adults	Primary Prophylaxis – G-CSF	G-CSF reduces incidence of neutropenia, duration of neutropenia and accelerates recovery, and enables an increase in the dose of chemotherapy.
10.	Liberati, 1991	Non-Hodgkin's Lymphoma	Clinical Trial	Adults	Primary Prophylaxis – GM-CSF	GM-CSF improved neutrophil count after chemotherapy administration, but had side effects.
11.	Trillet-Lenior, 1993	Small Cell Lung Cancer	Clinical Trial	Unknown	Primary Prophylaxis - Filgrastim	Reduces febrile neutropenia. No effect on infection-related mortality and early mortality.
12.	Lyman, 1993	Any malignancy	Simulation – Decision Analysis (probabilities based on Crawford, 1991 study)	NA	Primary Prophylaxis and Therapeutic-Filgrastim	Reduces cost of hospitalization if used prophylactically. Cost effective only if risk of neutropenic fever is higher than 40% for the administered chemotherapy regimen. Therapeutic use is not cost effective.
13.	Glaspy, 1993	Small Cell Lung Cancer	Clinical Trial	All Adults	Primary Prophylaxis – Filgrastim	Filgrastim had significantly fewer and less resource-intensive hospitalizations. Filgrastim minimized the total charges, costs and Medicare payments.
14.	Gerhartz, 1993	Non-Hodgkin's Lymphoma	Clinical Trial	All Adults	Primary Prophylaxis – GM-CSF	GM-CSF reduced neutropenia, days with fever and days of hospitalization for infection, and improved chemotherapy response.
15.	Kaku, 1993	Non-Hodgkin's Lymphoma	Clinical Trial	All Adults	Secondary Prophylaxis – GM-CSF	GM-CSF prevented neutropenia, increased granulocyte count and reduced the duration of low granulocyte

	Study Reference	Type of tumor studied	Type of Study	Age Range	Treatment type	Outcome
						counts.
16.	Shaffer, 1993	Advanced Malignancies	Clinical Trial	All Adults	Primary Prophylaxis – GM-CSF	GM-CSF had no effect on neutropenia or dose intensity improvement.
17.	Gebbia, 1993	Any advanced solid tumor	Clinical Trial	38-66	Primary Prophylaxis - Lenograstim	Reduces febrile neutropenia.
18.	Gebbia, 1994	Any advanced solid tumor	Clinical Trial	40-75	Primary Prophylaxis – Lenograstim	Reduces febrile neutropenia.
19.	Zagonel, 1994	Non-Hodgkin's Lymphoma	Pilot Study	60-70	Primary Prophylaxis - G-CSF	G-CSF sustains chemotherapy administration, reduces hospitalization days, severe infections and mucositis, and overall treatment costs of cancer patients on chemotherapy.
20.	Aviles, 1994	Diffuse large cell lymphoma	Clinical Trial		Primary Prophylaxis - G-CSF	G-CSF kept leukocyte and granulocyte count higher, total number of days of leukopenia shorter, delays in treatment and infection episodes less frequent. Complete response was better in patients who received G-CSF.
21.	Ardizzoni, 1994	Breast Cancer	Clinical Trial	Adult	Primary Prophylaxis - GM-CSF	G-CSF helps increase chemotherapy dose intensity
22.	Eguchi, 1994	Non-small-cell lung cancer	Clinical Trial	≤ 76	Secondary prophylaxis – GM-CSF	GM-CSF reduced the duration of chemotherapy-induced granulocytopenia
23.	Eguchi, 1994	Small-cell lung cancer	Clinical Trial	All adults	Primary Prophylaxis – G-CSF	G-CSF reduced the incidence of neutropenia.
24.	Engelhard, 1994	Non-Hodgkin's Lymphoma	Clinical Trial	18-73	Primary Prophylaxis – GM-CSF	GM-CSF significantly reduced the length and nadir of neutropenia, the length of fever episodes, the frequency of all and of severe infections, and of hospitalization and antibiotic requirements. There was no effect on response rate and overall survival

	Study Reference	Type of tumor studied	Type of Study	Age Range	Treatment type	Outcome
						between the GM-CSF treatment and control groups. GM-CSF helped maintain chemotherapy dose intensity.
25.	Hamm, 1994	Small-cell lung cancer	Clinical Trial	All adults	Primary Prophylaxis – GM-CSF	GM-CSF reduces chemotherapy-associated neutropenia
26.	Maher, 1994	Cancer other than myeloid leukemia	Clinical Trial	Adults >15 years	Therapeutic G-CSF – Filgratsim	Filgrastim accelerated neutrophil recovery, shortened the duration of febrile neutropenia and shortened length of stay for neutropenia hospitalization.
27.	Miles, 1994	Small-cell lung cancer	Clinical Trial	All adults	Primary Prophylaxis – G-CSF	G-CSF significantly decreased dose reductions due to neutropenia
28.	Rampling, 1994	Intracerebral malignant glioma	Clinical Trial	Adults	Primary Prophylaxis – GM-CSF	GM-CSF reduced neutropenia occurrence and increased neutrophil count.
29.	Rowe, 1995	Acute Myelogenous Leukemia	Clinical Trial	55-70	GM-CSF	Reduces the duration of neutropenia and therapy-related mortality and morbidity
30.	Dranitsaris, 1995	Hodgkin's and Non-Hodgkin's Lymphoma	Analysis of retrospective chart review	All Adults	Primary Prophylaxis – G-CSF	G-CSF use lead to fewer hospital days but the total net cost/patient was similar with and without G-CSF, such that the initial G-CSF expenditure is offset by reduced hospitalization.
31.	Stone, 1995	Acute myelogenous leukemia	Clinical Trial	≥ 65	Primary and Secondary Prophylaxis GM-CSF	GM-CSF did not seem to improve treatment-related mortality rate or the rate of remission, though it did reduce number of neutropenia days.
32.	Chevallier, 1995	Inflammatory Breast Cancer	Clinical Trial	23-65	Primary Prophylaxis – Lenograstim	No effect on febrile neutropenia infection-related mortality and early mortality.
33.	Bui, 1995	Soft Tissue	Clinical Trial	21-69	Primary	Reduces febrile

	Study Reference	Type of tumor studied	Type of Study	Age Range	Treatment type	Outcome
		Sarcoma			Prophylaxis – Lenograstim	neutropenia. No effect on infection-related mortality and early mortality.
34.	Bajorin, 1995	Germ cell tumors	Clinical Trial	Adults	Primary Prophylaxis – GM-CSF	GM-CSF reduced the incidence of infections in the first cycle of chemotherapy, but no benefit beyond the initial chemotherapy cycle was evident.
35.	Bergmann, 1995	Non-Hodgkin's Lymphoma	Clinical Trial	All adults	Primary Prophylaxis – GM-CSF	The analyses revealed a significant reduction of neutropenia and duration of neutropenia in the GM-CSF group.
36.	Bunn, 1995	Limited-stage small-cell lung cancer	Clinical Trial	All adults	Primary Prophylaxis – GM-CSF	GM-CSF administration 'increased' the frequency and duration of life-threatening thrombocytopenia, toxic deaths, nonhematologic toxicities, days in hospital, incidence of intravenous antibiotic use, and transfusions. GM-CSF increased post-chemotherapy WBC and neutrophil counts, but had no effect on the frequency of grade 4 leukopenia or neutropenia. GM-CSF had no effect on survival and response rate.
37.	Chi, 1995	Head and neck cancer	Clinical Trial	Adults	Primary Prophylaxis – GM-CSF	GM-CSF can significantly reduce the severity and duration of chemotherapy-induced oral mucositis.
38.	Hansen, 1995	Breast Cancer	Clinical Trial	Adult	Primary Prophylaxis – GM-CSF	GM-CSF reduced granulocyte nadir duration and severity. No difference in frequency of neutropenic fever or antibiotic use. GM-

	Study Reference	Type of tumor studied	Type of Study	Age Range	Treatment type	Outcome
						CSF improved dose intensity and response to chemotherapy.
39.	Katano, 1995	Breast Cancer	Clinical Trial	Adult	Primary and Secondary Prophylaxis – G-CSF	G-CSF can effectively treat and prevent chemotherapy-induced oral mucositis
40.	Logothetis, 1995	Urothelial tumor	Clinical Trial	All Adults	Primary Prophylaxis – GM-CSF	GM-CSF did not effect the dose-intensity or incidence of infection.
41.	Seymour, 1995	Solid cancer or lymphoma	Clinical Trial	All Adults	Primary Prophylaxis – Lenograstim	Dose strength of lenograstim had a significant effect on the duration of neutropenia, the absolute neutrophil count and the time to ANC nadir
42.	Woll, 1995	Small Cell Lung Cancer	Clinical Trial	All Adults	Primary Prophylaxis – Lenograstim	WBC and neutrophil counts were higher in G-CSF patients than in the control group. No significant differences in the incidence of febrile neutropenia, antibiotic or transfusion requirements, or days in hospital. G-CSF helped increase dose intensity and improve 2-year survival.
43.	Weiss, 1996	Advanced Malignancy	Clinical Trial	≥ 18	Primary Prophylaxis – GM-CSF	GM-CSF provides no clinically useful improvement in granulocyte tolerance of therapy
44.	Yau, 1996	Lymphoma or breast carcinoma	Clinical Trial	Adults	Primary Prophylaxis – GM-CSF	GM-CSF significantly shortens the duration of neutropenia and readmission only during the first course
45.	Uyl-de Groot, 1996	Any malignancy	Markov Model	All adults	Primary Prophylaxis and Therapeutic - Any G-CSF	Both prophylactic and therapeutic G-CSF are cost minimizing. Prophylactic G-CSF is cost minimizing only if the chemotherapy administered has a neutropenic fever risk higher than 50%.
46.	Muhonen,	Metastasis	Clinical Trial	34-65	Primary	Reduces occurrence of

	Study Reference	Type of tumor studied	Type of Study	Age Range	Treatment type	Outcome
	1996	Breast Cancer			Prophylaxis - Filgrastim	neutropenia.
47.	Webster, 1996	Breast Cancer	Pilot study	All Adults	Secondary Prophylactic G-CSF	Sustains pre-planned full dose intensity of chemotherapy, and reduces chemotherapy delays and dose reductions.
48.	Jones, 1996	Breast Cancer	Clinical Trial	Adults	Primary Prophylaxis – Sargramostim	GM-CSF significantly enhanced ANC recovery after FAC chemotherapy; it decreased the incidence and duration of associated neutropenia and moderately increased the dose-intensity of adjuvant chemotherapy.
49.	Paterakis, 1996	Non small-cell lung cancer, small-cell lung cancer, ovarian and breast cancer	Clinical Trial	All Adults	Primary Prophylaxis – GM-CSF	Positive effect of GM-CSF on the erythroid tissue of patients receiving chemotherapy for solid tumors.
50.	Zinzani, 1997	Non-Hodgkin's Lymphoma	Clinical Trial	60-82	Primary Prophylaxis - Filgrastim	Reduces febrile neutropenia. No effect on infection-related mortality and early mortality.
51.	Heil, 1997	Acute Myeloid Leukemia	Clinical Trial	≥ 16	Primary Prophylaxis - Filgrastim	Filgrastim reduces the duration of neutropenia, duration of fever, parenteral antibiotic use, and hospitalization. It also helps in sustaining dose intensity.
52.	Gisselbrecht, 1997	Non-Hodgkin's Lymphoma	Clinical Trial	15-55	Primary Prophylaxis - Lenograstim	Reduces febrile neutropenia. No effect on infection-related mortality and early mortality.
53.	Moore, 1997	Acute Myeloid Leukemia	Clinical Trial	Adults <60	Primary Prophylaxis and Therapeutic - G-CSF	Reduces duration of granulocytopenia, need for hospitalization, duration of hospitalization, and

	Study Reference	Type of tumor studied	Type of Study	Age Range	Treatment type	Outcome
						duration of thrombocytopenia
54.	Ganser, 1997	Acute Myeloid Leukemia	Literature review	Adults	Any G-CSF	Reduces duration of neutropenia. Ambiguous effect on complete remission rates, event-free survival, and overall survival
55.	Bassan, 1997	Acute lymphoblastic leukemia	Clinical Trial	Adults	Primary Prophylaxis - Filgrastim	G-CSF limited the incidence of severe neutropenia and related complications. Though costs were high in the G-CSF group chiefly due to the cost of Filgrastim itself.
56.	Fridrik, 1997	Non-Hodgkin's Lymphoma	Clinical Trial	18-75	Primary Prophylaxis - Filgrastim	Filgrastim helped sustain dose intensity but did not affect febrile neutropenia rates.
57.	Fukuoka, 1997	Small-cell lung cancer	Clinical Trial	All Adults	Primary Prophylaxis - G-CSF	G-CSF helped dose intensity increase.
58.	Fossa, 1998	Germ Cell Tumor	Clinical Trial	15-65	Primary Prophylaxis - Filgrastim	Reduces febrile neutropenia and early mortality. No effect on infection-related mortality.
59.	Lyman, 1998	Any malignancy	Decision analysis model	All adults	Primary Prophylaxis - Any G-CSF	G-CSF is cost effective only if risk of neutropenic fever is higher than 20% for the administered chemotherapy.
60.	Dunlop, 1998	Hodgkin's disease	Clinical Trial	Adults	Primary Prophylaxis – Filgrastim	Filgrastim reduced the median duration of leucopenia, but had no effect on days of hospitalization, admissions for infectious complications, duration, grade and incidence of infections and incidence of febrile neutropenia.
61.	Feng, 1998	Any malignancy	Clinical Trial	Adults	Primary Prophylaxis – GM-CSF	Prevented neutropenia and shortened the duration of

	Study Reference	Type of tumor studied	Type of Study	Age Range	Treatment type	Outcome
					(leucomax)	neutropenia.
62.	Hidalgo, 1998	Ovarian Carcinoma	Clinical Trial	27-74	Primary Prophylaxis – G-CSF	Improved dose intensity increment and reduced occurrence of neutropenia.
63.	Steward, 1998	Small Cell Lung Cancer	Clinical Trial	38-75	Primary Prophylaxis – GM-CSF	GM-CSF did not reduce neutropenia related complications like febrile neutropenia. It did help increase dose intensity.
64.	Stoger, 1998	Breast Cancer	Clinical Trial	Adults	Primary Prophylaxis – GM-CSF	GM-CSF helped increase dose intensity.
65.	Gatzemeier, 2000	Small Cell Lung Cancer	Clinical Trial	39-75	Primary Prophylaxis – Lenograstim	No effect on infection-related mortality and early mortality.
66.	Pfreundschuh, 2001	Hodgkin's disease	Clinical Trial	18-60	Primary Prophylaxis – GM-CSF	GM-CSF helps increase dose intensity.
67.	Lyman, 2002	Any malignancy	Meta-Analysis	All adults	Primary Prophylaxis - Any G-CSF	Reduces risk of febrile neutropenia, infection, and infection related mortality. Sustain dose intensity.
68.	Chrischilles, 2002	Non-Hodgkin's Lymphoma	Primary data analysis	≥ 18	Primary and Secondary Prophylaxis – Agent not specified	G-CSF use reduced neutropenia hospitalization and duration of hospitalization
69.	Osby, 2002	Non-Hodgkin's Lymphoma	Clinical Trial	≥ 60	Primary Prophylaxis – G-CSF	G-CSF treatment efficiently accelerated granulocyte recovery following chemotherapy.
70.	Doorduijn, 2003	Non-Hodgkin's Lymphoma	Clinical Trial	65-90	Primary Prophylaxis - Filgrastim	No effect on febrile neutropenia, infection-related mortality and early mortality.
71.	Osby, 2003	Non-Hodgkin's Lymphoma	Clinical Trial	60-86	Primary Prophylaxis - Filgrastim	Reduces febrile neutropenia. No effect on early mortality.
72.	Chrischilles, 2003	Non-Hodgkin's Lymphoma	Secondary data analysis (SEER-Medicare)	≥ 65	Primary Prophylaxis - Filgrastim (duration)	Longer duration of Filgrastim administration reduces neutropenia hospitalization and increases time to hospitalization after chemotherapy.

	Study Reference	Type of tumor studied	Type of Study	Age Range	Treatment type	Outcome
73.	Scott, 2003	Non-Hodgkin's Lymphoma	Secondary data analysis	All adults	Primary and Secondary Prophylaxis - Filgrastim	Primary prophylaxis and longer duration ($\geq$7 days) secondary prophylaxis reduces the occurrence of febrile neutropenia
74.	Grigg, 2003	Non-Hodgkin's Lymphoma	Clinical Trial	≥ 60	Primary Prophylaxis - G-CSF	G-CSF reduced duration of severe neutropenia.
75.	Papaldo, 2003	Early stage breast cancer	Clinical Trial	Adults	Primary Prophylaxis - G-CSF	G-CSF does not improve disease free and overall survival.
76.	Weycker, 2004	Non-Hodgkin's Lymphoma	Secondary data analysis	All adults	Primary Prophylaxis - Any G-CSF	Reduces neutropenia hospitalization and infection-related hospitalization.
77.	Wang, 2004	Non-Hodgkin's Lymphoma	Clinical Trial	Adult	Primary Prophylaxis - G-CSF	Use of G-CSF prevents leukopenia.
78.	Kuderer, 2005	Non-myeloid malignancy	Meta-analysis	All adults	Primary Prophylaxis - Pegfilgrastim, Lenograstim and Filgrastim	G-CSF in general reduces febrile neutropenia, infection-related mortality and increases delivered dose intensity.
79.	Timmer-Bonte, 2005	Small Cell Lung Cancer	Clinical Trial	36-81	Primary Prophylaxis - Filgrastim	Reduces febrile neutropenia. No effect on infection-related mortality and early mortality.
80.	Vogel, 2005	Breast Cancer	Clinical Trial	21-88	Primary Prophylaxis - Pegfilgrastim	Reduces febrile neutropenia and early mortality. No effect on infection-related mortality.
81.	Weycker, 2006	Non-Hodgkin's Lymphoma, Breast Cancer, Lung Cancer	Secondary data analysis	≥ 18	Primary Prophylaxis - Filgrastim (duration)	Higher duration of Filgrastim administration reduced neutropenia and infection related hospitalizations.
82.	Shayne, 2006	Breast Cancer	Secondary data analysis	All adults	Primary Prophylaxis - Any G-CSF	G-CSF helps sustain chemotherapy dose intensity.
83.	Burton, 2006	Non-Hodgkin's Lymphoma	Clinical Trial	$\geq$60 years	Primary Prophylaxis – G-CSF	There was no significant difference in the recurrence-free or overall survival with the addition of G-CSF.
84.	Eldar-Lissai, 2007	Any solid tumor	Cost-Utility analysis	18-65	Primary Prophylaxis -	Pegfilgrastim was more cost-effective as

	Study Reference	Type of tumor studied	Type of Study	Age Range	Treatment type	Outcome
					Pegfilgrastim and Filgrastim	well as cost minimizing as compared to filgrastim and no therapy. Filgrastim is not cost-effective as compared to no treatment.
85.	Shayne, 2007	Any malignancy	Analysis of Prospectively collected data	≥ 70	Primary Prophylaxis - Any G-CSF	Use of G-CSF reduced the occurrence of Severe and Febrile Neutropenia.
86.	Kuderer, 2007	Any malignancy	Meta-analysis	All adults	Primary Prophylaxis - Pegfilgrastim, Lenograstim and Filgrastim	G-CSF in general reduces febrile neutropenia, infection-related mortality and early mortality. G-CSF improves chemotherapy dose intensity.
87.	Sung, 2007	Any malignancy	Meta-analysis	All adults	Primary, Secondary or Therapeutic use of any G-CSF agent	Prophylactic G-CSFs have little or no effect on mortality but decrease rates of infection in patients receiving cancer chemotherapy.

Table 3 2006 ASCO recommendation summary for the use of G-CSF

	Indication	Recommendation
1.	Primary prophylaxis	CSF are recommended when the risk of febrile neutropenia is in the range of 20% or higher based on the chemotherapy regimen. For patients requiring "dose-dense" regimens based on scientific evidence, CSF is required and recommended. Primary prophylaxis is recommended for the prevention of febrile neutropenia in patients who have a high risk of febrile neutropenia based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen.
2.	Primary prophylaxis: Special circumstances	Certain clinical factors predispose to increased complications from prolonged neutropenia, including: patient age $\geq$ 65 years; poor performance status; previous episodes of febrile neutropenia; extensive prior treatment including large radiation ports; administration of combined chemoradiotherapy; bone marrow involvement by tumor-producing cytopenias; poor nutritional status; the presence of open wounds or active infections; more advanced cancer, as well as other serious comorbidities. In such situations, primary prophylaxis with CSF is often appropriate, even with regimens with febrile neutropenia rates of < 20%.
3.	Secondary Prophylaxis	Secondary prophylaxis with CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative.
4.	Therapeutic use: Afebrile Neutropenia	CSF should not be routinely used for patients with neutropenia who are afebrile.
5.	Therapeutic use: Febrile Neutropenia	CSF should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSF should be considered in patients with fever and neutropenia who are at high-risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected prolonged (> 10 days) and profound (< 0.1 + 109/L) neutropenia, age $\geq$ 65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever.

Table 4 Variables used in the analysis and their source from the SEER-Medicare data

Variable Name	Source	Claims Codes	Time when observed
Independent variables			
Granulocyte Colony Stimulating Factor	Medicare Claims	J1440; J1441; J2505; J2820	Within the first five days of first course chemotherapy initiation.
Demographic characteristics			
Age at diagnosis	SEER and Medicare Enrollment Database		
Race/Ethnicity	SEER		
Marital Status	SEER		
Education	SEER (from census extraction)		
Income	SEER (from census extraction)		
Urban residence	SEER (from the area resource file extraction)		
Region	SEER		
Year of Diagnosis	SEER		
Clinical Characteristics			
Modified Charlson Charlson Index	Medicare Claims	Modified Charlson Charlson Index Algorithm (SEER Medicare website)	One year prior to initiation of first course chemotherapy
Presence of other cancers before	SEER		
History of infection one month before chemotherapy initiation	Medicare Claims	ICD-9-CM Diagnosis: 001.xx-139.xx; 320.xx; 321.xx; 323.0x-323.7x; 324.xx; 326.xx; 460.xx-466.xx; 480.xx-487.xx; 567.xx; 590.xx; 598.0x; 599.0x; 680.xx-686.xx; 790.7x-790.8x; V09.xx, 995.90-995.93	One year prior to initiation of first course chemotherapy

Variable Name	Source	Claims Codes	Time when observed
Patients on antibiotics one month before chemotherapy initiation	Medicare Claims	ICD-9-CM Procedure: 99.21; 99.22 CPT: 90788; 99556 HCPCS: C1024 C9019 C9001 C9227 G8012 G8366 G8367 Q0144 S0016 S0072 S0021 S0024 S0029 S0030 S0032 S0034 S0039 S0040 S0071 S0073 S0074 S0075 S0080 S0081 S0085 S0096 S0177 S5106 S5017 S9539 S9494 S9497 S9500 S9504 J0120 J0200 J0278 J0286 J0285 J0290 J0295 J0390 J0456 J0530 J0540 J0550 J0560 J0570 J0580 J0637 J0690 J0692 J0694 J0695 J0696 J0697 J0698 J0710 J0713 J0715 J0720 J0740 J0743 J0744 J0770 J1835 J1335 J1362 J1364 J1450 J1452 J1455 J1570 J1580 J1590 J1835 J1840 J1850 J1890 J1910 J1956 J2010 J2020 J2070 J2185 J2248 J2460 J2510 J2540 J2543 J2545 J2700 J2770 J3000 J3260 J3305 J3320 J3370 J3465 J7682 J7685 J7310 J7315 J7316	One year prior to initiation of first course chemotherapy
Recent hospitalization one month before chemotherapy initiation	Medicare Claims	Any Medpar hospitalization claim one month prior to chemotherapy initiation	One year prior to initiation of first course chemotherapy
Tumor Stage	SEER (AJCC staging)		
Tumor size	SEER		
Tumor Grade	SEER		
Node +	SEER		
ER status	SEER		
PR status	SEER		
Procedures Performed			
Surgery	SEER and Medicare claims	ICD-9-CM Diagnosis: V4571; V5041; V524; V4382 ICD-9-CM Procedure: 85.20-85.29; 85.33-85.39; 85.40-85.49; 85.50-85.59; 85.70-85.79; 85.82-85.85; 85.87; 85.90-85.99 CPT: 19110-19126; 19160-19162; 19180-19272; 00404-00406; 19340-19350; 19357-19396; 00402 HCPCS: S2066-S2068	One indicator for surgery after diagnosis but before initiation of first course chemotherapy; Another indicator for surgery after initiation of first course chemotherapy and before the end of first course chemotherapy

Variable Name	Source	Claims Codes	Time when observed
Lymph node dissection	SEER and Medicare claims	CPT: 38500-38999 ICD-9-CM Procedure: 40.20-40.99	One indicator for dissection after diagnosis but before initiation of first course chemotherapy; Another indicator for dissection after initiation of first course chemotherapy and before the end of first course chemotherapy
Radiation Therapy	SEER and Medicare claims	ICD-9-CM Diagnosis: V58.00- V58.09; V66.1; V67.1 ICD-9-CM Procedure: 92.20-92.29 CPT: 01922; 76950; 76960; 76965; 77400-77499; 77520-77525; 77750-77799; 77261-77299; 77300-77399 HCPCS: A4650; C9714-C9715; C9726; C9728; S8049 Center: 0255; 0330; 0333; 0339; 0371 DRG: 409	Radiation after diagnosis but before initiation of first course chemotherapy
Type of chemotherapy regimen in first cycle – Anthracycline	Medicare Claims	HCPCS: J9000; J9001; C9415; C1167; J9178; J9180; J9150; J9151; C9424; J9211; C9429; J9293	Administration of Anthracycline in the first cycle
Number of Drugs in first cycle	Medicare Claims	HCPCS: J9000 J9001 C9415 C1167 J9178 J9180 J9150 J9151 C9424 J9211 C9429 J9293 J8530 J9070 J9080 J9090 J9091 J9092 J9093 J9094 J9095 J9096 J9097 C9420 C9421 J8610 J9250 J9260 J9170 J9190 J9264 J9265 C9127 C9431 S1016 J9355 J8520 J8521C1084 J9160 C1086 J8700 C1166 J9098 J9100 J9110 C1178 J8510 C9017 S0178 C9004 J9300 C9110 J9010 J0207 J0640 J3570 J8600 J9245 J9015 J9017 J8560 J9181 J9182 J9020 J9025 J9027 J9031 J9035 J9040 J9041 J9045 J9050 J9055 J9060 J9062 J9065 J9120 J9130 J9140 J9165 J9185 J9200 J9201 J9202 J9208 J9209 J9212 J9213 J9214 J9215 J9216 J9217 J9218 J9219 J9225 J9226 J9230 J9261 J9263 J9266 J9268 J9270 J9280 J9290 J9291 J9303 J9305 J9310 J9320 J9340 J9350 J9357 J9360 J9370 J9375 J9380 J9390 J9395 J9600 Q2017 S0088 S0172 S0179 S0182	The different drugs administered in the first cycle
Duration between first and second cycle	Medicare Claims		

Variable Name	Source	Claims Codes	Time when observed
Dependent Variables			
Neutropenia / Neutropenia Hospitalization	Medicare Claims	ICD-9-CM Diagnosis: 288.0x	Three indicators for the first hospitalization – one month after initiation of chemotherapy; three months after initiation of chemotherapy; six months after initiation of chemotherapy;
Neutropenia Hospitalization – Length of Stay	Medicare Claims	Length of Stay associated with a 288.0x	
Neutropenia Hospitalization - Expenditure	Medicare Claims	Expenditure associated with a 288.0x	
Overall Expenditure	Medicare Claims		Any expenditures after initiation of chemotherapy – within one month; within three months; within six months
Any Infection	Medicare Claims	ICD-9-CM Diagnosis: 001.xx-139.xx; 320.xx; 321.xx; 323.0x-323.7x; 324.xx; 326.xx; 460.xx-466.xx; 480.xx-487.xx; 567.xx; 590.xx; 598.0x; 599.0x; 680.xx-686.xx; 790.7x-790.8x; V09.xx, 995.90-995.93	Any infection after initiation of chemotherapy – within one month; within three months; within six months
Radiation therapy during the first course treatment period	SEER and Medicare claims	ICD-9-CM Diagnosis: V58.00-V58.09; V66.1; V67.1 ICD-9-CM Procedure: 92.20-92.29 CPT: 01922; 76950; 76960; 76965; 77400-77499; 77520-77525; 77750- 77799; 77261-77299; 77300-77399 HCPCS: A4650; C9714-C9715; C9726; C9728; S8049 Center: 0255; 0330; 0333; 0339; 0371 DRG: 409	Any radiation after initiation of first course chemotherapy, until the end of the first course.
Number of cycles in first course chemotherapy	Medicare Claims	ICD-9-CM Diagnosis: V58.1x ICD-9-CM Procedure: 99.25 CPT: 96400-96549; 99555 HCPCS: J9000-J9999; J8520; J8521; J8530; J8610; J8999; C9127; C9415; C9420; C9421; C9431; S1016; C8953-C8955; C8957; S9329-S9331; G0292; G0355; G0357-G0362; Q0083-Q0085 Center: 0331; 0332; 0335 Betos: O1D DRG: 410; 492	From chemotherapy initiation to end of first course

Variable Name	Source	Claims Codes	Time when observed
Other variables for inclusion and exclusion of observation			
Gender	SEER and Medicare Enrollment Database		
Enrollment in both part A and B; no enrollment in HMO	Medicare Enrollment Database		One year before and after diagnosis
End stage renal disease	Medicare Enrollment Database		Before and during the study period
Stem cell or bone marrow transplantation	Medicare Claims	ICD-9-CM Diagnosis: V42.81-V4-82 ICD-9-CM Procedure: 41.0x CPT: 38240-38242 HCPCS: S2150 Center: 362	

Table 5 Descriptive statistics for the independent variables in the analyses, by receipt and duration of receipt of primary prophylactic G-CSF

Variable name	Receipt of G-CSF		Duration of Receipt	
	No G-CSF (10104)	G-CSF (337)	G-CSF <5 days (151)	G-CSF >=5 days (186)
Socio-demographic characteristics				
Age at diagnosis	72.207*	71.712*	71.818	71.626
	(4.954)	(4.508)	(4.556)	(4.480)
White	0.852**	0.893**	0.854**	0.925**
	(0.355)	(0.309)	(0.354)	(0.265)
Married	0.507	0.516	0.517	0.516
	(0.500)	(0.500)	(0.501)	(0.501)
Education				
Proportion of adults with no high school diploma in the census tract	0.154	0.161	0.180**	0.145**
	(0.116)	(0.125)	(0.144)	(0.105)
Proportion of adults with only high school diploma in the census tract	0.237	0.240	0.237	0.242
	(0.101)	(0.102)	(0.107)	(0.098)
Proportion of adults with some college diploma in the census tract	0.244**	0.270**	0.258**	0.280**
	(0.090)	(0.096)	(0.109)	(0.083)
Proportion of adults with at least 4 years of college in the census tract	0.232	0.245	0.235	0.253
	(0.169)	(0.161)	(0.171)	(0.152)
Household income	46881.27	48246.40	46326.19	49805.28
	(23178.01)	(19704.64)	(20175.82)	(19227.14)
Urban/Rural Residence	0.983	0.994	0.987	1.000
	(0.128)	(0.077)	(0.115)	(0.000)
Seer site/ Region				
San Francisco	0.035**	0.074**	0.086	0.065
	(0.184)	(0.262)	(0.281)	(0.246)
Connecticut	0.084**	0.119**	0.113	0.124
	(0.278)	(0.324)	(0.317)	(0.330)
Detroit	0.134	0.107	0.093	0.118
	(0.340)	(0.309)	(0.291)	(0.324)
Hawaii	0.025**	0.006**	0.013	0.000
	(0.156)	(0.077)	(0.115)	(0.000)
Iowa	0.094**	0.036**	0.026	0.043
	(0.291)	(0.186)	(0.161)	(0.203)
New Mexico	0.028	0.015	0.020	0.011
	(0.165)	(0.121)	(0.140)	(0.103)
Seattle	0.073	0.050	0.060	0.043
	(0.261)	(0.219)	(0.238)	(0.203)
Utah	0.042**	0.021**	0.026	0.016
	(0.202)	(0.143)	(0.161)	(0.126)
Atlanta	0.048**	0.024**	0.026	0.022
	(0.214)	(0.152)	(0.161)	(0.145)
San Jose	0.027	0.021	0.033	0.011
	(0.163)	(0.143)	(0.180)	(0.103)
Los Angeles	0.104**	0.157**	0.132	0.177
	(0.306)	(0.365)	(0.340)	(0.383)
Greater California	0.110**	0.181**	0.166	0.194
	(0.313)	(0.386)	(0.373)	(0.396)

Variable name	Receipt of G-CSF		Duration of Receipt	
	No G-CSF (10104)	G-CSF (337)	G-CSF <5 days (151)	G-CSF >=5 days (186)
Kentucky	0.047** (0.211)	0.012** (0.108)	0.026** (0.161)	0.000** (0.000)
Louisiana	0.040** (0.197)	0.065** (0.247)	0.066 (0.250)	0.065 (0.246)
New Jersey	0.108 (0.311)	0.113 (0.317)	0.113 (0.317)	0.113 (0.317)
Diagnosis Year				
Year 1994	0.056** (0.230)	0.027** (0.161)	0.040 (0.196)	0.016 (0.126)
Year 1995	0.056 (0.230)	0.036 (0.186)	0.040 (0.196)	0.032 (0.177)
Year 1996	0.055* (0.227)	0.033* (0.178)	0.026 (0.161)	0.038 (0.191)
Year 1997	0.071* (0.256)	0.047* (0.213)	0.040 (0.196)	0.054 (0.226)
Year 1998	0.087* (0.281)	0.059* (0.237)	0.066 (0.250)	0.054 (0.226)
Year 1999	0.091 (0.287)	0.068 (0.253)	0.073 (0.261)	0.065 (0.246)
Year 2000	0.194 (0.396)	0.190 (0.393)	0.205 (0.405)	0.177 (0.383)
Year 2001	0.196** (0.397)	0.300** (0.459)	0.258 (0.439)	0.333 (0.473)
Year 2002	0.195** (0.396)	0.240** (0.428)	0.252 (0.435)	0.231 (0.423)
Clinical Characteristics				
Modified CCI	0.474 (0.833)	0.472 (0.824)	0.490 (0.832)	0.457 (0.819)
No other cancers before breast cancer	0.944 (0.230)	0.932 (0.253)	0.960* (0.196)	0.909* (0.289)
History of infection one month before chemotherapy initiation	0.108 (0.311)	0.131 (0.337)	0.086** (0.281)	0.167** (0.374)
Patients on antibiotics one month before chemotherapy initiation	0.031** (0.172)	0.053** (0.225)	0.073 (0.261)	0.038 (0.191)
Recent hospitalization one month before chemotherapy initiation	0.234 (0.424)	0.226 (0.419)	0.225 (0.419)	0.226 (0.419)
Tumor Characteristics				
Tumor Stage				
Stage 1	0.215 (0.411)	0.199 (0.400)	0.232 (0.423)	0.172 (0.378)
Stage 2	0.631 (0.483)	0.591 (0.492)	0.576 (0.496)	0.602 (0.491)
Stage 3	0.154** (0.361)	0.211** (0.408)	0.192 (0.395)	0.226 (0.419)
Tumor Size	64.317** (187.019)	85.217** (228.277)	60.238* (173.506)	105.495* (263.272)
Tumor Grade	0.456 (0.498)	0.430 (0.496)	0.457 (0.500)	0.409 (0.493)

Variable name	Receipt of G-CSF		Duration of Receipt	
	No G-CSF (10104)	G-CSF (337)	G-CSF <5 days (151)	G-CSF >=5 days (186)
Node +	0.600*	0.647*	0.596*	0.688*
	(0.490)	(0.479)	(0.492)	(0.464)
ER status	0.570	0.549	0.563	0.538
	(0.495)	(0.498)	(0.498)	(0.500)
PR status	0.459	0.451	0.457	0.446
	(0.498)	(0.498)	(0.500)	(0.498)
Procedures Performed				
Surgery				
Surgery before chemotherapy initiation	0.922	0.908	0.954**	0.871**
	(0.268)	(0.289)	(0.211)	(0.336)
Surgery after chemotherapy initiation	0.035**	0.059**	0.033*	0.081*
	(0.184)	(0.237)	(0.180)	(0.273)
Surgery time unknown	0.031	0.021	0.007*	0.032*
	(0.175)	(0.143)	(0.081)	(0.177)
Lymph node dissection before chemotherapy initiation	0.431	0.439	0.411	0.462
	(0.495)	(0.497)	(0.494)	(0.500)
Lymph node dissection after chemotherapy initiation	0.013	0.018	0.013	0.022
	(0.114)	(0.132)	(0.115)	(0.145)
Lymph node dissection time unknown	0.501	0.490	0.510	0.473
	(0.500)	(0.501)	(0.502)	(0.501)
Radiation before chemotherapy initiation	0.186	0.199	0.192	0.204
	(0.389)	(0.400)	(0.395)	(0.404)
Type of chemotherapy regimen in first cycle - Anthracycline	0.387**	0.706**	0.556**	0.828**
	(0.487)	(0.456)	(0.498)	(0.378)
Number of Drugs in first cycle	1.878	1.917	1.755**	2.048**
	(1.057)	(0.889)	(1.033)	(0.730)
Square of Number of Drugs in first cycle	4.645	4.463	4.139*	4.726*
	(3.412)	(2.921)	(3.143)	(2.708)
Duration between first and second	17.566	18.108	20.228**	16.387**
	(12.306)	(10.922)	(12.174)	(9.478)
Square of Duration between first and second	460.008	446.842	556.422**	357.882**
	(778.746)	(552.396)	(666.800)	(419.454)

Note: Standard Deviations in the parenthesis
　　　* Significance level α=0.10
　　　** Significance level α=0.05

Table 6 Regressions exploring primary prophylactic G-CSF administration and duration of primary prophylactic G-CSF administration

Variable name	Logistic regression for probability of G-CSF administration (10441)	Logistic regression for probability of adequate G-CSF administration (337)	Linear regression for duration of G-CSF administration (337)
Socio-demographic characteristics			
Age at diagnosis	3.680E-05	0.010	-0.039
	(0.013)	(0.032)	(0.068)
Race (White)	0.706**	0.348	-0.442
	(0.218)	(0.543)	(1.132)
Marital Status (Married)	0.026	-0.346	-0.076
	(0.117)	(0.290)	(0.609)
Education			
Proportion of adults with no high school diploma in the census tract	-0.274	-3.992*	0.093
	(1.160)	(2.332)	(4.837)
Proportion of adults with only high school diploma in the census tract	-2.120*	-0.207	4.136
	(1.288)	(2.604)	(5.522)
Proportion of adults with some college diploma in the census tract	1.160	0.346	-0.574
	(1.170)	(2.252)	(5.020)
Proportion of adults with at least 4 years of college in the census tract	-1.052	-1.494	3.412
	(1.065)	(2.006)	(4.496)
Household income	-1.01E-05**	0.000	0.000
	(4.200E-06)	(0.000)	(0.000)
Urban/Rural Residence	0.345	Dropped	5.231
	(0.737)		(4.279)
Seer Site/Region			
Connecticut	-0.188	0.773	1.023
	(0.284)	(0.671)	(1.405)
Detroit	-1.094**	0.145	0.199
	(0.284)	(0.670)	(1.454)
Hawaii	-1.847**	Dropped	-1.615
	(0.753)		(4.033)
Iowa	-1.926**	-0.096	-1.335
	(0.391)	(0.934)	(1.949)
New Mexico	-1.585**	-0.289	-0.761
	(0.512)	(1.209)	(2.637)
Seattle	-1.331**	-0.541	4.249**
	(0.338)	(0.804)	(1.715)
Utah	-1.954**	0.109	0.142
	(0.454)	(1.135)	(2.390)
Atlanta	-1.488**	-0.746	-2.196
	(0.422)	(1.145)	(2.256)
San Jose	-1.032**	-0.657	-0.018
	(0.445)	(1.183)	(2.380)
Los Angeles	-0.413	0.766	1.193
	(0.261)	(0.597)	(1.281)
Greater California	-0.987**	0.137	1.450
	(0.274)	(0.662)	(1.407)

Variable name	Logistic regression for probability of G-CSF administration (10441)	Logistic regression for probability of adequate G-CSF administration (337)	Linear regression for duration of G-CSF administration (337)
Kentucky	-2.669** (0.567)	Dropped	-2.287 (3.097)
Louisiana	-0.866** (0.340)	-0.114 (0.831)	-0.870 (1.711)
New Jersey	-0.787** (0.303)	-0.109 (0.742)	0.489 (1.570)
Diagnosis Year			
Year 1995	0.225 (0.452)	0.033 (1.104)	0.674 (2.380)
Year 1996	0.134 (0.462)	1.693 (1.245)	0.992 (2.505)
Year 1997	0.150 (0.429)	0.850 (1.098)	3.254 (2.353)
Year 1998	0.251 (0.415)	0.276 (1.027)	-1.646 (2.220)
Year 1999	0.206 (0.408)	0.253 (1.011)	-0.787 (2.228)
Year 2000	0.787* (0.490)	0.891 (1.087)	-1.184 (2.371)
Year 2001	1.224** (0.485)	1.247 (1.077)	-0.106 (2.354)
Year 2002	0.994** (0.488)	0.976 (1.063)	0.621 (2.321)
Clinical Characteristics			
Modified CCI	0.052 (0.073)	0.031 (0.171)	-0.356 (0.367)
No other cancers before breast cancer	-0.309 (0.230)	-1.326** (0.643)	-1.391 (1.173)
History of infection one month before chemotherapy initiation	0.203 (0.172)	0.819* (0.454)	0.522 (0.889)
Patients on antibiotics one month before chemotherapy initiation	0.330 (0.261)	-1.104* (0.603)	-3.434** (1.276)
Recent hospitalization one month before chemotherapy initiation	0.013 (0.140)	-0.231 (0.344)	-0.224 (0.721)
Tumor Characteristics			
Tumor Stage			
Stage 2	-0.287 (0.197)	0.030 (0.486)	-0.665 (1.022)
Stage 3	-0.017 (0.261)	0.144 (0.662)	-0.090 (1.385)
Tumor Size	1.060E-04 (3.153E-04)	0.001 (0.001)	0.001 (0.002)
Tumor Grade	-0.206* (0.120)	-0.447 (0.308)	-0.899 (0.664)
Node +	0.044	0.198	1.274

Variable name	Logistic regression for probability of G-CSF administration (10441)	Logistic regression for probability of adequate G-CSF administration (337)	Linear regression for duration of G-CSF administration (337)
	(0.167)	(0.407)	(0.873)
ER status	-0.252	-0.885*	-0.680
	(0.172)	(0.465)	(0.961)
PR status	0.140	0.547	0.719
	(0.169)	(0.463)	(0.941)
Procedures Performed			
Surgery			
Surgery before chemotherapy initiation	0.119	-1.158	-1.525
	(0.577)	(1.735)	(3.334)
Surgery after chemotherapy initiation	0.419	-0.646	-2.217
	(0.615)	(1.876)	(3.531)
Surgery time unknown	-0.437	0.430	2.227
	(0.679)	(1.976)	(3.636)
Lymph node dissection before chemotherapy initiation	-0.069	1.506*	1.021
	(0.297)	(0.861)	(1.644)
Lymph node dissection after chemotherapy initiation	-0.088	2.648	1.288
	(0.550)	(2.511)	(3.055)
Lymph node dissection time unknown	0.030	1.125	1.538
	(0.291)	(0.849)	(1.634)
Radiation before chemotherapy initiation	0.163	0.135	-0.811
	(0.146)	(0.368)	(0.764)
Type of chemotherapy regimen in first cycle - Anthracycline	1.553**	0.549	2.711**
	(0.166)	(0.452)	(0.967)
Number of Drugs in first cycle	-0.585**	1.384**	0.408
	(0.230)	(0.627)	(1.286)
Square of Number of Drugs in first cycle	0.121*	-0.280	-0.120
	(0.064)	(0.176)	(0.369)
Duration between first and second	-0.034**	-0.083**	-0.191**
	(0.013)	(0.039)	(0.071)
Square of Duration between first and second	3.479E-04*	0.001	0.002
	(1.868E-04)	(0.001)	(0.001)
Indicator for only one cycle in the first course	-1.561**	-1.087	-3.248
	(0.430)	(1.156)	(2.341)
Constant	-2.539	0.076	4.110
	(1.596)	(3.327)	(8.475)

Note: Standard Errors in the parenthesis
* Significance level α=0.10
** Significance level α=0.05

Table 7 Descriptive statistics for the main outcome variables in the analyses, by receipt and duration of receipt of primary prophylactic G-CSF

Variable name	No G-CSF (10104)	G-CSF (337)	G-CSF <5 days (151)	G-CSF >=5 days (186)
Neutropenia Hospitalization				
1 month	0.023**	0.045**	0.060*	0.032*
	(0.149)	(0.207)	(0.162)	(0.130)
3 month	0.054	0.059	0.073*	0.048*
	(0.226)	(0.237)	(0.134)	(0.136)
6 month	0.071	0.074	0.079	0.070
	(0.257)	(0.262)	(0.271)	(0.256)
Neutropenia Hospitalization – Length of Stay if hospitalized				
1 month	6.065	4.467	4.556	4.333
(245 Obs Before Matching)	(7.090)	(1.922)	(2.128)	(1.751)
3 month	5.645	4.500	4.364	4.667
(564 Obs Before Matching)	(5.387)	(1.850)	(1.963)	(1.803)
6 month	5.598	4.800	4.417	5.154
(744 Obs Before Matching)	(5.285)	(2.915)	(1.881)	(3.671)
Logarithm of Length of Stay - 1 month	1.484	1.410	1.423	1.390
(245 Obs Before Matching)	(0.738)	(0.437)	(0.459)	(0.442)
Logarithm of Length of Stay - 3 month	1.486	1.424	1.390	1.464
(564 Obs Before Matching)	(0.664)	(0.416)	(0.422)	(0.430)
Logarithm of Length of Stay - 6 month	1.489	1.441	1.408	1.472
(744 Obs Before Matching)	(0.652)	(0.491)	(0.408)	(0.572)
Neutropenia Hospitalization – Expenditure if hospitalized				
1 month	6855	5502	6318	4280
(245 Obs Before Matching)	(10590)	(2562)	(2648)	(2043)
3 month	5976	5761	6216	5204
(564 Obs Before Matching)	(7233)	(2410)	(2570)	(2214)
6 month	5875	5703	6101	5336
(744 Obs Before Matching)	(6484)	(2270)	(2483)	(2086)
Logarithm of Expenditure - 1 month	8.619	8.504	8.662	8.266
(245 Obs Before Matching)	(0.554)	(0.499)	(0.471)	(0.479)
Logarithm of Expenditure - 3 month	8.542	8.564	8.648	8.461
(564 Obs Before Matching)	(0.501)	(0.468)	(0.458)	(0.486)
Logarithm of Expenditure - 6 month	8.536	8.561	8.634	8.494
(744 Obs Before Matching)	(0.491)	(0.448)	(0.439)	(0.462)
Overall Expenditure				
1 year	17597**	30345**	26804**	3219**
	(17156)	(19927)	(20467)	(19052)
Logarithm of Expenditure – 1 year	9.418**	10.101**	9.902**	10.262**
	(0.926)	(0.754)	(0.886)	(0.580)
Systemic therapy				
Administration of radiation therapy during the first course of chemotherapy	0.147**	0.205**	0.205	0.204
	(0.354)	(0.404)	(0.405)	(0.404)
Number of Cycles in first course	8.831**	9.887**	8.775**	10.790**
	(6.579)	(7.445)	(7.841)	(6.999)
Number of chemotherapy cycles in first course > 5	0.188**	0.273**	0.232	0.306
	(0.390)	(0.446)	(0.423)	(0.462)

Note: Standard Deviations in the parenthesis
    * Significance level α=0.10
    ** Significance level α=0.05

Table 8 Descriptive statistics for the independent variables in the analyses, by receipt of primary prophylactic G-CSF, before and after matching

Variable name	Before Matching		After Matching	
	No G-CSF (10104)	G-CSF (337)	No G-CSF (1423)	G-CSF (337)
Socio-demographic characteristics				
Age at diagnosis	72.207*	71.712*	71.897	71.712
	(4.954)	(4.508)	(4.704)	(4.508)
White	0.852**	0.893**	0.863	0.893
	(0.355)	(0.309)	(0.344)	(0.309)
Married	0.507	0.516	0.521	0.516
	(0.500)	(0.500)	(0.500)	(0.500)
Education				
Proportion of adults with no high school diploma in the census tract	0.154	0.161	0.156	0.161
	(0.116)	(0.125)	(0.108)	(0.125)
Proportion of adults with only high school diploma in the census tract	0.237	0.240	0.243	0.240
	(0.101)	(0.102)	(0.095)	(0.102)
Proportion of adults with some college diploma in the census tract	0.244**	0.270**	0.265	0.270
	(0.090)	(0.096)	(0.089)	(0.096)
Proportion of adults with at least 4 years of college in the census tract	0.232	0.245	0.242	0.245
	(0.169)	(0.161)	(0.153)	(0.161)
Household income	46881.27	48246.40	48202.50	48246.40
	(23178.01)	(19704.64)	(20306.43)	(19704.64)
Urban/Rural Residence	0.983	0.994	0.996	0.994
	(0.128)	(0.077)	(0.059)	(0.077)
Seer site/ Region				
San Francisco	0.035**	0.074**	0.052	0.074
	(0.184)	(0.262)	(0.222)	(0.262)
Connecticut	0.084**	0.119**	0.113	0.119
	(0.278)	(0.324)	(0.317)	(0.324)
Detroit	0.134	0.107	0.111	0.107
	(0.340)	(0.309)	(0.314)	(0.309)
Hawaii	0.025**	0.006**	0.007	0.006
	(0.156)	(0.077)	(0.084)	(0.077)
Iowa	0.094**	0.036**	0.053	0.036
	(0.291)	(0.186)	(0.225)	(0.186)
New Mexico	0.028	0.015	0.013	0.015
	(0.165)	(0.121)	(0.115)	(0.121)
Seattle	0.073	0.050	0.053	0.050
	(0.261)	(0.219)	(0.225)	(0.219)
Utah	0.042**	0.021**	0.024	0.021
	(0.202)	(0.143)	(0.153)	(0.143)
Atlanta	0.048**	0.024**	0.027	0.024
	(0.214)	(0.152)	(0.161)	(0.152)
San Jose	0.027	0.021	0.025	0.021
	(0.163)	(0.143)	(0.155)	(0.143)
Los Angeles	0.104**	0.157**	0.153	0.157
	(0.306)	(0.365)	(0.360)	(0.365)
Greater California	0.110**	0.181**	0.181	0.181
	(0.313)	(0.386)	(0.385)	(0.386)
Kentucky	0.047**	0.012**	0.014	0.012
	(0.211)	(0.108)	(0.118)	(0.108)

Variable name	Before Matching		After Matching	
	No G-CSF (10104)	G-CSF (337)	No G-CSF (1423)	G-CSF (337)
Louisiana	0.040**	0.065**	0.061	0.065
	(0.197)	(0.247)	(0.240)	(0.247)
New Jersey	0.108	0.113	0.112	0.113
	(0.311)	(0.317)	(0.315)	(0.317)
Diagnosis Year				
Year 1994	0.056**	0.027**	0.041	0.027
	(0.230)	(0.161)	(0.198)	(0.161)
Year 1995	0.056	0.036	0.040	0.036
	(0.230)	(0.186)	(0.196)	(0.186)
Year 1996	0.055*	0.033*	0.018*	0.033*
	(0.227)	(0.178)	(0.131)	(0.178)
Year 1997	0.071*	0.047*	0.039	0.047
	(0.256)	(0.213)	(0.193)	(0.213)
Year 1998	0.087*	0.059*	0.058	0.059
	(0.281)	(0.237)	(0.233)	(0.237)
Year 1999	0.091	0.068	0.110**	0.068**
	(0.287)	(0.253)	(0.313)	(0.253)
Year 2000	0.194	0.190	0.195	0.190
	(0.396)	(0.393)	(0.397)	(0.393)
Year 2001	0.196**	0.300**	0.276	0.300
	(0.397)	(0.459)	(0.447)	(0.459)
Year 2002	0.195**	0.240**	0.223	0.240
	(0.396)	(0.428)	(0.417)	(0.428)
Clinical Characteristics				
Modified CCI	0.474	0.472	0.425	0.472
	(0.833)	(0.824)	(0.766)	(0.824)
No other cancers before breast cancer	0.944	0.932	0.963**	0.932**
	(0.230)	(0.253)	(0.189)	(0.253)
History of infection one month before chemotherapy initiation	0.108	0.131	0.092**	0.131**
	(0.311)	(0.337)	(0.289)	(0.337)
Patients on antibiotics one month before chemotherapy initiation	0.031**	0.053**	0.053	0.053
	(0.172)	(0.225)	(0.224)	(0.225)
Recent hospitalization one month before chemotherapy initiation	0.234	0.226	0.188	0.226
	(0.424)	(0.419)	(0.391)	(0.419)
Tumor Characteristics				
Tumor Stage				
Stage 1	0.215	0.199	0.193	0.199
	(0.411)	(0.400)	(0.395)	(0.400)
Stage 2	0.631	0.591	0.604	0.591
	(0.483)	(0.492)	(0.489)	(0.492)
Stage 3	0.154**	0.211**	0.203	0.211
	(0.361)	(0.408)	(0.402)	(0.408)
Tumor Size	64.317**	85.217**	73.558	85.217
	(187.019)	(228.277)	(204.874)	(228.277)
Tumor Grade	0.456	0.430	0.436	0.430
	(0.498)	(0.496)	(0.496)	(0.496)
Node +	0.600*	0.647*	0.663	0.647
	(0.490)	(0.479)	(0.473)	(0.479)

Variable name	Before Matching		After Matching	
	No G-CSF (10104)	**G-CSF (337)**	**No G-CSF (1423)**	**G-CSF (337)**
ER status	0.570	0.549	0.552	0.549
	(0.495)	(0.498)	(0.497)	(0.498)
PR status	0.459	0.451	0.453	0.451
	(0.498)	(0.498)	(0.498)	(0.498)
Procedures Performed				
Surgery				
Surgery before chemotherapy initiation	0.922	0.908	0.919	0.908
	(0.268)	(0.289)	(0.273)	(0.289)
Surgery after chemotherapy initiation	0.035**	0.059**	0.055	0.059
	(0.184)	(0.237)	(0.228)	(0.237)
Surgery time unknown	0.031	0.021	0.023	0.021
	(0.175)	(0.143)	(0.151)	(0.143)
Lymph node dissection before chemotherapy initiation	0.431	0.439	0.459	0.439
	(0.495)	(0.497)	(0.498)	(0.497)
Lymph node dissection after chemotherapy initiation	0.013	0.018	0.013	0.018
	(0.114)	(0.132)	(0.115)	(0.132)
Lymph node dissection time unknown	0.501	0.490	0.488	0.490
	(0.500)	(0.501)	(0.500)	(0.501)
Radiation before chemotherapy initiation	0.186	0.199	0.152**	0.199**
	(0.389)	(0.400)	(0.359)	(0.400)
Type of chemotherapy regimen in first cycle - Anthracycline	0.387**	0.706**	0.599**	0.706**
	(0.487)	(0.456)	(0.490)	(0.456)
Number of Drugs in first cycle	1.878	1.917	1.944	1.917
	(1.057)	(0.889)	(0.875)	(0.889)
Square of Number of Drugs in first cycle	4.645	4.463	4.543	4.463
	(3.412)	(2.921)	(2.856)	(2.921)
Duration between first and second	17.566	18.108	17.261	18.108
	(12.306)	(10.922)	(9.501)	(10.922)
Square of Duration between first and second	460.008	446.842	388.164**	446.842**
	(778.746)	(552.396)	(430.288)	(552.396)

Note: Standard Deviations in the parenthesis

* Significance level α=0.10

** Significance level α=0.05

Table 9 Descriptive statistics for the main outcome variables included, by receipt of primary prophylactic G-CSF, before and after matching

Variable name	No G-CSF (10104)	G-CSF (337)	No G-CSF (1423)	G-CSF (337)
Neutropenia Hospitalization				
1 month	0.023**	0.045**	0.023**	0.045**
	(0.149)	(0.207)	(0.151)	(0.207)
3 month	0.054	0.059	0.063	0.059
	(0.226)	(0.237)	(0.225)	(0.237)
6 month	0.071	0.074	0.078	0.074
	(0.257)	(0.262)	(0.248)	(0.262)
Neutropenia Hospitalization – Length of Stay if hospitalized				
1 month	6.065	4.467	7.545	4.467
(245 Obs Before Matching; 48 Obs After Matching)	(7.090)	(1.922)	(7.207)	(1.922)
3 month	5.645	4.500	6.342	4.500
(564 Obs Before Matching; 96 Obs After Matching)	(5.387)	(1.850)	(5.710)	(1.850)
6 month	5.598	4.800	5.957	4.800
(744 Obs Before Matching; 119 Obs After Matching)	(5.285)	(2.915)	(5.310)	(2.915)
Logarithm of Length of Stay - 1 month	1.484	1.410	1.754*	1.410*
(245 Obs Before Matching; 48 Obs After Matching)	(0.738)	(0.437)	(0.694)	(0.437)
Logarithm of Length of Stay - 3 month	1.486	1.424	1.592	1.424
(564 Obs Before Matching; 96 Obs After Matching)	(0.664)	(0.416)	(0.691)	(0.416)
Logarithm of Length of Stay - 6 month	1.489	1.441	1.534	1.441
(744 Obs Before Matching; 119 Obs After Matching)	(0.652)	(0.491)	(0.687)	(0.491)
Neutropenia Hospitalization – Expenditure if hospitalized				
1 month	6855.14	5502.40	7980.49*	5502.40*
(245 Obs Before Matching; 48 Obs After Matching)	(10590.41)	(2562.37)	(4568.20)	(2562.37)
3 month	5975.47	5760.90	6615.18	5760.90
(564 Obs Before Matching; 96 Obs After Matching)	(7232.51)	(2410.01)	(3964.96)	(2410.01)
6 month	5874.70	5702.80	6446.04	5702.80
(744 Obs Before Matching; 119 Obs After Matching)	(6483.62)	(2270.21)	(4141.91)	(2270.21)
Logarithm of Expenditure - 1 month	8.619	8.504	8.853**	8.504**
(245 Obs Before Matching; 48 Obs After Matching)	(0.554)	(0.499)	(0.513)	(0.499)
Logarithm of Expenditure - 3 month	8.542	8.563	8.651	8.564
(564 Obs Before Matching; 96 Obs After Matching)	(0.501)	(0.468)	(0.537)	(0.468)
Logarithm of Expenditure - 6 month	8.536	8.561	8.632	8.561
(744 Obs Before Matching; 119 Obs After Matching)	(0.491)	(0.447)	(0.535)	(0.448)
Overall Expenditure				
1 year	17596.50**	30344.69**	18851.18**	30344.69**
	(17155.56)	(19926.37)	(15703.82)	(19926.37)
Logarithm of Expenditure – 1 year	9.418**	10.101**	9.544**	10.101**
	(0.926)	(0.754)	(0.846)	(0.754)
Systemic therapy				
Administration of radiation therapy during the first course of chemotherapy	0.147**	0.205**	0.146**	0.205**
	(0.354)	(0.404)	(0.353)	(0.404)
Number of Cycles in first course	8.831**	9.887**	8.678**	9.887**
	(6.579)	(7.445)	(6.534)	(7.445)
Number of chemotherapy cycles in first course > 5	0.188**	0.273**	0.186**	0.273**
	(0.390)	(0.446)	(0.389)	(0.446)

Note: Standard Deviations in the parenthesis
* Significance level α=0.10
** Significance level α=0.05

Table 10 Effect of primary prophylactic G-CSF administration and duration of G-CSF administration on the key outcome variables

Variable name	Before Matching (10441)	After Matching (1760)	Effect of G-CSF duration (<5 days versus >=5 days) (337)	Effect of G-CSF duration with duration as a continuous variable (337)
Neutropenia Hospitalization				
1 month	0.684** (0.352)	0.366 (0.284)	-1.637* (0.826)	-0.171* (-0.095)
3 month	0.056 (0.278)	-0.181** (0.091)	-1.855** (0.892)	-0.217** (-0.084)
6 month	0.100 (0.251)	-0.200** (0.088)	-0.681* (0.308)	0.004 (0.067)
Neutropenia Hospitalization – Length of Stay if hospitalized				
Logarithm of Length of Stay – 1 month (245 Obs Before Matching; 48 Obs After Matching)	-0.018 (0.198)	NA	NA	NA
Logarithm of Length of Stay – 3 month (564 Obs Before Matching; 96 Obs After Matching)	-0.078 (0.150)	-0.140 (0.210)	NA	NA
Logarithm of Length of Stay – 6 month (744 Obs Before Matching; 119 Obs After Matching)	-0.049 (0.132)	-0.039 (0.181)	NA	NA
Neutropenia Hospitalization – Expenditure if hospitalized				
Logarithm of Expenditure - 1 month (245 Obs Before Matching; 48 Obs After Matching)	-0.246 (0.155)	NA	NA	NA
Logarithm of Expenditure - 3 month (564 Obs Before Matching; 96 Obs After Matching)	-0.106 (0.108)	-0.227 (0.187)	NA	NA
Logarithm of Expenditure - 6 month (744 Obs Before Matching; 119 Obs After Matching)	-0.073 (0.094)	-0.176 (0.142)	NA	NA
Overall Expenditure				
Logarithm – 1 year	0.408** (0.045)	0.454** (0.045)	0.179** (0.082)	0.017** (0.008)
Systemic Therapy				
Receipt of radiation therapy during the first course of chemotherapy	0.404** (0.152)	0.513** (0.177)	0.060** (0.025)	0.096** (0.041)
Number of Cycles in the first course > 5	0.300** (0.145)	0.419** (0.169)	0.094** (0.038)	0.168** (0.048)

Note: Standard Errors in the parenthesis
* Significance level $\alpha=0.10$
** Significance level $\alpha=0.05$

Table 11 Marginal effect of primary prophylactic G-CSF administration on the key outcome variables after matching

Variable name	Probability without primary prophylactic G-CSF administration	Probability with primary prophylactic G-CSF administration	Marginal Effects after Matching (1760)	Confidence Interval of Marginal Effects	Percentage change due to G-CSF administration
Neutropenia Hospitalization					
1 month	0.023 (0.021)	0.033 (0.029)	0.010 (0.008)	-0.006 to 0.025	41.64%
3 month	0.054 (0.014)	0.046 (0.011)	-0.008** (0.002)	-0.012 to -0.005	-15.47%
6 month	0.072 (0.021)	0.060 (0.015)	-0.012** (0.003)	-0.018 to -0.006	-16.65%
Systemic Therapy					
Receipt of radiation therapy during the first course of chemotherapy	0.184 (0.132)	0.261 (0.162)	0.077** (0.033)	0.012 to 0.142	41.82%
Number of Cycles in the first course > 5	0.204 (0.178)	0.264 (0.203)	0.060** (0.030)	0.001 to 0.118	29.16%

Variable name	Average length of stay		Marginal Effects after Matching
	Without G-CSF	With G-CSF	
Neutropenia Hospitalization – Length of Stay if hospitalized			
Length of Stay – 1 month (245 Obs Before Matching; 48 Obs After Matching)	NA	NA	NA
Length of Stay – 3 month (564 Obs Before Matching; 96 Obs After Matching)	8.737 (11.676)	7.593 (10.148)	-14.99%
Length of Stay – 6 month (744 Obs Before Matching; 119 Obs After Matching)	7.433 (7.768)	7.152 (7.473)	-5.35%
Neutropenia Hospitalization – Expenditure if hospitalized			
Expenditure - 1 month (245 Obs Before Matching; 48 Obs After Matching)	NA	NA	NA
Expenditure - 3 month (564 Obs Before Matching; 96 Obs After Matching)	8845.86 (6908.23)	7052.42 (5507.63)	-21.65%
Expenditure - 6 month (744 Obs Before Matching; 119 Obs After Matching)	8068.93 (5797.94)	6768.05 (4863.19)	-16.97%
Overall Expenditure			
Overall Expenditure – 1 year	20218.18 (9246.02)	31825.56 (14554.21)	57.25%**

Note: Standard Errors in the parenthesis
 * Significance level α=0.10
 ** Significance level α=0.05

Table 12 Marginal effect of duration of primary prophylactic G-CSF administration on the key outcome variables

Variable name	Effect of G-CSF duration – Increase due to one additional day	Probability with inadequate (<5 days) G-CSF receipt	Probability with adequate (>=5 days) G-CSF receipt	Marginal Effects	Confidence Interval of Marginal Effects	Percentage change due to G-CSF receipt
Neutropenia Hospitalization						
1 month	-0.007* (0.004)	0.110 (0.056)	0.041 (0.025)	-0.070* (0.040)	-0.148 to 0.009	-63.09%
3 month	-0.010** (0.004)	0.135 (0.070)	0.045 (0.011)	-0.089** (0.031)	-0.150 to -0.029	-66.32%
6 month	0.000 (0.000)	0.117 (0.070)	0.079 (0.046)	-0.038* (0.021)	-0.080 to 0.003	-32.72%
Systemic Therapy						
Receipt of radiation therapy during the first course of chemotherapy	0.013** (0.006)	0.276 (0.141)	0.284 (0.145)	0.008** (0.004)	0.001 to 0.016	02.97%
Number of Cycles in the first course above 5	0.018** (0.005)	0.286 (0.102)	0.297 (0.106)	0.011** (0.005)	0.001 to 0.020	03.76%

Variable name	Effect of G-CSF duration – Increase due to one additional day	Average expenditure without adequate G-CSF administration	Average expenditure with adequate G-CSF administration	Marginal Effect for adequate duration
Overall Expenditure – 1 year	1.74%**	29654.82 (11886.16)	35473.20 (14218.26)	19.22%**

Note: Standard Errors in the parenthesis
 * Significance level α=0.10
 ** Significance level α=0.05

Table 13 Descriptive details about regional trends in G-CSF administration

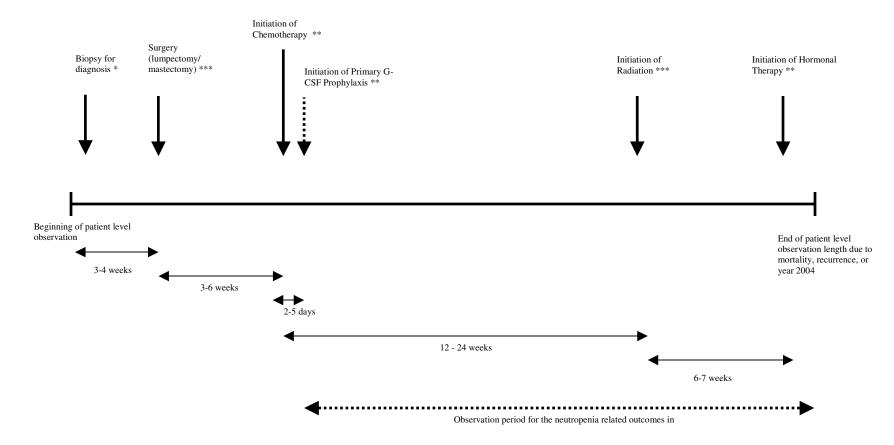| Region	Number of women receiving primary prophylactic G-CSF (Sample Size)	Rate of primary prophylactic G-CSF receipt in the region	Number of physicians who sometimes administer primary prophylactic G-CSF (Number of patients under them)	Number of physicians who administered primary prophylactic G-CSF to all of their patients (Number of patients under them)	Percentage of physicians administering G-CSF (Total number of physicians in the data)	Rate of primary prophylactic G-CSF administration by physicians who administer it
San Francisco	25 (379)	6.60%	16 (91)	3 (5)	15.20% (125)	26.04%
Greater California*	61 (1171)	5.21%	42 (262)	8 (10)	13.85% (361)	22.43%
Louisiana*	22 (431)	5.10%	16 (73)	2 (2)	12.08% (149)	29.33%
Los Angeles	53 (1107)	4.79%	34 (298)	3 (4)	11.97% (309)	17.55%
Connecticut	40 (890)	4.49%	27 (230)	6 (9)	14.10% (234)	16.74%
New Jersey*	38 (1132)	3.36%	33 (179)	6 (7)	10.51% (371)	20.43%
Detroit	36 (1388)	2.59%	22 (366)	2 (2)	10.67% (225)	9.78%
San Jose	7 (283)	2.47%	4 (26)	0 (0)	6.15% (65)	26.92%
Seattle	17 (757)	2.25%	17 (107)	2 (2)	10.50% (181)	15.60%
New Mexico	5 (287)	1.74%	2 (41)	0 (0)	2.08% (96)	12.20%
Atlanta	8 (494)	1.62%	6 (40)	3 (3)	7.14% (126)	18.61%
Utah	7 (436)	1.61%	7 (198)	0 (0)	14.00% (50)	3.54%
Iowa	12 (959)	1.25%	9 (160)	1 (1)	5.05% (198)	7.45%
Kentucky*	4 (474)	0.84%	4 (14)	1 (1)	3.21% (156)	26.67%
Hawaii	2 (253)	0.79%	2 (16)	0 (0)	3.17% (63)	12.50%
Rural Georgia	0 (34)	0.00%	0 (0)	0 (0)	0.00% (23)	0.00%

Note: *SEER regions that were added to the data in 2000.

Table 14 Components of total expenditure in the first year after chemotherapy initiation

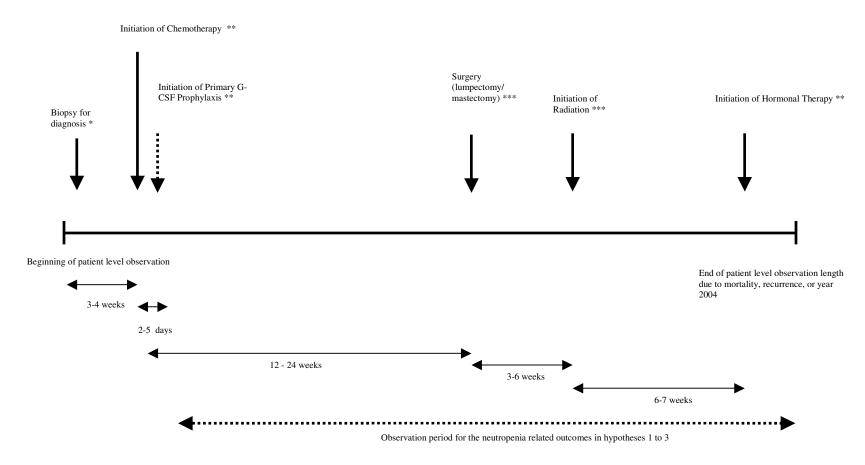| Type of Expenditure	Unmatched Data		Matched Data		Duration of receipt if primary prophylactic G-CSF administered	
	No primary prophylactic G-CSF (10104)	Primary prophylactic G-CSF (337)	No primary prophylactic G-CSF (1423)	Primary prophylactic G-CSF (337)	<5days (151)	>=5days (186)
First year G-CSF expenditure	1124** (2925)	7914** (6169)	1369** (3149)	7914** (6169)	6652** (6709)	8938** (5502)
First year Chemotherapy expenditure	5687** (7123)	11242** (8876)	6444** (6713)	11242** (8876)	11621** (8933)	10774** (8811)
Percentage of G-CSF expenditure in total first year expenditure	5.21%** (11.93%)	29.70%** (19.81%)	6.15%** (12.85%)	29.70%** (19.81%)	28.93% (23.93%)	30.33% (15.74%)
Percentage of Chemotherapy expenditure in total first year expenditure	33.65%** (22.26%)	38.44%** (21.92%)	35.47%** (21.52%)	38.44%** (21.92%)	42.00%** (24.01%)	35.55%** (19.66%)

FIGURES

Figure 1 Standard treatment protocol in stage I to III breast cancer

Initiation of
Chemotherapy **

Biopsy for
diagnosis *

Surgery
(lumpectomy/
mastectomy) ***

Initiation of Primary G-
CSF Prophylaxis **

Initiation of
Radiation ***

Initiation of Hormonal
Therapy **

Beginning of patient level
observation

End of patient level
observation length due to
mortality, recurrence, or
year 2004

3-4 weeks

3-6 weeks

2-5 days

12 - 24 weeks

6-7 weeks

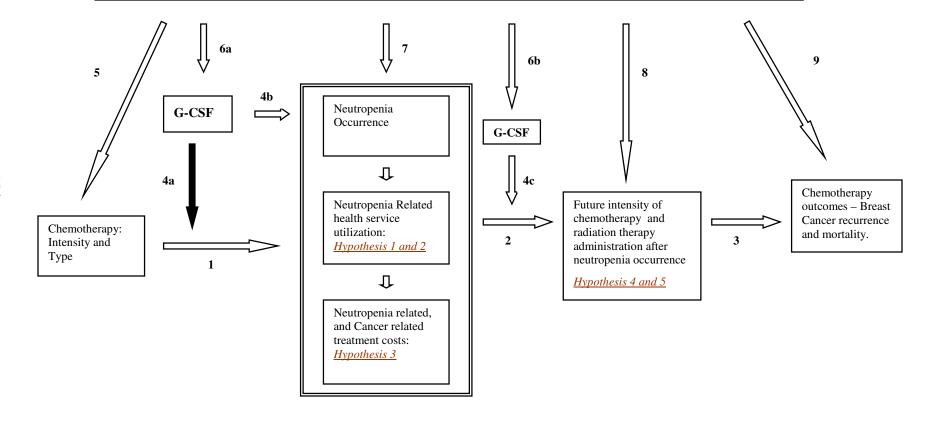Observation period for the neutropenia related outcomes in

Note: Dotted arrow indicates treatment and is absent in control group patients
   * Information Obtained from SEER
   ** Information Obtained from Medicare
   *** Information Obtained from SEER and Medicare

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Figure 2 Treatment protocol in advanced levels of stage III breast cancer

Initiation of Chemotherapy **

Initiation of Primary G-
CSF Prophylaxis **

Surgery
(lumpectomy/
mastectomy) ***

Initiation of
Radiation ***

Initiation of Hormonal Therapy **

Biopsy for
diagnosis *

Beginning of patient level observation

End of patient level observation length
due to mortality, recurrence, or year
2004

3-4 weeks

2-5 days

12 - 24 weeks

3-6 weeks

6-7 weeks

Observation period for the neutropenia related outcomes in hypotheses 1 to 3

Note: Dotted arrow indicates treatment and is absent in control group patients
        * Information Obtained from SEER
        ** Information Obtained from Medicare
        *** Information Obtained from SEER and Medicare

Figure 3 Conceptual framework

Socio-demographic characteristics (Age, Race, Marital Status, SES, Geographic area, Urbanacity), Clinical characteristics (Comorbidities, Tumor Characteristics, Presence of other cancers), Other therapies

5

6a

7

6b

8

9

156

4b

G-CSF

Neutropenia Occurrence

G-CSF

4a

4c

Chemotherapy: Intensity and Type

1

Neutropenia Related health service utilization:
Hypothesis 1 and 2

2

Future intensity of chemotherapy and radiation therapy administration after neutropenia occurrence

Hypothesis 4 and 5

3

Chemotherapy outcomes – Breast Cancer recurrence and mortality.

Neutropenia related, and Cancer related treatment costs:
Hypothesis 3

Note: Solid arrow indicates treatment analyzed in this study
                P= Primary Prophylaxis; T=Therapeutic Administration; S=Secondary Prophylaxis

Figure 4 Data extraction and final observations used in the analysis

All individuals with any breast cancer diagnosis until 2002 in the SEER data linked to Medicare claims until 2003: 310835

Inclusions based on characteristics from the PEDSF files:
- Age of diagnosis at or above 65 years (68.13%)*
- Only Female patients (99.88%)
- Stages 1 to 3 of breast cancer (62.59%)
- Diagnosis at or after 1991 in ensure availability of Medicare part B (75.20%)
- Enrollment in both Part A and B, and non-HMO enrollee for a year before and after diagnosis (62.40%)

Remaining observations: 72448 (23.31%)

Inclusions based on characteristics from the claims:
- Chemotherapy within 6 months of diagnosis (17.84%)
- Diagnosis after 1994 since no patient before 1994 received G-CSF (86.57%)
- Absence of end stage renal disease (99.88%)
- Absence of HIV/AIDS diagnosis (100%)
- Absence of Stem cell or bone marrows transplantation one year before and after chemotherapy (94.15%)

Women of interest in the sample: 10524 (14.53%)

Retained observations without missing values for variables needed in the analysis e.g. race, education, income, and observations from SEER registry in rural Georgia dropped as no one had received prophylactic G-CSF (99.21%)

Remaining observations: 10441 (99.21%)

MATCHING

Remaining observations: 1760

* Parenthesis indicates percentage of observations with those characteristics

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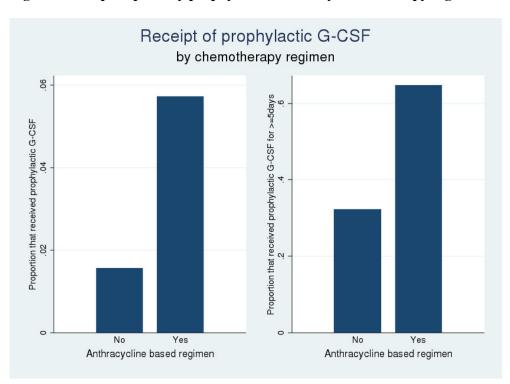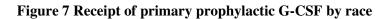**Figure 5 Receipt of primary prophylactic G-CSF by SEER region**

Figure 6 Receipt of primary prophylactic G-CSF by chemotherapy regimen

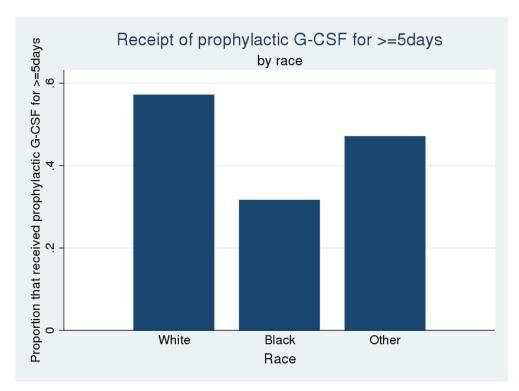**Figure 7 Receipt of primary prophylactic G-CSF by race**

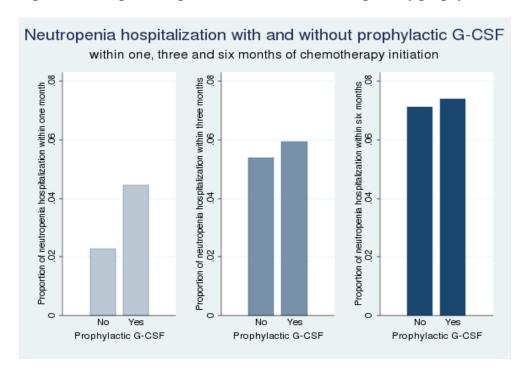**Figure 8 Neutropenia hospitalization with and without primary prophylactic G-CSF**

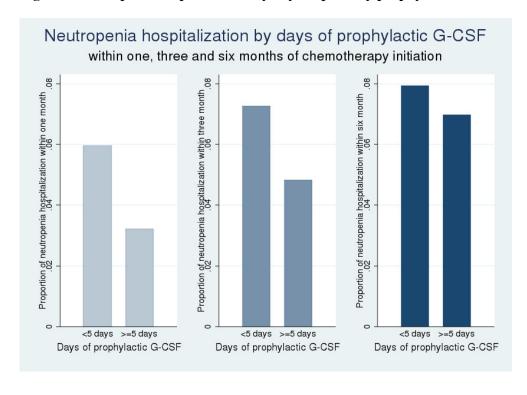**Figure 9 Neutropenia hospitalization by days of primary prophylactic G-CSF**

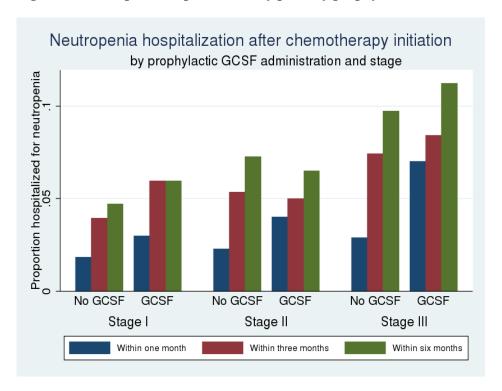**Figure 10 Neutropenia hospitalization by primary prophylactic G-CSF and tumor stage**

Figure 11 Neutropenia hospitalization by duration of primary prophylactic G-CSF and tumor stage

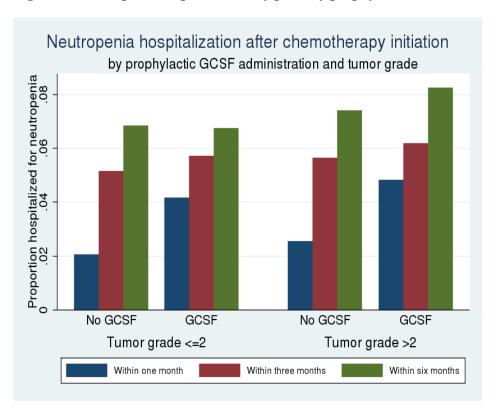**Figure 12 Neutropenia hospitalization by primary prophylactic G-CSF and tumor grade**

Figure 13 Neutropenia hospitalization by duration of primary prophylactic G-CSF and tumor grade
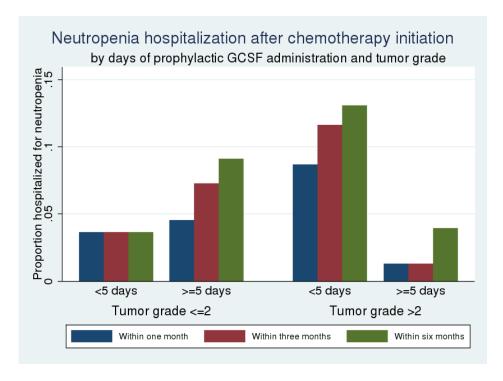
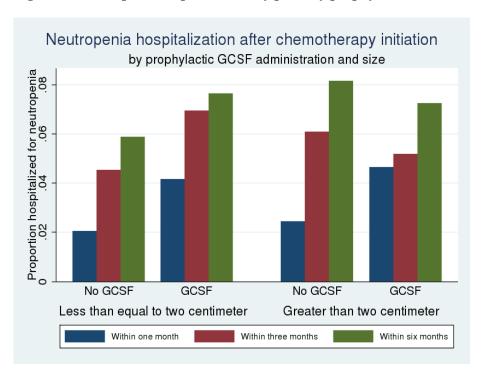**Figure 14 Neutropenia hospitalization by primary prophylactic G-CSF and size**

Figure 15 Neutropenia hospitalization by duration of primary prophylactic G-CSF and size
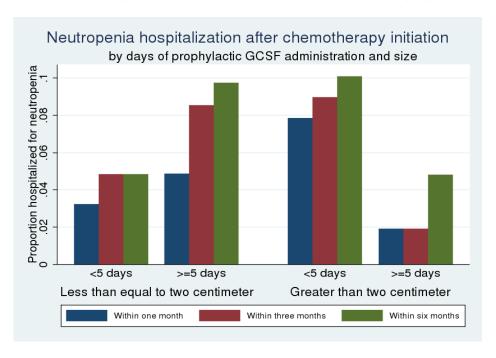
Figure 16 Neutropenia hospitalization length of stay by primary prophylactic G-CSF
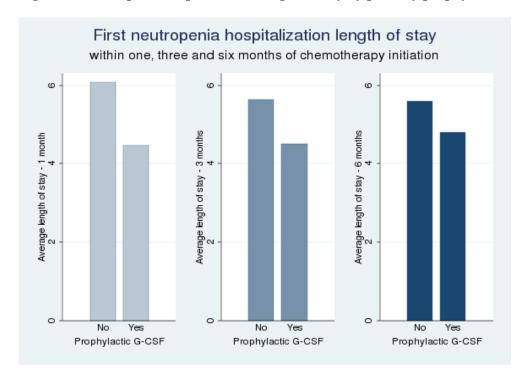

Figure 17 Neutropenia hospitalization length of stay by duration of primary prophylactic G-CSF
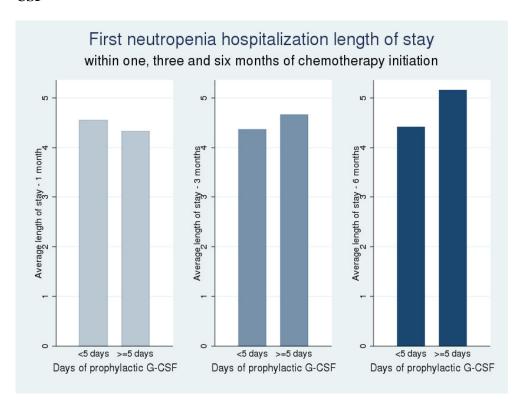
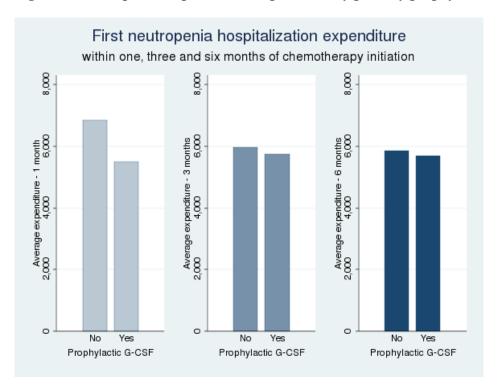**Figure 18 Neutropenia hospitalization expenditure by primary prophylactic G-CSF**

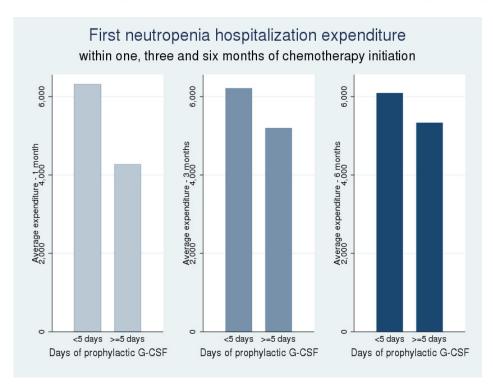**Figure 19 Neutropenia hospitalization expenditure by duration of primary prophylactic G-CSF**

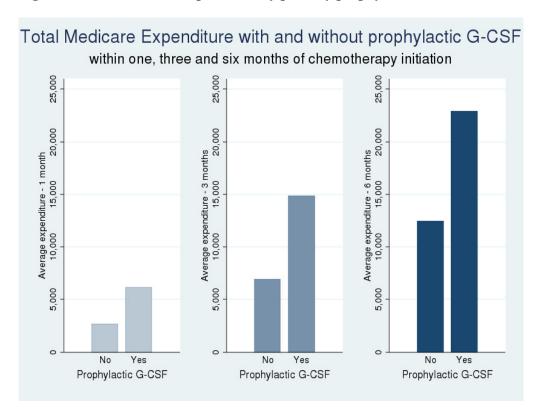**Figure 20 Total Medicare expenditure by primary prophylactic G-CSF**

Figure 21 Total Medicare expenditure by duration of primary prophylactic G-CSF
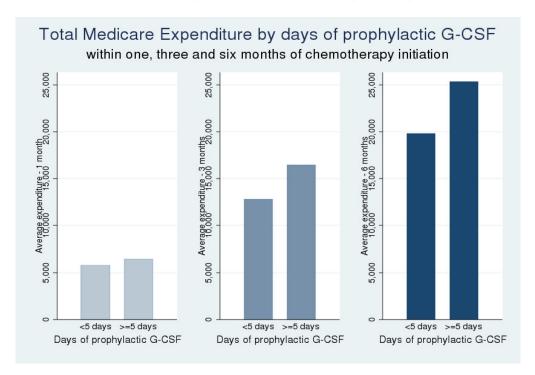
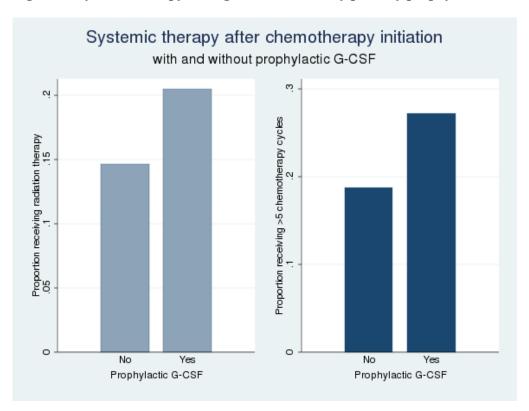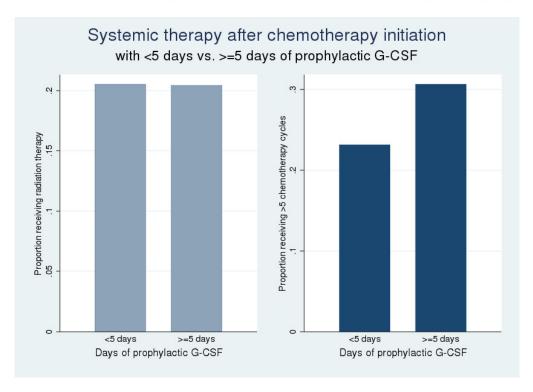**Figure 22 Systemic therapy during the first course by primary prophylactic G-CSF**

Figure 23 Systemic therapy during the first course by duration of primary prophylactic G-CSF

APPENDIX

Table A1 Descriptive statistics (mean and standard deviations) for the independent variables, by receipt of primary prophylactic G-CSF, before and after matching without controlling for therapeutic modalities while matching

Variable name	Before Matching		After Matching	
	No G-CSF (10104)	G-CSF (337)	No G-CSF (1709)	G-CSF (337)
Socio-demographic characteristics				
Age at diagnosis	72.207*	71.712*	71.896	71.712
	(4.954)	(4.508)	(4.441)	(4.508)
White	0.852**	0.893**	0.893	0.893
	(0.355)	(0.309)	(0.309)	(0.309)
Married	0.507	0.516	0.514	0.516
	(0.500)	(0.500)	(0.500)	(0.500)
Education				
Proportion of adults with no high school diploma in the census tract	0.154	0.161	0.154	0.161
	(0.116)	(0.125)	(0.113)	(0.125)
Proportion of adults with only high school diploma in the census tract	0.237	0.240	0.242	0.240
	(0.101)	(0.102)	(0.097)	(0.102)
Proportion of adults with some college diploma in the census tract	0.244**	0.270**	0.268	0.270
	(0.090)	(0.096)	(0.093)	(0.096)
Proportion of adults with at least 4 years of college in the census tract	0.232	0.245	0.245	0.245
	(0.169)	(0.161)	(0.157)	(0.161)
Household income	46881.27	48246.40	49237.95	48246.40
	(23178.01)	(19704.64)	(20820.18)	(19704.640)
Urban/Rural Residence	0.983	0.994	0.992	0.994
	(0.128)	(0.077)	(0.090)	(0.077)
Seer site/ Region				
San Francisco	0.035**	0.074**	0.053	0.074
	(0.184)	(0.262)	(0.223)	(0.262)
Connecticut	0.084**	0.119**	0.114	0.119
	(0.278)	(0.324)	(0.317)	(0.324)
Detroit	0.134	0.107	0.119	0.107
	(0.340)	(0.309)	(0.323)	(0.309)
Hawaii	0.025**	0.006**	0.009	0.006
	(0.156)	(0.077)	(0.093)	(0.077)
Iowa	0.094**	0.036**	0.040	0.036
	(0.291)	(0.186)	(0.197)	(0.186)
New Mexico	0.028	0.015	0.018	0.015
	(0.165)	(0.121)	(0.131)	(0.121)
Seattle	0.073	0.050	0.053	0.050
	(0.261)	(0.219)	(0.225)	(0.219)
Utah	0.042**	0.021**	0.023	0.021
	(0.202)	(0.143)	(0.151)	(0.143)
Atlanta	0.048**	0.024**	0.027	0.024
	(0.214)	(0.152)	(0.162)	(0.152)
San Jose	0.027	0.021	0.016	0.021
	(0.163)	(0.143)	(0.125)	(0.143)
Los Angeles	0.104**	0.157**	0.154	0.157
	(0.306)	(0.365)	(0.361)	(0.365)
Greater California	0.110**	0.181**	0.171	0.181
	(0.313)	(0.386)	(0.377)	(0.386)

Variable name	Before Matching		After Matching	
	No G-CSF (10104)	**G-CSF (337)**	**No G-CSF (1709)**	**G-CSF (337)**
Kentucky	0.047**	0.012**	0.020	0.012
	(0.211)	(0.108)	(0.140)	(0.108)
Louisiana	0.040**	0.065**	0.061	0.065
	(0.197)	(0.247)	(0.239)	(0.247)
New Jersey	0.108	0.113	0.123	0.113
	(0.311)	(0.317)	(0.328)	(0.317)
Diagnosis Year				
Year 1994	0.056**	0.027**	0.050*	0.027*
	(0.230)	(0.161)	(0.217)	(0.161)
Year 1995	0.056	0.036	0.033	0.036
	(0.230)	(0.186)	(0.180)	(0.186)
Year 1996	0.055*	0.033*	0.039	0.033
	(0.227)	(0.178)	(0.192)	(0.178)
Year 1997	0.071*	0.047*	0.044	0.047
	(0.256)	(0.213)	(0.206)	(0.213)
Year 1998	0.087*	0.059*	0.060	0.059
	(0.281)	(0.237)	(0.237)	(0.237)
Year 1999	0.091	0.068	0.070	0.068
	(0.287)	(0.253)	(0.256)	(0.253)
Year 2000	0.194	0.190	0.181	0.190
	(0.396)	(0.393)	(0.385)	(0.393)
Year 2001	0.196**	0.300**	0.276	0.300
	(0.397)	(0.459)	(0.447)	(0.459)
Year 2002	0.195**	0.240**	0.247	0.240
	(0.396)	(0.428)	(0.432)	(0.428)
Clinical Characteristics				
Modified CCI	0.474	0.472	0.438	0.472
	(0.833)	(0.824)	(0.760)	(0.824)
No other cancers before breast cancer	0.944	0.932	0.937	0.932
	(0.230)	(0.253)	(0.242)	(0.253)
History of infection one month before chemotherapy initiation	0.108	0.131	0.119	0.131
	(0.311)	(0.337)	(0.324)	(0.337)
Patients on antibiotics one month before chemotherapy initiation	0.031**	0.053**	0.043	0.053
	(0.172)	(0.225)	(0.202)	(0.225)
Recent hospitalization one month before chemotherapy initiation	0.234	0.226	0.233	0.226
	(0.424)	(0.419)	(0.423)	(0.419)
Tumor Characteristics				
Tumor Stage				
Stage 1	0.215	0.199	0.188	0.199
	(0.411)	(0.400)	(0.391)	(0.400)
Stage 2	0.631	0.591	0.618	0.591
	(0.483)	(0.492)	(0.486)	(0.492)
Stage 3	0.154**	0.211**	0.194	0.211
	(0.361)	(0.408)	(0.395)	(0.408)
Tumor Size	64.317**	85.217**	64.149*	85.217*
	(187.019)	(228.277)	(182.780)	(228.277)
Tumor Grade – Indicator for higher grade	0.456	0.430	0.447	0.430
	(0.498)	(0.496)	(0.497)	(0.496)

Variable name	Before Matching		After Matching	
	No G-CSF (10104)	G-CSF (337)	No G-CSF (1709)	G-CSF (337)
Node +	0.600* (0.490)	0.647* (0.479)	0.650 (0.477)	0.647 (0.479)
ER status	0.570 (0.495)	0.549 (0.498)	0.565 (0.496)	0.549 (0.498)
PR status	0.459 (0.498)	0.451 (0.498)	0.466 (0.499)	0.451 (0.498)
Procedures Performed				
Surgery				
Surgery before chemotherapy initiation	0.922 (0.268)	0.908 (0.289)	0.923 (0.266)	0.908 (0.289)
Surgery after chemotherapy initiation	0.035** (0.184)	0.059** (0.237)	0.037* (0.190)	0.059* (0.237)
Surgery time unknown	0.031 (0.175)	0.021 (0.143)	0.029 (0.167)	0.021 (0.143)
Lymph node dissection before chemotherapy initiation	0.431 (0.495)	0.439 (0.497)	0.459 (0.498)	0.439 (0.497)
Lymph node dissection after chemotherapy initiation	0.013 (0.114)	0.018 (0.132)	0.016 (0.127)	0.018 (0.132)
Lymph node dissection time unknown	0.501 (0.500)	0.490 (0.501)	0.475 (0.500)	0.490 (0.501)
Radiation before chemotherapy initiation	0.186 (0.389)	0.199 (0.400)	0.181 (0.385)	0.199 (0.400)
Type of chemotherapy regimen in first cycle - Anthracycline	0.387** (0.487)	0.706** (0.456)	0.431** (0.495)	0.706** (0.456)
Number of Drugs in first cycle	1.878 (1.057)	1.917 (0.889)	1.891 (1.032)	1.917 (0.889)
Square of Number of Drugs in first cycle	4.645 (3.412)	4.463 (2.921)	4.638 (3.328)	4.463 (2.921)
Duration between first and second	17.566 (12.306)	18.108 (10.922)	17.656 (11.610)	18.108 (10.922)
Square of Duration between first and second	460.008 (778.746)	446.842 (552.396)	446.458 (725.760)	446.842 (552.396)

Note: Standard Deviations in the parenthesis
    * Significance level α=0.10
    ** Significance level α=0.05

Table A2 Descriptive statistics (mean and standard deviations) for the outcome variables, by receipt of primary prophylactic G-CSF, before and after matching without controlling for therapeutic modalities

Variable name	Before Matching		After Matching	
	No G-CSF (10104)	G-CSF (337)	No G-CSF (1709)	G-CSF (337)
Neutropenia Hospitalization				
1 month	0.023**	0.045**	0.029	0.045
	(0.149)	(0.207)	(0.167)	(0.207)
3 month	0.054	0.059	0.054	0.059
	(0.226)	(0.237)	(0.226)	(0.237)
6 month	0.071	0.074	0.072	0.074
	(0.257)	(0.262)	(0.259)	(0.262)
Neutropenia Hospitalization – Length of Stay if hospitalized				
1 month	6.065	4.467	6.551	4.467
(245 Obs Before Matching; 64 Obs After Matching)	(7.090)	(1.922)	(6.699)	(1.922)
3 month	5.645	4.500	6.141	4.500
(564 Obs Before Matching; 112 Obs After Matching)	(5.387)	(1.850)	(5.650)	(1.850)
6 month	5.598	4.800	6.177	4.800
(744 Obs Before Matching; 149 Obs After Matching)	(5.285)	(2.915)	(5.180)	(2.915)
Logarithm of Length of Stay - 1 month	1.484	1.410	1.554	1.410
(245 Obs Before Matching; 64 Obs After Matching)	(0.738)	(0.437)	(0.777)	(0.437)
Logarithm of Length of Stay - 3 month	1.486	1.424	1.535	1.424
(564 Obs Before Matching; 112 Obs After Matching)	(0.664)	(0.416)	(0.729)	(0.416)
Logarithm of Length of Stay - 6 month	1.489	1.441	1.569	1.441
(744 Obs Before Matching; 149 Obs After Matching)	(0.652)	(0.491)	(0.701)	(0.491)
Neutropenia Hospitalization – Expenditure if hospitalized				
1 month	6855.14	5502.40	6647.35	5502.40
(245 Obs Before Matching; 64 Obs After Matching)	(10590.41)	(2562.37)	(3977.51)	(2562.37)
3 month	5975.47	5760.90	6180.02	5760.90
(564 Obs Before Matching; 112 Obs After Matching)	(7232.51)	(2410.01)	(3616.70)	(2410.01)
6 month	5874.70	5702.80	6195.03	5702.80
(744 Obs Before Matching; 149 Obs After Matching)	(6483.62)	(2270.21)	(3651.04)	(2270.21)
Logarithm of Expenditure - 1 month	8.619	8.504	8.687	8.504
(245 Obs Before Matching; 64 Obs After Matching)	(0.554)	(0.499)	(0.516)	(0.499)
Logarithm of Expenditure - 3 month	8.542	8.563	8.602	8.564
(564 Obs Before Matching; 112 Obs After Matching)	(0.501)	(0.468)	(0.521)	(0.468)
Logarithm of Expenditure - 6 month	8.536	8.561	8.607	8.561
(744 Obs Before Matching; 149 Obs After Matching)	(0.491)	(0.447)	(0.504)	(0.448)
Overall Expenditure				
1 year	17596.50**	30344.69**	19015.14**	30344.69**
	(17155.56)	(19926.37)	(16322.04)	(19926.37)
Logarithm of Expenditure – 1 year	9.418**	10.101**	9.525**	10.101**
	(0.926)	(0.754)	(0.884)	(0.754)
Systemic therapy				
Administration of radiation therapy during the first course of chemotherapy	0.147**	0.205**	0.165*	0.205*
	(0.354)	(0.404)	(0.371)	(0.404)
Number of Cycles in first course	8.831**	9.887**	9.097*	9.887*
	(6.579)	(7.445)	(6.838)	(7.445)
Number of chemotherapy cycles in first course > 5	0.188**	0.273**	0.197**	0.273**
	(0.390)	(0.446)	(0.397)	(0.446)

Note: Standard Deviations in the parenthesis

* Significance level α=0.10

** Significance level α=0.05

Table A3 Effect of primary prophylactic G-CSF administration and duration of G-CSF administration on the key outcome variables without controlling for treatment variables

Variable name	Before Matching	After Matching	Effect of G-CSF duration (<5 days versus >=5 days)	Effect of G-CSF duration with duration as a continuous variable
	10441	2046	337	337
Neutropenia Hospitalization				
1 month	0.628**	0.355	-1.377*	-0.137
	(0.278)	(0.315)	(0.828)	(0.113)
3 month	0.038	0.024	-1.153*	-0.116
	(0.238)	(0.263)	(0.644)	(0.094)
6 month	-0.004	-0.016	-0.711	-0.036
	(0.215)	(0.234)	(0.568)	(0.061)
Neutropenia Hospitalization – Length of Stay if hospitalized				
Logarithm of Length of Stay – 1 month (245 Obs Before Matching; 64 Obs After Matching)	-0.132 (0.209)	-0.481 (0.300)	NA	NA
Logarithm of Length of Stay – 3 month (564 Obs Before Matching; 112 Obs After Matching)	-0.162 (0.152)	-0.286 (0.213)	NA	NA
Logarithm of Length of Stay – 6 month (744 Obs Before Matching; 149 Obs After Matching)	-0.096 (0.133)	-0.113 (0.173)	NA	NA
Neutropenia Hospitalization – Expenditure if hospitalized				
Logarithm of Expenditure - 1 month (245 Obs Before Matching; 64 Obs After Matching)	-0.255* (0.148)	-0.469 (0.230)	NA	NA
Logarithm of Expenditure - 3 month (564 Obs Before Matching; 112 Obs After Matching)	-0.130 (0.107)	-0.191 (0.143)	NA	NA
Logarithm of Expenditure - 6 month (744 Obs Before Matching; 149 Obs After Matching)	-0.080 (0.093)	-0.105 (0.120)	NA	NA
Overall Expenditure				
Logarithm – 1 year	0.513**	0.535**	0.290**	0.026**
	(0.047)	(0.047)	(0.081)	(0.008)
Systemic Therapy				
Receipt of radiation therapy during the first course of chemotherapy	0.338** (0.141)	0.253* (0.154)	0.084 (0.324)	0.049* (0.028)
Number of Cycles in the first course > 5	0.412** (0.130)	0.470** (0.144)	0.275 (0.310)	0.126** (0.034)

Note: Standard Errors in the parenthesis
* Significance level α=0.10
** Significance level α=0.05

Table A4 Marginal effect of primary prophylactic G-CSF administration on the key outcome variables without controlling for treatment variables

Variable name	Probability without primary prophylactic G-CSF administration	Probability with primary prophylactic G-CSF administration	Marginal Effects after Matching (2046)	Confidence Interval of Marginal Effects	Percentage change due to G-CSF administration
Neutropenia Hospitalization					
1 month	0.030 (0.032)	0.042 (0.043)	0.012 (0.011)	-0.010 to 0.033	38.94%
3 month	0.056 (0.046)	0.057 (0.046)	0.001 (0.001)	-0.001 to 0.003	02.18%
6 month	0.074 (0.048)	0.073 (0.047)	-0.001 (0.001)	-0.002 to 0.000	-01.40%
Systemic Therapy					
Receipt of radiation therapy during the first course of chemotherapy	0.166 (0.072)	0.202 (0.083)	0.036* (0.012)	0.013 to 0.059	21.97%
Number of Cycles in the first course >5	0.196 (0.104)	0.274 (0.129)	0.078** (0.026)	0.026 to 0.129	39.45%

Variable name	Average length of stay		Marginal Effects after Matching
	Without G-CSF	With G-CSF	
Neutropenia Hospitalization – Length of Stay if hospitalized			
Length of Stay – 1 month (64 Obs After Matching)	12.086 (17.698)	7.469 (10.937)	-40.92%
Length of Stay – 3 month (112 Obs After Matching)	7.692 (6.805)	5.780 (5.113)	-26.55%
Length of Stay – 6 month (149 Obs After Matching)	6.834 (3.352)	6.106 (2.995)	-11.97%
Neutropenia Hospitalization – Expenditure if hospitalized			
Expenditure - 1 month (64 Obs After Matching)	10110.86 (11695.66)	6324.86 (7316.24)	-39.08%
Expenditure - 3 month (112 Obs After Matching)	7768.47 (5407.69)	6420.21 (4469.16)	-18.19%
Expenditure - 6 month (149 Obs After Matching)	6764.18 (2270.89)	6086.14 (2043.26)	-10.68%
Overall Expenditure			
Overall Expenditure – 1 year	20152.48 (7540.84)	34393.25 (12869.59)	70.47%**

Note: Standard Errors in the parenthesis
* Significance level α=0.10
** Significance level α=0.05

Table A5 Marginal effect of duration of primary prophylactic G-CSF administration on the key outcome variables without controlling for treatment variables

Variable name	Effect of G-CSF duration – Increase due to one additional day	Probability with inadequate (<5 days) G-CSF receipt	Probability with adequate (>=5 days) G-CSF receipt	Marginal Effects	Confidence Interval of Marginal Effects	Percentage change due to G-CSF receipt
Neutropenia Hospitalization						
1 month	-0.006 (0.009)	0.102 (0.164)	0.039 (0.087)	-0.063* (0.084)	-0.227 to 0.101	-61.86%
3 month	-0.006 (0.008)	0.109 (0.163)	0.048 (0.092)	-0.061* (0.077)	-0.212 to 0.090	-56.02%
6 month	-0.002 (0.003)	0.115 (0.168)	0.071 (0.119)	-0.044 (0.053)	-0.148 to 0.060	-38.58%
Systemic Therapy						
Receipt of radiation therapy during the first course of chemotherapy	0.007* (0.003)	0.210 (0.155)	0.222 (0.160)	0.012 (0.006)	0.001 to 0.023	05.78%
Number of Cycles in the first course > 5	0.019** (0.010)	0.256 (0.192)	0.301 (0.209)	0.044 (0.021)	0.003 to 0.085	17.23%

Variable name	Effect of G-CSF duration – Increase due to one additional day	Average expenditure without adequate G-CSF administration	Average expenditure with adequate G-CSF administration	Marginal Effect for adequate duration
Overall Expenditure – 1 year	2.62%**	27759.42 (9265.351)	37091.89 (12380.28)	33.18%**

Note: Standard Errors in the parenthesis
* Significance level α=0.10
** Significance level α=0.05

Table A6 Descriptive statistics for the independent variables, by receipt of primary prophylactic G-CSF, before and after matching without controlling for chemotherapy and radiation therapy variables

Variable name	Before Matching		After Matching	
	No G-CSF (10104)	G-CSF (337)	No G-CSF (1753)	G-CSF (337)
Socio-demographic characteristics				
Age at diagnosis	72.207*	71.712*	71.905	71.712
	(4.954)	(4.508)	(4.465)	(4.508)
White	0.852**	0.893**	0.900	0.893
	(0.355)	(0.309)	(0.300)	(0.309)
Married	0.507	0.516	0.537	0.516
	(0.500)	(0.500)	(0.499)	(0.500)
Education				
Proportion of adults with no high school diploma in the census tract	0.154	0.161	0.154	0.161
	(0.116)	(0.125)	(0.113)	(0.125)
Proportion of adults with only high school diploma in the census tract	0.237	0.240	0.242	0.240
	(0.101)	(0.102)	(0.097)	(0.102)
Proportion of adults with some college diploma in the census tract	0.244**	0.270**	0.267	0.270
	(0.090)	(0.096)	(0.090)	(0.096)
Proportion of adults with at least 4 years of college in the census tract	0.232	0.245	0.244	0.245
	(0.169)	(0.161)	(0.157)	(0.161)
Household income	46881.27	48246.40	48729.39	48246.40
	(23178.01)	(19704.64)	(20509.73)	(19704.64)
Urban/Rural Residence	0.983	0.994	0.995	0.994
	(0.128)	(0.077)	(0.072)	(0.077)
Seer site/ Region				
San Francisco	0.035**	0.074**	0.043**	0.074**
	(0.184)	(0.262)	(0.202)	(0.262)
Connecticut	0.084**	0.119**	0.115	0.119
	(0.278)	(0.324)	(0.319)	(0.324)
Detroit	0.134	0.107	0.108	0.107
	(0.340)	(0.309)	(0.311)	(0.309)
Hawaii	0.025**	0.006**	0.006	0.006
	(0.156)	(0.077)	(0.079)	(0.077)
Iowa	0.094**	0.036**	0.041	0.036
	(0.291)	(0.186)	(0.199)	(0.186)
New Mexico	0.028	0.015	0.017	0.015
	(0.165)	(0.121)	(0.128)	(0.121)
Seattle	0.073	0.050	0.056	0.050
	(0.261)	(0.219)	(0.230)	(0.219)
Utah	0.042**	0.021**	0.024	0.021
	(0.202)	(0.143)	(0.153)	(0.143)
Atlanta	0.048**	0.024**	0.025	0.024
	(0.214)	(0.152)	(0.155)	(0.152)
San Jose	0.027	0.021	0.019	0.021
	(0.163)	(0.143)	(0.136)	(0.143)
Los Angeles	0.104**	0.157**	0.170	0.157
	(0.306)	(0.365)	(0.376)	(0.365)
Greater California	0.110**	0.181**	0.185	0.181
	(0.313)	(0.386)	(0.389)	(0.386)
Kentucky	0.047**	0.012**	0.022	0.012
	(0.211)	(0.108)	(0.148)	(0.108)

Variable name	Before Matching		After Matching	
	No G-CSF (10104)	**G-CSF (337)**	**No G-CSF (1753)**	**G-CSF (337)**
Louisiana	0.040**	0.065**	0.061	0.065
	(0.197)	(0.247)	(0.239)	(0.247)
New Jersey	0.108	0.113	0.108	0.113
	(0.311)	(0.317)	(0.311)	(0.317)
Diagnosis Year				
Year 1994	0.056**	0.027**	0.050*	0.027*
	(0.230)	(0.161)	(0.217)	(0.161)
Year 1995	0.056	0.036	0.037	0.036
	(0.230)	(0.186)	(0.190)	(0.186)
Year 1996	0.055*	0.033*	0.037	0.033
	(0.227)	(0.178)	(0.190)	(0.178)
Year 1997	0.071*	0.047*	0.047	0.047
	(0.256)	(0.213)	(0.212)	(0.213)
Year 1998	0.087*	0.059*	0.059	0.059
	(0.281)	(0.237)	(0.236)	(0.237)
Year 1999	0.091	0.068	0.074	0.068
	(0.287)	(0.253)	(0.261)	(0.253)
Year 2000	0.194	0.190	0.200	0.190
	(0.396)	(0.393)	(0.400)	(0.393)
Year 2001	0.196**	0.300**	0.261	0.300
	(0.397)	(0.459)	(0.439)	(0.459)
Year 2002	0.195**	0.240**	0.236	0.240
	(0.396)	(0.428)	(0.424)	(0.428)
Clinical Characteristics				
Modified CCI	0.474	0.472	0.398*	0.472*
	(0.833)	(0.824)	(0.676)	(0.824)
No other cancers before breast cancer	0.944	0.932	0.938	0.932
	(0.230)	(0.253)	(0.242)	(0.253)
History of infection one month before chemotherapy initiation	0.108	0.131	0.119	0.131
	(0.311)	(0.337)	(0.324)	(0.337)
Patients on antibiotics one month before chemotherapy initiation	0.031**	0.053**	0.030**	0.053**
	(0.172)	(0.225)	(0.171)	(0.225)
Recent hospitalization one month before chemotherapy initiation	0.234	0.226	0.244	0.226
	(0.424)	(0.419)	(0.429)	(0.419)
Tumor Characteristics				
Tumor Stage				
Stage 1	0.215	0.199	0.182	0.199
	(0.411)	(0.400)	(0.386)	(0.400)
Stage 2	0.631	0.591	0.626	0.591
	(0.483)	(0.492)	(0.484)	(0.492)
Stage 3	0.154**	0.211**	0.192	0.211
	(0.361)	(0.408)	(0.394)	(0.408)
Tumor Size	64.317**	85.217**	76.885	85.217
	(187.019)	(228.277)	(212.199)	(228.277)
Tumor Grade – Indicator for higher grade	0.456	0.430	0.438	0.430
	(0.498)	(0.496)	(0.496)	(0.496)
Node +	0.600*	0.647*	0.654	0.647
	(0.490)	(0.479)	(0.476)	(0.479)

Variable name	Before Matching		After Matching	
	No G-CSF (10104)	**G-CSF (337)**	**No G-CSF (1753)**	**G-CSF (337)**
ER status	0.570	0.549	0.576	0.549
	(0.495)	(0.498)	(0.494)	(0.498)
PR status	0.459	0.451	0.472	0.451
	(0.498)	(0.498)	(0.499)	(0.498)
Procedures Performed				
Surgery				
Surgery before chemotherapy initiation	0.922	0.908	0.913	0.908
	(0.268)	(0.289)	(0.281)	(0.289)
Surgery after chemotherapy initiation	0.035**	0.059**	0.055	0.059
	(0.184)	(0.237)	(0.229)	(0.237)
Surgery time unknown	0.031	0.021	0.022	0.021
	(0.175)	(0.143)	(0.146)	(0.143)
Lymph node dissection before chemotherapy initiation	0.431	0.439	0.436	0.439
	(0.495)	(0.497)	(0.496)	(0.497)
Lymph node dissection after chemotherapy initiation	0.013	0.018	0.017	0.018
	(0.114)	(0.132)	(0.128)	(0.132)
Lymph node dissection time unknown	0.501	0.490	0.505	0.490
	(0.500)	(0.501)	(0.500)	(0.501)
Radiation before chemotherapy initiation	0.186	0.199	0.179	0.199
	(0.389)	(0.400)	(0.384)	(0.400)
Type of chemotherapy regimen in first cycle - Anthracycline	0.387**	0.706**	0.426**	0.706**
	(0.487)	(0.456)	(0.495)	(0.456)
Number of Drugs in first cycle	1.878	1.917	1.905	1.917
	(1.057)	(0.889)	(1.026)	(0.889)
Square of Number of Drugs in first cycle	4.645	4.463	4.679	4.463
	(3.412)	(2.921)	(3.323)	(2.921)
Duration between first and second	17.566	18.108	17.782	18.108
	(12.306)	(10.922)	(11.936)	(10.922)
Square of Duration between first and second	460.008	446.842	458.590	446.842
	(778.746)	(552.396)	(768.238)	(552.396)

Note: Standard Deviations in the parenthesis

    * Significance level α=0.10

    ** Significance level α=0.05

Table A7 Descriptive statistics for the outcome variables, by receipt of primary prophylactic G-CSF, before and after matching without controlling for chemotherapy and radiation therapy variables

Variable name	Before Matching		After Matching	
	No G-CSF (10104)	G-CSF (337)	No G-CSF (1753)	G-CSF (337)
Neutropenia Hospitalization				
1 month	0.023**	0.045**	0.029	0.045
	(0.149)	(0.207)	(0.168)	(0.207)
3 month	0.054	0.059	0.060	0.059
	(0.226)	(0.237)	(0.237)	(0.237)
6 month	0.071	0.074	0.078	0.074
	(0.257)	(0.262)	(0.268)	(0.262)
Neutropenia Hospitalization – Length of Stay if hospitalized				
1 month	6.065	4.467	5.765	4.467
(245 Obs Before Matching; 66 Obs After Matching)	(7.090)	(1.922)	(4.572)	(1.922)
3 month	5.645	4.500	5.381	4.500
(564 Obs Before Matching; 125 Obs After Matching)	(5.387)	(1.850)	(4.027)	(1.850)
6 month	5.598	4.800	5.387	4.800
(744 Obs Before Matching; 162 Obs After Matching)	(5.285)	(2.915)	(3.764)	(2.915)
Logarithm of Length of Stay - 1 month	1.484	1.410	1.477	1.410
(245 Obs Before Matching; 66 Obs After Matching)	(0.738)	(0.437)	(0.758)	(0.437)
Logarithm of Length of Stay - 3 month	1.486	1.424	1.446	1.424
(564 Obs Before Matching; 125 Obs After Matching)	(0.664)	(0.416)	(0.702)	(0.416)
Logarithm of Length of Stay - 6 month	1.489	1.441	1.468	1.441
(744 Obs Before Matching; 162 Obs After Matching)	(0.652)	(0.491)	(0.673)	(0.491)
Neutropenia Hospitalization – Expenditure if hospitalized				
1 month	6855.14	5502.40	7168.26	5502.40
(245 Obs Before Matching; 66 Obs After Matching)	(10590.41)	(2562.37)	(4584.87)	(2562.37)
3 month	5975.47	5760.90	6225.82	5760.90
(564 Obs Before Matching; 125 Obs After Matching)	(7232.51)	(2410.01)	(3718.85)	(2410.01)
6 month	5874.70	5702.80	6273.75	5702.80
(744 Obs Before Matching; 162 Obs After Matching)	(6483.62)	(2270.21)	(3780.45)	(2270.21)
Logarithm of Expenditure - 1 month	8.619	8.504	8.773*	8.504*
(245 Obs Before Matching; 66 Obs After Matching)	(0.554)	(0.499)	(0.535)	(0.499)
Logarithm of Expenditure - 3 month	8.542	8.563	8.624	8.564
(564 Obs Before Matching; 125 Obs After Matching)	(0.501)	(0.468)	(0.507)	(0.468)
Logarithm of Expenditure - 6 month	8.536	8.561	8.627	8.561
(744 Obs Before Matching; 162 Obs After Matching)	(0.491)	(0.447)	(0.502)	(0.448)
Overall Expenditure				
1 year	17596.50**	30344.69**	19610.49**	30344.69**
	(17155.56)	(19926.37)	(17150.94)	(19926.37)
Logarithm of Expenditure – 1 year	9.418**	10.101**	9.552**	10.101**
	(0.926)	(0.754)	(0.876)	(0.754)
Systemic therapy				
Administration of radiation therapy during the first course of chemotherapy	0.147**	0.205**	0.155**	0.205**
	(0.354)	(0.404)	(0.362)	(0.404)
Number of Cycles in first course	8.831**	9.887**	9.031**	9.887**
	(6.579)	(7.445)	(6.458)	(7.445)
Number of chemotherapy cycles in first course > 5	0.188**	0.273**	0.196**	0.273**
	(0.390)	(0.446)	(0.397)	(0.446)

Note: Standard Deviations in the parenthesis
   * Significance level α=0.10
   ** Significance level α=0.05

Table A8 Effect of primary prophylactic G-CSF administration and duration of G-CSF administration on the key outcome variables without controlling for chemotherapy and radiation therapy variables

Variable name	Before Matching	After Matching	Effect of G-CSF duration (<5 days versus >=5 days)	Effect of G-CSF duration with duration as a continuous variable
	10441	**2090**	**337**	**337**
Neutropenia Hospitalization				
1 month	0.635**	0.361	-1.107	-0.091
	(0.279)	(0.318)	(0.889)	(0.122)
3 month	0.040	-0.081	-1.132	-0.098
	(0.239)	(0.261)	(0.719)	(0.104)
6 month	-0.005	-0.092	-0.795	-0.012
	(0.215)	(0.234)	(0.633)	(0.065)
Neutropenia Hospitalization – Length of Stay if hospitalized				
Logarithm of Length of Stay – 1 month	-0.166	-0.366	NA	NA
(245 Obs Before Matching; 66 Obs After Matching)	(0.210)	(0.421)		
Logarithm of Length of Stay – 3 month	-0.178	-0.079	NA	NA
(564 Obs Before Matching; 125 Obs After Matching)	(0.154)	(0.194)		
Logarithm of Length of Stay – 6 month	-0.104	-0.007	NA	NA
(744 Obs Before Matching; 162 Obs After Matching)	(0.134)	(0.154)		
Neutropenia Hospitalization – Expenditure if hospitalized				
Logarithm of Expenditure - 1 month	-0.254	-0.297	NA	NA
(245 Obs Before Matching; 66 Obs After Matching)	(0.151)	(0.327)		
Logarithm of Expenditure - 3 month	-0.127	-0.196	NA	NA
(564 Obs Before Matching; 125 Obs After Matching)	(0.108)	(0.138)		
Logarithm of Expenditure - 6 month	-0.079	-0.132	NA	NA
(744 Obs Before Matching; 162 Obs After Matching)	(0.093)	(0.119)		
Overall Expenditure				
Logarithm – 1 year	0.510**	0.495**	0.296**	0.027**
	(0.046)	(0.046)	(0.081)	(0.008)
Systemic Therapy				
Receipt of radiation therapy during the first course of chemotherapy	0.334**	0.318**	0.069**	0.067**
	(0.144)	(0.157)	(0.040)	(0.031)
Number of Cycles in the first course > 5	0.392**	0.455**	0.296**	0.132**
	(0.131)	(0.144)	(0.021)	(0.036)

Note: Standard Errors in the parenthesis
    * Significance level α=0.10
    ** Significance level α=0.05

Table A9 Marginal effect of primary prophylactic G-CSF administration on the key outcome variables without controlling for chemotherapy and radiation therapy variables

Variable name	Probability without primary prophylactic G-CSF administration	Probability with primary prophylactic G-CSF administration	Marginal Effects after Matching (2090)	Confidence Interval of Marginal Effects	Percentage change due to G-CSF administration
Neutropenia Hospitalization					
1 month	0.031 (0.039)	0.044 (0.050)	0.012 (0.012)	-0.012 to 0.036	38.92%
3 month	0.063 (0.047)	0.059 (0.044)	-0.004* (0.003)	-0.010 to 0.001	-07.06%
6 month	0.080 (0.055)	0.074 (0.052)	-0.006* (0.004)	-0.014 to 0.001	-07.86%
Systemic Therapy					
Receipt of radiation therapy during the first course of chemotherapy	0.156 (0.085)	0.200 (0.099)	0.044** (0.015)	0.014 to 0.073	27.92%
Number of Cycles in the first course > 5	0.197 (0.108)	0.273 (0.130)	0.075** (0.024)	0.027 to 0.123	37.88%

Variable name	Average length of stay		Marginal Effects after Matching
	Without G-CSF	With G-CSF	
Neutropenia Hospitalization – Length of Stay if hospitalized			
Length of Stay – 1 month (66 Obs After Matching)	7.678 (8.567)	5.324 (5.941)	-36.54%
Length of Stay – 3 month (125 Obs After Matching)	5.609 (2.700)	5.183 (2.495)	-9.34%
Length of Stay – 6 month (162 Obs After Matching)	5.502 (2.525)	5.466 (2.508)	-1.84%
Neutropenia Hospitalization – Expenditure if hospitalized			
Expenditure - 1 month (66 Obs After Matching)	8568.50 (10680.35)	6363.64 (7932.06)	-29.60%
Expenditure - 3 month (125 Obs After Matching)	6756.74 (2535.27)	5552.43 (2083.39)	-18.60%
Expenditure - 6 month (162 Obs After Matching)	6618.93 (1833.87)	5798.94 (1606.67)	-13.01%
Overall Expenditure			
Overall Expenditure – 1 year	20691.19 (8959.14)	33927.10 (14690.20)	63.79%**

Note: Standard Errors in the parenthesis
* Significance level α=0.10
** Significance level α=0.05

Table A10 Marginal effect of duration of primary prophylactic G-CSF administration on the key outcome variables without controlling for chemotherapy and radiation therapy variables

Variable name	Effect of G-CSF duration – Increase due to one additional day	Probability with inadequate (<5 days) G-CSF receipt	Probability with adequate (>=5 days) G-CSF receipt	Marginal Effects	Confidence Interval of Marginal Effects	Percentage change due to G-CSF receipt
Neutropenia Hospitalization						
1 month	-0.004 (0.006)	0.092 (0.166)	0.044 (0.105)	-0.048 (0.069)	-0.183 to 0.088	-51.74%
3 month	-0.005 (0.007)	0.110 (0.177)	0.051 (0.105)	-0.058 (0.080)	-0.216 to 0.099	-53.26%
6 month	-0.001 (0.001)	0.122 (0.186)	0.073 (0.131)	-0.049 (0.061)	-0.169 to 0.072	-40.12%
Systemic Therapy						
Receipt of radiation therapy during the first course of chemotherapy	0.009** (0.005)	0.216 (0.184)	0.226 (0.187)	0.009** (0.005)	0.000 to 0.019	04.37%
Number of Cycles in the first course > 5	0.019** (0.011)	0.260 (0.210)	0.306 (0.226)	0.046** (0.023)	0.001 to 0.091	17.67%

Variable name	Effect of G-CSF duration – Increase due to one additional day	Average expenditure without adequate G-CSF administration	Average expenditure with adequate G-CSF administration	Marginal Effect for adequate duration
Overall Expenditure – 1 year	2.69%**	27789.74 (10074.50)	37356.51 (13542.70)	33.98%**

Note: Standard Errors in the parenthesis
  * Significance level α=0.10
  ** Significance level α=0.05

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