THE VALIDITY OF ADMINISTRATIVE DATA AND PATTERNS OF CHEMOTHERAPY USE AMONG ELDERLY COLORECTAL CANCER PATIENTS

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ABSTRACT

JENNIFER L. LUND: The validity of administrative data and patterns of chemotherapy use among elderly colorectal cancer patients
(Under the direction of Dr. Til Stürmer)

Chemotherapy represents an integral part of the treatment plan for many cancer patients, proven to decrease recurrence and overall mortality. Recent trials demonstrated that adding oxaliplatin to 5-fluorouracil/leucovorin significantly improved survival for stage III colon cancer patients. However, few studies have examined the translation of these findings into routine practice, particularly among the elderly, who are underrepresented in trials.

Two population-based data sources were linked to assess the utility of Medicare claims in identifying chemotherapy and specific agents administered to elderly stage II/III colorectal cancer (CRC), in-situ/early stage breast, non-small cell lung, and ovarian cancer patients. The National Cancer Institute's Patterns of Care (POC) studies collected data on chemotherapy by reviewing hospital and medical records and contacting physicians. POC data were linked and compared to Medicare claims and measures of agreement and validity were estimated.

Using validated definitions, we constructed a cohort of stage II/III CRC patients from the Surveillance, Epidemiology, and End Results program (SEER)-Medicare linked database to 1) estimate trends in the utilization of agents over time and 2) identify patient, physician, and hospital characteristics associated

with the receipt of oxaliplatin using Poisson regression models and a generalized estimating equation (GEE) strategy for non-nested clustering.

Overall, the sensitivity and specificity of Medicare claims to identify any chemotherapy were high; however, we found variation across agents, sites and administration modalities. Shifts in utilization of specific agents were seen from 2000–2007, with increasing oxaliplatin and capecitabine use. Younger age, being married, fewer comorbidities, low-poverty areas, colon cancer diagnosis, and stage III disease were associated with oxaliplatin use.

Validated Medicare definitions identified a substantial increase in oxaliplatin utilization from 2004-2007 for both on- and off-label indications. Patient characteristics were most influential in explaining the variation in oxaliplatin receipt. Off-label use of chemotherapeutic agents was relatively common. Physicians should carefully weigh the minimal (if any) or unknown benefits of treatment against potentially serious side effects when deciding whether to treat a patient off-label.

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ABBREVIATIONS

AJCC	American Joint Commission on Cancer
CRC	Colorectal cancer
DFS	Disease free survival
FDA	Food and Drug Administration
GEE	Generalized estimating equation
mCRC	Metastatic colorectal cancer
NCCN	National Comprehensive Cancer Network
NPV	Negative predictive value
OS	Overall survival
PFS	Progression free survival
PPV	Positive predictive value
RCT	Randomized controlled trial
Se	Sensitivity
SEER	Surveillance, Epidemiology and End Results Program
Sp	Specificity

CHAPTER 1

STATEMENT OF SPECIFIC AIMS

Colorectal cancer (CRC) is the third leading cause of cancer death in men and women in the United States (US) and accounts for approximately 142,000 new cases each year. The incidence of CRC increases steadily with age, with men generally having a higher incidence rate than women.[1] However, when the number of cases by age and sex are estimated, older women tend to take on a large portion of the overall burden, as they generally have longer life expectancies. CRC is a disease primarily of the elderly with a median age at diagnosis of 72 years old, representing a significant disease burden among elderly individuals in the US.

Chemotherapy plays an important role in the treatment plan of cancer, as it has been shown to decrease the risk of recurrence and overall mortality. Recent clinical trials have documented the efficacy of new chemotherapeutic agents for the treatment of CRC. In particular, a recent trial demonstrated that adding oxaliplatin to fluorouracil plus leucovorin (5-FU) significantly improved 5-year disease-free and 6-year overall survival for individuals diagnosed with stage III, but not stage II colon cancer. In November 2004, the Food and Drug Administration approved oxaliplatin for the treatment of stage III colon cancer.

Medicare claims are frequently used to track trends and evaluate chemotherapy use in the elderly because of their longitudinal and population-based

features. Prior studies have shown that Medicare claims can be reliably used to identify overall chemotherapy use; however, their ability to identify a variety of specific agents, including oxaliplatin, remains unknown. Furthermore, few studies have examined the translation of trial evidence on oxaliplatin into routine practice, particularly among individuals diagnosed with stage II colon or stage II or III rectal cancers (off-label indications) and the elderly, who are often excluded from trials.

This dissertation addressed the following questions:

1) Can Medicare claims be used to accurately capture the receipt of any chemotherapy and specific chemotherapeutic agents as part of the initial course of treatment among individuals diagnosed with early stage breast cancer, stage II and III CRC, non-small cell lung cancer, and ovarian cancer?

2a) What is the prevalence of specific chemotherapeutic agent utilization from 2000-2007 among stage II and III CRC?

2b) What are the independent patient, physician, and hospital characteristics that influence the receipt of oxaliplatin?

To answer these questions, the following specific aims were addressed in this research:

Specific Aim 1

Assess the utility of Medicare claims to capture the receipt of any chemotherapy and specific agents delivered to patients diagnosed at age ≥65 with stage II or III colorectal cancer (CRC), in situ or early stage breast, non-small cell lung cancer (NSCLC), or ovarian cancer using various post-diagnosis claims windows.

Hypothesis - Specific Aim 1

The Se and Sp of Medicare claims to identify the receipt of any chemotherapy will be high (>85%) for all cancer sites. A longer post-diagnosis window will improve the Se for identifying the receipt of specific chemotherapeutic agents in Medicare data. The Se and Sp of specific agents will vary by agent, cancer site, mode of administration, and post-diagnosis period.

Rationale for Specific Aim 1

Prior studies have confirmed that Medicare claims can be used to identify the receipt of any chemotherapy. However, the validity of using Medicare claims to identify the use of newly approved agents such as oxaliplatin and capecitabine have not been evaluated. In addition, there is a lack of guidance on how long of a post-diagnosis window is appropriate for the assessment of the initial course of chemotherapy. An updated assessment of prior studies may provide insight into improvements in coding of specific agents over time.

Specific Aim 2a

Estimate the prevalence of specific chemotherapeutic agent utilization (5-FU, capecitabine, oxaliplatin, irinotecan, and bevacizumab) from 2000-2007 among elderly stage II and III CRC patients. Stratify the prevalence analysis by cancer site and stage to examine on- and off-label utilization.

Hypothesis - Specific Aim 2a

The prevalence of 5-FU will decrease over the period from 2000-2007 for all cancer site and stage groups, while the prevalence of capecitabine and oxaliplatin will be highest among stage III colon cancer patients (i.e., on-label indication). The utilization of irinotecan will decrease over the time period. Bevacizumab utilization will be low over the entire time period for all cancer site and stage groups.

Rationale for Specific Aim 2a

Prior studies have focused mainly on examining trends in the receipt of any chemotherapy or guideline concordant treatment. The few studies that have examined trends in specific chemotherapeutic utilization have mainly focused on patients diagnosed with stage III colon or metastatic CRC. Little is known about the utilization of specific chemotherapeutic agents among stage II colon and stage II and III rectal cancer patients. Updated information will provide a more timely representation of current patterns of chemotherapy use.

Specific Aim 2b

Identify independent patient, physician, and hospital characteristics associated with the receipt of oxaliplatin among elderly stage II and III CRC patients who receive chemotherapy. Stratify analyses by on- and off-label indication.

Hypothesis - Specific Aim 2b

Younger patients and those with little comorbidity will be more likely to receive oxaliplatin. By conditioning on the receipt of chemotherapy, race/ethnicity and other

area level measures of socioeconomic status (SES) will not be associated with the receipt of oxaliplatin. Physicians who more recently graduated from medical school will be more likely to provide oxaliplatin to their patients. Patients undergoing surgery at larger hospitals, those with an NCI clinical or comprehensive cancer center designation, and those with NCI cooperative group participation will be more likely to receive oxaliplatin.

Rationale for Specific Aim 2b

Prior studies have shown that a number of patient and tumor characteristics are strongly associated with the receipt of any chemotherapy. However, few studies have examined patient, physician, and hospital factors related to receipt of oxaliplatin among those who receive some chemotherapy. Of the studies that have been conducted, stage II colon and stage II and III rectal cancer patients are often excluded from analysis. Off-label use of oxaliplatin is common, but it is unknown whether the factors that predict on- and off-label use are the same.

CHAPTER 2

REVIEW OF LITERATURE

A. BACKGROUND

Public health significance of colorectal cancer

Colorectal cancer (CRC) places a significant burden on the United States (US) health care system as the third leading cause of cancer death among men and women. In 2010, there were an estimated 142,570 newly diagnosed cases and 51,370 deaths attributable to CRC, leading to approximately $8.9 billion in health care spending.[2,3] The median age at diagnosis for CRC is 71 years old; therefore, as the overall US population ages, the burden of incident and likely prevalent CRC will continue to increase.[4-6]

The TNM system is one of the most commonly used cancer staging systems and was developed by the American Joint Commission on Cancer (AJCC) and the International Union Against Cancer (UICC). The TNM staging system requires three pieces of information to stage a cancer: 1) the tumor size and number of tumors (T); 2) lymph node involvement (N); and 3) the presence or absence of metastasis (M). The prognosis for a patient depends greatly on the stage of cancer at diagnosis. For example, the 5-year overall survival for stage I CRC is higher than 90% while the overall survival declines to less than 10% for stage IV CRC.[7]

Based upon data from the Surveillance, Epidemiology and End Results Program

(SEER), approximately 50% of all CRCs are diagnosed at stage II or III, representing a large proportion of the total CRC burden.[8] Five-year relative survival rates for stage II and III CRC are 70% and 56%, respectively, indicating the need for additional treatments or wider dissemination and access to effective treatments that extend survival and improve quality of life.[9]

Role of chemotherapy in the treatment of stage II and III colorectal cancer

Guidelines for the treatment of stage II and III CRC have changed over time, but have generally included a combination of surgery, radiation, and/or chemotherapy.[10,11] For many individuals, chemotherapy (either neoadjuvant and/or adjuvant) represents an integral part of the treatment plan, proven to decrease the risk of disease recurrence and overall mortality.[12-19]

Randomized controlled trial evidence: stage II and III colon cancer

The mainstay of chemotherapeutic treatment since the late 1990's for colon cancer has been 5-fluorouracil (5-FU). 5-FU is a fluoropyrimidine that acts primarily through inhibiting thymidylate synthetase, the rate-limiting enzyme in pyrimidine nucleotide synthesis.[20] When 5-FU was combined with another vitamin, leucovorin, efficacy of the treatment was found to be greatly enhanced.[21]

Capecitabine is an oral chemotherapeutic prodrug, meaning that through a series of enzymatic steps, it preferentially forms 5-FU in tumor tissue.[22] Capecitabine was tested in an equivalency trial, the Xeloda in Adjuvant Colon Cancer Therapy (X-ACT) trial, which compared intravenous bolus 5-FU/LV (Mayo Clinic regimen) with

oral capecitabine for 6 months in stage III colon cancer. The study found that across study arms, there were no differences in disease free survival (DFS) or levels of toxicity.[19]

A number of fluoropyrimidine combinations were subsequently investigated in metastatic CRC (mCRC) patients starting the mid-1990's. These trials found that that the addition of oxaliplatin or irinotecan to 5-FU/LV substantially improved progression free survival (PFS) and overall survival (OS). To determine whether the improved efficacy observed in the metastatic setting translated into benefits in earlier stage disease, four trials were conducted among stage II and III colon cancer patients.

Three phase III RCTs were conducted examining the addition of oxaliplatin to various fluoropyrimidine regimens. The first was the Multicenter International Study of Oxaliplatin/5-FU/LV in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial, which included 2246 patients with stage II and stage III colon cancer and compared a 5-FU/LV regimen against an oxaliplatin-enhanced regimen (FOLFOX4) for 6 months. After 6 years of follow-up, FOLFOX4 extended DFS (HR=0.80; p=0.003) and OS (HR=0.84, p=0.046) for individuals diagnosed with stage II and III colon cancer compared to the 5-FU/LV regimen alone. However, when the follow-up trial results were stratified by stage, the increased effect of oxaliplatin on OS and DFS was driven primarily by stage III patients and no difference in OS was seen in the stage II group.[13] The second trial was the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial C-07, which evaluated the FLOX regimen (oxaliplatin added to weekly bolus of 5-FU/LV) in 2,492 patients with stage II and stage III colon

cancer. The DFS findings from this trial were consistent with those demonstrated in the MOSAIC study (HR=0.80, p=0.004).[23] The final combination trial was the NO16968 which examined whether capecitabine plus oxaliplatin (XELOX) was superior to bolus 5-FU/LV. Consistent with the prior two studies, adjuvant therapy with XELOX significantly improved DFS in stage III colon cancer in the (HR=0.80, p=0.0045).[24]

Two similar trials examining the addition of irinotecan to a 5-FU regimen were conducted among stage II and III colon cancer patients, based on the success of the combination treatment in the metastatic setting. However, all three trials failed to show any DFS or OS benefit for the combination.[25,26] A summary of these trials is provided in Table 2.1 below.

Randomized controlled trial evidence: stage II and III rectal cancer

Because of the location of rectal cancer and an increased risk of local recurrence and a poorer overall prognosis, its treatment is somewhat different than colon cancer. Specifically, rectal cancer management often requires radiation and different surgical techniques. Regarding chemotherapy treatment, in the late 1980's, postoperative chemotherapy was considered the standard of care as demonstrated in the NCCTG-864751 trial showing that the administration of 5-FU during pelvic irradiation improved the effect of combined-treatment postoperative adjuvant therapy in stage II and III rectal cancer patients.[27] A subsequent trial conducted in North America demonstrated that the addition of leucovorin to fluorouracil during radiation did not improve disease-free or overall survival.[28] Finally, in 2004, the German

Rectal Cancer Study Group randomized trial compared preoperative and postoperative chemoradiotherapy in 823 patients with stage II or III rectal cancer. Study results showed that preoperative chemoradiation therapy increased the rate of sphincter-sparing operations and lowered the overall rates of local recurrence and toxicities. Based on this data, preoperative chemoradiotherapy has become the standard of care in stage II and III rectal cancer.[29] A summary of these trials is provided in Table 2.2 below. Currently, RCT evidence from colon cancer is used to support pre- and post-operative treatment with oxaliplatin in rectal cancer patients. However, one RCT is underway examining the efficacy of preoperative chemoradiotherapy, surgery, and postoperative chemotherapy comparing chemotherapy regimens of capecitabine or 5-FU in combination with or without oxaliplatin among stage II and III rectal cancer patients. Preliminary findings show that the addition of oxaliplatin to preoperative 5-FU or capecitabine treatment did not improve preliminary outcomes, but resulted in substantial toxicity.[30]

Food and Drug Administration approval and off-label use of chemotherapy drugs

Food and Drug Administration (FDA) approval for all new drugs is based largely on the results of pivotal phase III trials. However, there are specific mechanisms in place such as fast track, accelerated approval, and priority review which seek to expedite the approval process and minimize the time from application to marketing of the drug. Often times, cancer drugs will receive fast track or priority status because they tend to address “serious diseases with unmet medical needs” or

they offer “major advances in treatment or provide a treatment where no adequate therapy exists.”[31]

However, when a drug is used for a purpose other than its approved FDA indication, it is considered an off-label use. Prescribing for off-label indications is common in oncology primarily due to a lack of effective treatments and the relatively low survival rates associated with late stage disease. In fact, according to the National Comprehensive Cancer Network (NCCN), between 50 – 75% of all cancer therapies in 2005 were used off-label.[32,33] Capecitabine and oxaliplatin are currently approved by the FDA for use in treatment of patients with metastatic CRC and for patients with stage III colon cancer.[34] However, little is known about the magnitude or distribution of its off-label use in individuals diagnosed with stage II colon or stage II or III rectal cancer.

Clinical guidelines and recommendations

Guidelines and recommendations for the treatment of CRC have changed substantially over time, primarily due to innovations in treatments. The NCCN guidelines are the recognized standard for clinical policy in oncology. The guidelines are updated on a continual basis and are developed through an explicit review of the evidence integrated with expert medical judgment by multidisciplinary panels.[10,11]

For individuals diagnosed with stage III colon cancer, the NCCN recommends 6 months of adjuvant chemotherapy treatment with FOLFOX, and oxaliplatin-containing regimen, as it has been shown to be superior to 5-FU/LV alone.[10] However, among patients that may be inappropriate to treat with FOLFOX (e.g.,

those with particular comorbidities), a regimen of 5-FU/LV may be recommended.[35-37]

Among individuals diagnosed with stage II colon cancer of high to intermediate risk of recurrence (as defined above as "high-risk"), NCCN believes that treatment with FOLFOX is reasonable.[38] Adjuvant therapy among low-risk stage II colon cancer patients remains controversial and the NCCN has recommended against its routine use in low-risk stage II patients.[39] However, a recent non-experimental study published by O'Connor et al found that adjuvant chemotherapy did not result in improved overall survival for stage II colon cancer patients with or without high risk features.[40]

Current NCCN recommendations for the treatment of stage II and III rectal cancer include initial surgery with chemoradiation therapy, although some controversy remains as to whether pre- or postoperative chemoradiation therapy is more beneficial.[11] For those individuals who receive preoperative chemoradiotherapy, postoperative treatment with oxaliplatin is recommended, yet specific sub-groups of individuals diagnosed with stage II rectal who may benefit are still unclear.[41-43] The current support for the use of oxaliplatin in rectal cancer is derived primarily from clinical trials in colon cancer.

B. IDENTIFICATION OF CHEMOTHERAPY IN ADMINISTRATIVE DATA

The role of administrative data sources in pharmacoepidemiology

Over the last 25 years, there has been increased interest in using automated healthcare claims databases for research. These data are prospectively collected for

administrative or billing purposes, but often contain detailed longitudinal information on demographic characteristics and healthcare utilization for a large number of covered individuals under discrete health insurance plans. These data are not subject to biases that may arise in primary data collection such as recall and interviewer bias because there is no direct interaction with the patients. Furthermore, some automated databases may be population-based, which aids in the generalizability of the findings to a defined group of individuals. Lastly, these data are particularly appealing because they tend to be cost-effective (relative to the costs of collecting primary data) and efficient (regarding the amount of time it may take to complete an analysis).[44] However, these data are often lacking important clinical information that may be required to conduct an unbiased study. As such, linkages between disease registries or electronic health records and administrative claims data can greatly improve the quality of the database for research purposes.

Uses of the Surveillance, Epidemiology, and End Results program (SEER)-Medicare linked database

One such example is the Surveillance, Epidemiology, and End Results program (SEER)–Medicare linked database. The SEER-Medicare consists of a linkage of two large population-based data sources providing detailed clinical and healthcare utilization information on Medicare beneficiaries diagnosed with cancer.[4] The SEER 17 registries collect demographic, clinical and tumor characteristics, vital status, and cause of death for all incident cancers reported for individuals who reside in one of the registries' defined geographic areas, currently covering approximately

28% of the US population.[45] These data have been linked to Medicare enrollment and Part A (Hospital insurance) and B (Medical insurance) claims data. Approximately 93% of all elderly cancer patients in SEER have been matched to Medicare enrollment files with an established algorithm, resulting in a linked database that includes over 3.3 million elderly individuals (age ≥ 65 years).[46] Nearly all Medicare beneficiaries are eligible for Part A and close to 93% opt to enroll in the Part B.[47]

Utility of SEER-Medicare data to identify chemotherapy use

The SEER-Medicare data can be used to examine a wide range of research topics across the trajectory of care for elderly cancer patients. In particular, the data are increasingly used to conduct non-experimental studies evaluating the uses, benefits, and harms of chemotherapeutic treatments among individuals excluded from trials, including older adults, those with multiple co-morbidities, and those treated off-label.

The validity of these studies relies upon a variety of issues, including the ability of claims data to accurately capture treatment(s) of interest, study endpoint(s), and other important design and clinical issues.[48] Measurement error in the assessment of chemotherapy could lead to biased study results. Prior studies have examined the validity of Medicare claims data to identify chemotherapy. A study by Warren et al[49] assessed the utility of Medicare claims data for identifying the receipt of chemotherapy among individuals diagnosed with in situ or early stage breast, stage II or III CRC, and ovarian cancer. The authors calculated the sensitivity of

Medicare claims dies to identify the receipt of chemotherapy compared to information obtained from the Patterns of Care (POC) studies in 1991 and 1995. The POC studies collected the gold standard treatment information through re-abstraction of hospital data, physician confirmation of outpatient treatment, and review of medical records. They authors found that for all cancer sites, the Se of identifying any chemotherapy use was high (>88%); yet, the Se and Sp of specific agents varied.[49]

Another study examined the validity of Medicare inpatient and outpatient claims for identifying specific agents in comparison to two Cancer and Leukemia Group B (CALGB) trials among breast (1995-1997) and lung (1998-2000) cancer patients. The study reported the Se and Sp for doxorubicin were 91% (95% CI: 79%, 98%) and 100%, respectively and for paclitaxel were 86% (79%, 92%) and 100%, respectively.[50]

Rationale for Aim 1:

Prior research studies support the validity of Medicare claims data to identify intravenously administered chemotherapy treatment for a variety of cancer sites,[49-53] but do not address more recently approved or orally administered agents or changes in validity using multiple claims windows following diagnosis.

Therefore, the first aim of this dissertation was to assess the utility of Medicare claims for capturing the receipt of any chemotherapy and specific agents delivered to patients diagnosed at age ≥65 with stage II or III colorectal cancer (CRC), in situ or early stage breast, non-small cell lung cancer (NSCLC), or ovarian

cancer. This assessment 1) evaluated the validity of selected single agent chemotherapies, including an orally-administered agent and 2) described the variation in measures of validity for any chemotherapy and specific treatments over multiple follow-up periods and across cancer sites. This updated validation study will provide contemporaneous information for researchers to use to assess the impact of treatment misclassification in their studies and conduct sensitivity analyses attempting to correct for this bias.

C. UTILIZATION OF CHEMOTHERAPY TREATMENT AMONG STAGE II AND III COLORECTAL CANCER PATIENTS

Generalizability of RCT evidence of chemotherapy treatment among colorectal cancer patients

RCTs examining the efficacy of chemotherapeutic treatments are conducted within relatively small, well-defined populations in order to isolate the effect of the treatment on DFS and OS. However, this selection reduces the generalizability of the study results to the general cancer population, which tends to be older and less healthy. The median age of patients enrolled in the two primary oxaliplatin trials, MOSAIC and NSABP C-07 were 61 and 59 years,[23,41] respectively; however, the median age of diagnosis for stage II and III CRC is 71 years. Additionally, trial participants were also relatively healthy, with over 90% having an Eastern Cooperative Oncology Group performance score of < 2,[54] indicating good overall health and physical activity. The discrepancy between the selected trial populations and the general CRC cancer population can lead to uncertainty in translation of the

RCT evidence into routine practice, particularly among the elderly and patients with more comorbidity.

Observational studies of chemotherapy utilization in stage II and III colorectal cancer

The overall use of drug therapies in community clinical practice is a combination of approved and off-label use. Tracking treatment utilization is important for assessing the dissemination of RCT evidence and clinical guidelines into routine clinical practice, particularly among populations who are excluded from trials, such as the elderly. Many studies have examined trends in the utilization of chemotherapy treatment or guideline concordant treatment over time; however few have focused specifically on stage II and III CRC patients. However, the National Cancer Institute (NCI) initiated the POC studies in response to a congressional mandate to report on the dissemination of state-of-the-art therapy into community practice. The POC studies utilize information from the SEER cancer registries and thus are population-based. The first study by Potosky et al[55] reported trends in adjuvant 5-FU utilization among a cohort of stage II and III colon cancer patients and adjuvant chemotherapy and radiotherapy utilization among stage II and III rectal cancer patients of all ages diagnosed from 1987-1995. The study found that stage III colon cancer patients had higher utilization of adjuvant 5-FU when compared to stage II colon cancer patients, which was consistent with clinical guidelines. Uptake of 5-FU was most notable between 1989 and 1990 for this group. Among the stage II and III rectal cancer patients, combined adjuvant chemotherapy with radiation increased starting around

1989, which marked the decline in the utilization of radiation therapy alone. Similar to colon cancer, the utilization of chemotherapy and radiotherapy were higher among stage III compared to stage II rectal cancer patients, reflecting the lower risk of recurrence in earlier stage cancer. For both colon and rectal cancers, utilization of chemotherapy was much lower for patients diagnosed at age ≥ 75 years over the entire time period, potentially signaling an issue with "ageism."[55] Pooled analyses have repeatedly found that elderly individuals derive similar benefit from adjuvant chemotherapy treatment with no increased toxicity.[56]

An update to the first POC study was published by Cronin et al and examined the dissemination of guideline concordant treatment for stage III colon and II and III rectal cancer patients of all ages diagnosed from 1987-1991, 1995, and 2000. Guideline concordant therapy was defined as adjuvant 5-FU treatment for stage III colon cancer and adjuvant 5-FU and radiotherapy for rectal cancer. Over the time period, guideline concordant therapy increased among stage III colon and stage II rectal cancer patients, but slightly decreased for stage III rectal cancer patients. Similar to the findings by Potosky et al, older individuals (≥ 75 years) were substantially less likely to receive guideline concordant therapy across all cancer site and stage groups in 1995 and 2000.

Ferro et al[57] published a cross-sectional study based on treatment information from 115 ambulatory centers in the US to examine the utilization of 8 of the most commonly prescribed chemotherapeutic regimens by 421 individuals diagnosed with CRC between 2002 and 2005. Almost 50% of the individuals in this cohort were diagnosed with mCRC. The most common regimens were 5-FU/LV

(35%), irinotecan-containing (26%), and oxaliplatin-containing (25%) treatments. This pattern was generally consistent across regions, however, use of oxaliplatin varied somewhat by region (29.7% in the South vs. 2.5% in the West), which may reflect patterns in HMO penetration. As expected, the percentage utilization of oxaliplatin substantially increased from 0% in March 2002 to 61% by 2005.

The SEER-Medicare data have also been used to track the utilization of chemotherapy treatment for CRC. A recent cohort study by Hsiao et al[58] sought to compare the effectiveness and utilization of 5-FU/LV, irinotecan-based and oxaliplatin-based chemotherapeutic regimens for elderly (≥ 66 years) stage III colon cancer patients diagnosed from 2002-2005. The study identified 4,614 stage III colon cancer patients who received chemotherapy after colon resection. Over the time period, 5-FU/LV utilization decreased from 32% in 2002 to 15% in 2005, irinotecan-based regimens decreased from 37% in 2000 to 14% in 2005, and oxaliplatin-based regimens increased from 35% in 2004 to 57% in 2005. A similar pattern of age effects on utilization was seen, where the initial uptake and prevalence of treatment with newer agents (i.e., irinotecan and oxaliplatin) was low among patients diagnosed at older ages.

The most recent study published on the utilization of specific chemotherapies for stage II and III colon cancer was conducted by Abrams et al [59] and used data from an outpatient chemotherapy ordering system in the US. This cross-sectional study identified patients receiving adjuvant chemotherapy between 2004 and the beginning of 2010. In 2004, 39% of stage III colon cancer patients received oxaliplatin with a fluoropyrimidine, but by 2007, this percentage increased to 90%.

Stage II colon cancer patients also experienced a rapid increase in oxaliplatin receipt, reaching 79% by 2008. Older age was again associated with decreased receipt of oxaliplatin in both stage II and III colon cancer patients. Table 2.3 summarizes the study characteristics and results from the relevant literature on chemotherapy utilization among stage II and III CRC patients.

Rationale for Aim 2a:

Considering the breadth of literature in this area, questions remained about the utilization of a specific chemotherapeutic agents among stage II and III CRC patients. The majority of studies report utilization data through the end of 2005, with the exception of Abrams et al. Therefore, more timely data on the prevalence of treatment with specific chemotherapeutic agents for elderly stage II and III CRC patients and trends over a longer period of time are indicated. In addition, many specific chemotherapeutic agents of interest are only approved for stage III colon and stage IV CRC, but are being used off-label in stage II colon and stage II and III rectal cancer. The benefits of treatment in these groups are unknown or possibly minimal, yet known side effects associated with these treatments exist. Therefore, it is important to understand patterns in utilization of specific agents among off-label groups, particularly in stage II and III rectal cancer where limited data exist. Capecitabine is an oral prodrug that has been shown to have equivalent efficacy to 5-FU/LV, but with less toxicity. However, data on trends in the replacement of 5-FU with capecitabine are lacking.

This dissertation addressed the above questions using a more

contemporaneous data source (the SEER-Medicare linked database containing health care utilization data through 2008) and stratified analyses by cancer site and stage in order to report trends in off-label use.

D. OBSERVATIONAL STUDIES ON THE INFLUENCE OF PATIENT, PHYSICIAN, AND HOSPITAL CHARACTERISTICS ASSOCIATED WITH THE RECEIPT OF OXALIPLATIN IN STAGE II AND III CRC

A vast literature has developed around examining patterns of health services use among cancer patients. For simplicity, the literature can be divided into three phases on the continuum of care: 1) diagnosis and initial treatment, including surgery, chemotherapy, radiotherapy, 2) post-diagnostic surveillance and survivorship, and 3) terminal or end-of-life care.[46] To evaluate patterns of care among cancer patients, a conceptual model such as the Andersen Behavioral Model,[60] adapted and pictured below in Figure 2.1, are often used to provide a framework for developing research studies.

The focus of this review is to summarize the literature that specifically examines patterns of oxaliplatin treatment among stage II and III CRC. However, a great deal of work has already focused more broadly on patient, physician, and facility characteristics associated with the receipt of any chemotherapy among CRC patients. I will first briefly summarize the broad chemotherapy literature and then focus specifically on the literature relevant to oxaliplatin.

Patient, physician and hospital characteristics and the receipt of chemotherapy

among stage II and III CRC

As shown in the conceptual model above, patient characteristics such as age, sex, race/ethnicity, marital status, comorbid conditions, and income can all be classified as predisposing factors that may be related to the receipt of health services. A number of studies have examined patient factors that are associated with chemotherapy treatment in stage II and III CRC. One area of research has focused on racial disparities and the receipt of chemotherapy. Findings have consistently shown that Black Non-Hispanics diagnosed with stage II or III CRC are substantially less likely to receive chemotherapy than White Non-Hispanics, even after controlling for consultation with a medical oncologist.[55,61-69] Access to care, patient preferences, and patient-provider interactions have all been hypothesized as potential areas for further research to investigate reasons for this disparity.

Another area of intense research has investigated the effect of age at diagnosis and the receipt of chemotherapy. In general, findings have demonstrated that younger stage II and III CRC patients are much more likely to receive chemotherapy than older patients.[55,61,64,65,67-72] Physicians may be more concerned when treating elderly patients because of their overall health status and issues with the toxicity of chemotherapeutic treatment. But, as discussed previously, treatment among elderly patients has been shown to be as effective with similar levels of toxicity when compared to younger patients.[56,73]

Many studies have shown that patients with multiple comorbidities are less likely than those with no or few comorbidities to receive chemotherapy treatment.[55,61,64,65,67,68,70,71,74,75] Administrative databases often rely upon the

Charlson Comorbidity Index (CCI)[76] or an adaptation of the CCI to capture the health status of the patient;[77] however, particular comorbidities such as previous heart failure, chronic obstructive pulmonary disorder (COPD), diabetes or dementia have also been directly associated with decreased chemotherapy use among stage II and III CRC patients.[74,75]

Consistent with clinical guidelines, observational studies have also shown that characteristics of a patient's tumor are strongly linked to the receipt of chemotherapy among stage II and III CRC patients. Cancer of the rectum vs. colon, stage III vs. II disease, less differentiated tumors, and less than 12 lymph nodes examined have all been associated with increased chemotherapy treatment(cite).

The Andersen conceptual model also emphasizes the role of enabling factors in the health services utilization. The availability and quality of health care personnel and facilities may be important enabling forces. However, few studies have been conducted on examining the influence of physician and hospital characteristics on a patient's receipt of chemotherapy among stage II and III CRC. Only one study by Baldwin et al[62] examined patient, physician, and hospital characteristics associated with the receipt of chemotherapy among stage III colon cancer patients in order to explain black-white differences. In unadjusted analysis, physicians who were younger, male, white, with fewer years of practice experience, having higher volumes of CRC consultations, working in solo practice, and being board certified in internal medicine were less likely to treat black patients with chemotherapy compared to white patients. Similarly, in unadjusted analyses, black patients were less likely to receive chemotherapy treatment at hospitals with higher hospital patient

volume, teaching affiliation, NCI cancer centers affiliation or Oncology group membership. However, after multivariate adjustment and accounting for clustering, the study reported that the majority of the black-white disparity in chemotherapy receipt was explained by patient characteristics and that physician and hospital characteristics contributed very little to the overall models.

A study by Keating et al[71] surveyed physicians treating cancer patients and asked them about their recommendations for chemotherapy treatment according to age and comorbidity of patients. The authors also examined the influence of physician and practice characteristics on the administration of chemotherapy treatment. Overall, the study found that physicians varied in their recommendations for chemotherapy among older and sicker patients. Younger physician age was associated with an increased prevalence of treatment; however, other physician and practice characteristics did not strongly influence the treatment decision. Physician age would seem to be a proxy for length of time passed since medical school and residency training with the assumption that younger doctors were trained most recently and may be aware of the most recent evidence on chemotherapy treatment for elderly and those with multiple comorbidities.

Patient, physician and hospital characteristics and the receipt of oxaliplatin among stage II and III CRC

Oxaliplatin was approved by the FDA for the adjuvant treatment of resectable stage III colon cancer in November 2004.[34] As it is a relatively new treatment, there are few studies that have examined the patterns of oxaliplatin receipt in the routine

practice setting. Five studies were identified that have examined patient and/or physician characteristics associated with the receipt of oxaliplatin. These studies are summarized in Table 2.4 below. No studies have examined characteristics of the hospital where patients receive surgery and its influence on the receipt of oxaliplatin (similar to the study design of Baldwin et al[62]).

Two of these studies examined on-label use of oxaliplatin among individuals receiving chemotherapy. [58,70] The first study by Kahn et al was a population- and health system-based observational study examining adjuvant chemotherapy use and the occurrence of adverse events by age among 675 stage III colon cancer patients. Initial chemotherapy treatment was defined within the 6-months following surgical resection and assessed through medical record review. The second study by Hsiao et al utilized the SEER-Medicare database to compare the effectiveness and utilization trends of irinotecan and oxaliplatin regimens with those of 5-FU/LV among 4,614 stage III colon cancer patients. In bivariate analysis, these studies found that older age was strongly associated with a decreased prevalence of oxaliplatin receipt. However, no further multivariate analysis was conducted investigating the associations between patient-level characteristics and the receipt of oxaliplatin.

A more recent study by Lund et al[78] utilized the POC 2005 data to examine independent patient-level predictors for the receipt of oxaliplatin among a random sample of stage II/III CRC patients diagnosed in 2005. In 2005, 69% and 39% of CRC patients treated with chemotherapy in a SEER area received oxaliplatin for on- and off-label indications, respectively. Older age (65+ vs. <65) decreased the prevalence of both on- (prevalence ratio (PR)=0.47, 95% CI: 0.34, 0.64) and off-label

(PR=0.62, 95% CI: 0.45, 0.85) oxaliplatin use. For off-label indications, compared to patients diagnosed with stage II colon cancer, patients diagnosed with stage II (PR=0.37, 95% CI: 0.25, 0.55) and stage III (PR=0.70, 95% CI: 0.51, 0.95) rectal cancer were less likely to receive oxaliplatin. There was some evidence that Hispanics were less likely to receive oxaliplatin off-label as compared to White Non-Hispanics (PR=0.71, 95% CI: 0.47, 1.07). In addition, regional variation was seen where individuals residing in the South and East had a lower prevalence of oxaliplatin treatment compared to those treated in the West.

Another study by Becker et al examined the role of both patient and physician characteristics in the receipt of oxaliplatin among stage III colon cancer patients.[79] This study was limited to 1,884 elderly individuals diagnosed with stage III colon cancer from September 2004-December 2005 using the SEER-Medicare database. Only 44% of the individuals in the analysis received chemotherapy and just over 50% of them received oxaliplatin. The authors conducted a multivariate logistic regression using generalized estimating equations (GEE) to account for clustering by physician to examine patient and physician predictors of the receipt of oxaliplatin; however, their analysis included individuals who did not receive any chemotherapy treatment. Patient factors including younger age (OR=3.64, 95% CI: 2.38-5.57), white race (OR=1.93, 95% CI: 1.06-3.49), being married (OR=2.21, 95% CI: 1.60-3.07), fewer comorbidities (OR=2.84, 95%: CI 1.81-4.45), urban location (OR=2.37, 95% CI: 1.35-4.05), and moderate/poorly differentiated cancer (OR=2.47, 95% CI: 1.30-4.67) were associated with the receipt of oxaliplatin. The only physician characteristic that had an influence on oxaliplatin receipt was having a younger

physician (OR=1.66, 95% CI: 1.12-2.46). The results of this study potentially mix the effects of patient and physician characteristics associated and overall chemotherapy receipt with the effects of these factors and the receipt of oxaliplatin (among a chemotherapy treated population).

A cross-sectional study by Abrams et al[59] examined predictors of initiation of adjuvant chemotherapy in stage II and III colon cancer patients. This was the first study to report off-label patterns of oxaliplatin in stage II colon cancer. The study relied upon information from IntelliDose, an outpatient medical oncology practice ordering system for chemotherapy, and included 2,560 patients diagnosed from January 2004–April 2010. Treatment information was captured by physicians ordering specific chemotherapeutic agents and doses. This analysis was limited to individuals receiving chemotherapy and reported that older patients (80+ vs. <50: OR=0.05 (95% CI: 0.03, 0.09), those with diminished performance status (ECOG 2 vs. 0: OR=0.34 (95% CI: 0.21, 0.56), and those treated in a private practice settings (OR=0.44 (95% CI: 0.27, 0.70) were significantly less likely to receive oxaliplatin. However, the authors were unable to examine the association between race, insurance coverage, socioeconomic status, and the number of lymph nodes examined, which are likely important factors in treatment selection.

Rationale for Aim 2b:

Little research has focused on patterns of oxaliplatin use among stage II and III CRC. Of the existing studies, most have examined on-label use of oxaliplatin; however, off-label use is common and should be further investigated. Only two

studies have examined the influence of patient and physician characteristics in oxaliplatin treatment; however, these two studies included two different source populations, one that conditioned upon chemotherapy receipt and one that did not. Therefore, inconsistencies in the results may be due to a mixing of the effects of chemotherapy receipt and oxaliplatin receipt, specifically. It is possible to examine the role of hospital where a patient receives surgery and their influence on oxaliplatin receipt. Baldwin argued that even though chemotherapy is almost always administered in the outpatient setting, the characteristics of the hospital where surgery took place may influence chemotherapy receipt through the medical oncologists' readmission of patients to the resection hospital, and therefore could represent a point of early education regarding the benefits of adjuvant chemotherapy.

This dissertation addressed the above issues by examining the influence of patient, physician, and hospital characteristics on the receipt of oxaliplatin among stage II and III CRC patients and stratified analyses by cancer site and stage in order to examine patterns of off-label use.

E. SUMMARY

Significance of the study

This study addressed two primary research questions. The first aim provided updated information on the validity of Medicare claims to identify the initial course of chemotherapy treatment (including the specific agents administered) among patients diagnosed with a variety of cancers in 2000, 2002, and 2005. The second aims

yielded detailed information about 1) the prevalence of treatment with specific chemotherapeutic agents for the treatment of stage II and III CRC and trends in their utilization from 2000-2007; and 2) the patient, physician, and hospital characteristics associated with the receipt of oxaliplatin treatment.

These findings can be useful in three ways:

Report updated validation information for researchers using the SEER-Medicare data for chemotherapy-related research: Large healthcare databases are increasingly used to examine the dissemination and benefits and harms of chemotherapy treatment in routine practice, particularly among patients excluded from trials (e.g., the elderly). Misclassification of chemotherapy could bias estimates of frequency and association. An updated assessment of the work by Warren et al[49] is indicated as questions remain regarding the validity of Medicare claims to identify newly approved chemotherapeutic agents, the appropriate time window for assessment of initial chemotherapeutic treatment, and the validity of orally administered agents. This research can be used to assess the impact of potential misclassification in studies relying upon the SEER-Medicare linked database and to conduct sensitivity analyses which attempt to correct for such misclassification.

Provide a more accurate picture of oxaliplatin utilization in the community: Drug utilization in routine clinical practice consists of both on- and off-label use. Oxaliplatin is currently approved by the FDA for the treatment of resectable stage III colon cancer, yet prior studies have shown that patients diagnosed with stage II colon and stage II and III rectal cancer frequently receive oxaliplatin as part of their initial course of treatment.[78,79] Prior studies have generally focused on utilization

among patients treated primarily for metastatic disease at a small number of clinics, which may not reflect patterns of care in the larger community practice. Our study will be the first to assess on- and off-label use of oxaliplatin treatment in a large, population-based community practice setting.

Inform targeted interventions to improve dissemination and appropriate use of oxaliplatin in clinical practice: Observational studies investigating the influence of patient, physician and hospital characteristics and the receipt of oxaliplatin are necessary to help elucidate the gap between the current state of knowledge based on RCT evidence and the reality of treating diverse populations in the community setting. Findings from these studies may highlight areas of potential overuse and underuse of oxaliplatin and may be helpful in developing targeted interventions to encourage more safe and equitable dissemination of treatment.

Table 2.1 Selected clinical trials of adjuvant chemotherapy in stage II and III colon cancer

Trial	N	End Point	Stage	Trial Conclusions	References
INT-0035	929	OS	III	5-FU/levamisole superior to observation	Moertel et al
NSABP C-04	2078	DFS, OS	Dukes B/C	5 FU/LV superior to 5-FU/levamisole	Wolmark et al
INT-0089	3759	DFS	II and III	Equivalency of 6 and 12 mo treatment cycles and of high dose vs. low dose LV	Haller et al
QUASAR	3239	OS	II (92%)	5-FU/LV superior to observation	Gray et al
GERCOR C96	905	DFS	Dukes B2/C	Equivalency of LV5-FU2 and monthly 5-FU/LV	André et al
X-ACT	1987	DFS	III	Capecitabine equivalency with LV5-FU bolus; less toxic	Twelves et al
MOSAIC	2246	DFS	II and III	FOLFOX4 superior to LV5-FU2	André et al
NSABP C-07	2407	DFS	II and III	Bolus 5-FU/LV oxaliplatin (FLOX) superior to 5-FU/LV	Kuebler et al
NO16968	1886	DFS	III	Capecitabine plus oxaliplatin (XELOX) superior to standard bolus 5-FU/LV	Haller et al
CALGB 89803	1264	OS	III	No advantage for bolus IFL in stage III adjuvant CRC	Saltz et al
PETACC-3	3278	DFS	II and III	LV5-FU2 CPT11 not superior to LV5-FU2	Van Cutsem et al

**Adapted from Rousseau 2010*

Table 2.2 Selected clinical trials of adjuvant chemotherapy in stage II and III rectal cancer

Trial	N	End Point	Stage	Trial Conclusions	References
NCCTG-864751	660	DFS	II and III	5-FU during pelvic irradiation improved the effect of combined-treatment postoperative adjuvant therapy	O'Connell et al
INT-0114	1,696	DFS	II and III	No benefit of addition of leucovorin, levamisole, or both to 5-FU administered postoperatively	Tepper et al
SWOG-9304	1,917	DFS, OS	II and III	No DFS, OS or locoregional failure (LRF) benefit from adding leucovorin to 5-FU administered postoperatively	Smalley et al
German Rectal Cancer Study Group	823	OS	II and III	Preoperative chemoradiotherapy vs. postoperative chemoradiotherapy improved local control and was associated with reduced toxicity	Sauer et al

Table 2.3: Summary of observational studies chemotherapy treatment utilization among stage II and III CRC patients

Author Data source	N (age range)	Cancer site and stage	Years of analysis	Type of chemotherapy	Definition	Results
Potosky et al Patterns of Care Studies	N=2,145 20 years and older	Stage II and III CRC	1990, 1991, 1995	5-FU, 5-FU + radiation therapy	Re-abstraction of hospital records and physician verification of initial treatment planned or received	Colon: * 5-FU prevalence of treatment was higher in stage III compared to II disease * Differences by age, younger patients having higher utilization Rectum: * Increase in RT + chemotherapy in 1989 and decrease in RT alone * 5-FU prevalence +/- RT was higher in stage III compared to II disease
Cronin et al Patterns of Care Studies	N=827 in 2000 20 years and older	Stage III colon and stage II and III rectal cancer	1987-1991, 1995, 2000	Guideline concordant treatment Stage III Colon: Adjuvant 5-FU Stage II/III Rectal: Adjuvant 5-FU + RT	Re-abstraction of hospital records and physician verification of initial treatment planned or received	Colon: * Guideline concordant treatment increased over time. * Older patients less likely to receive guideline concordant care Rectum: * Guideline concordant treatment increase for stage II rectal cancer, but decreased for stage III rectal cancer

Ferro et al Nationwide prospective registry of patients initiating chemotherapy	N=421 21 - 97 years old	Stage I - IV CRC (Over 50% had mCRC)	2002-2005	Focus on top 3 utilized regimens: FOLFOX, IFL/FOLFIRI, and 5-FU/LV	Detailed case report form completed for 4 cycles of chemotherapy	Prevalence over the period: * 5-FU/LV (35%), IFL (26%), and FOLFOX (25%) Prevalence by year: * Oxaliplatin increased from 0% in 2002 to 61% in 2005
Hsiao et al SEER-Medicare database	N=4,615 66 - >80 years old	Stage III colon	2002-2005	5-FU/LV alone, Irinotecan-based regimen, Oxaliplatin-based regimen	HCPCS codes in Medicare claims	Prevalence by year: 2002-2005 5-FU: 32%, 32%, 21%, 15% Irinotecan: 37%, 33%, 16%, 14% Oxaliplatin (2004-2005): 35%, 57%
Abrams et al Outpatient medical oncology practices subscribing to the IntelliDose (Waltham, MA)	N=2,560 25-102 years old	Stage II or III colon	2004 - mid-2010	FOLFOX/CapeOx, 5-FU/LV/capecitabine, bevacizumab	Physicians entered specific chemotherapeutic agents and doses into ordering system	Stage III: * In 2004, 39% were treated with oxaliplatin * In 2008, prevalence peaked at 91% Stage II: * In 2008, 79% were treated with oxaliplatin Stage II and III: * Bevacizumab use peaked at 12% in 2006 and rapidly decreased after

Table 2.4: Summary of observational studies regarding patient and physician characteristics associated with oxaliplatin receipt among stage II and III CRC patients

Author Data source	N (age range)	Cancer site and stage	Years of analysis	Type of chemotherapy	Definition	Patient-level results	Physician-level results
Kahn et al Cancer Care Outcomes Research and Surveillance (CanCORs) Study	N=675 18 - >80 years old	Stage III colon	2003-2005	Initial chemotherapy treatment classified as oxaliplatin-containing, non–oxaliplatin-containing, and unknown regimens.	Chemotherapy was defined within 6 months after surgical resection and prior to any cancer recurrence using medical records	*Among adjuvant chemotherapy users, 14 (14%) of patients 75 years and older and 178 (44%) of younger patients used an oxaliplatin-containing regimen (difference, 30%; 95% CI, 21%-38%).	na
Hsiao et al SEER-Medicare	N=4,614 66 - >80 years old	Stage III colon (all receiving chemotherapy)	2002-2005	5-FU/LV alone, Irinotecan-based regimen, Oxaliplatin-based regimen	HCPCS codes in Medicare claims	* 17.6% (n=814) received oxaliplatin * Compared to patients 66-69 years old, patients ≥80 were less likely to receive oxaliplatin or irinotecan than younger patients (7.9% vs. 30%)	na
Lund et al Patterns of Care studies	N=1,602 20 years and older	Stage II and III CRC	2005	Oxaliplatin agent receipt	Re-abstraction of hospital records and physician verification of initial treatment planned or received	* Older age (65+ vs. <65): - On-label: PR=0.47 (95% CI: 0.34, 0.64) - Off-label PR=0.62 (95% CI: 0.45, 0.85) * Off-label indications (compared to stage II colon cancer patients) - Stage II rectal: PR=0.37 (95% CI: 0.25, 0.55) - Stage III: PR=0.70 (95% CI: 0.51, 0.95)	na

Becker et al SEER-Medicare	N=1,884 65+ years old	Stage III colon	September 2004 - December 2005	Oxaliplatin-containing regimen	HCPCS codes in Medicare claims	* 44% received chemotherapy and only 53.7% of them received oxaliplatin * Younger age: OR= 3.64 (95% CI: 2.38-5.57) * White race: OR= 1.93 (95% CI 1.06-3.49) * Being married: OR=2.21 (95% CI 1.60-3.07) * Fewer comorbidities: OR=2.84 (95% CI: 1.81-4.45) * Urban location: OR=2.37 (95% CI: 1.35-4.05) * moderate/poorly differentiated cancer: OR=2.47 (95% CI: 1.30-4.67)	Younger physician: OR=1.66 (95% CI: 1.12-2.46)
Abrams et al Outpatient medical oncology practices subscribing to the IntelliDose (Waltham, MA)	N=2,560 25-102 years old	Stage II or III colon (all receiving chemotherapy)	2004 - mid-2010	FOLFOX/CapeOx, 5-FU/LV/capecitabine, bevacizumab	Physicians entered specific chemotherapeutic agents and doses into ordering system	Stage II vs. II: OR=4.08 (95% CI: 3.19, 5.21) 50-59 vs. <50: OR=0.44 (95% CI: 0.23, 0.82) 60-69 vs. <50: OR=0.33 (95% CI: 0.18, 0.60) 70-79 vs. <50: OR=0.16 (95% CI: 0.09, 0.29) 80+ vs. <50: OR=0.05 (95% CI: 0.03, 0.09) ECOG 2 vs. 0: OR=0.34 (95% CI:0.21, 0.56) ECOG 1 vs. 0: OR=0.62 (95% CI: 0.47, 0.82) NE vs. MW: OR=0.64 (95% CI: 0.48, 0.87)	Private vs. Academic: OR=0.44 (95% CI: 0.27, 0.70) > 18 vs. ≤ 6 MAP: OR=1.46 (95% CI: 1.02, 2.11)

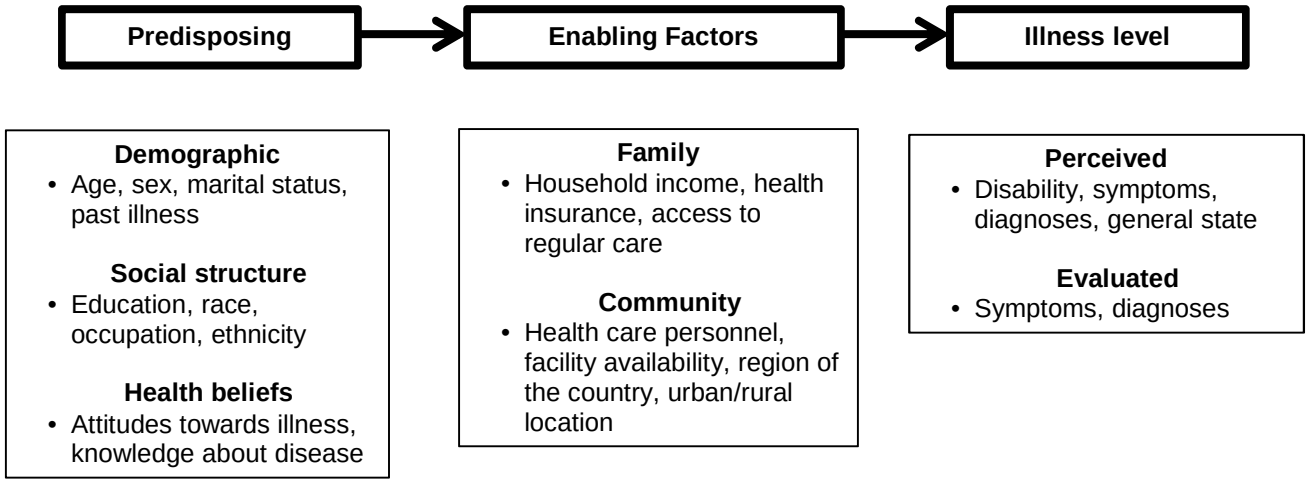


Figure 2.1. The Behavioral Model of Health Services Use. Adapted from the Behavioral Model of Health Service Use by Andersen, Joana, et al., 1975

CHAPTER 3

METHODS

This research consisted of two main components 1) an assessment of the utility of Medicare claims for capturing the receipt of any chemotherapy and specific agents delivered to patients diagnosed at age ≥65 with stage II or III colorectal cancer (CRC), in situ or early stage breast, non-small cell lung cancer (NSCLC), or ovarian cancer (*Specific Aim 1*), 2a) a description of trends in the utilization of specific chemotherapeutic agents for the treatment of stage II and III CRC (*Specific Aim 2a*), and 2b) an analysis of patient, physician, and hospital characteristics associated with the receipt of oxaliplatin from 2004-2007 (*Specific Aim 2b*). The methods that are common to both components will be described, followed by the methods specific to each component. Information from the SEER-Medicare linked database was used for all analyses. The University of North Carolina Public Health and Nursing Institutional Ethics Review Board approved the study protocol.

A. DATA SOURCES

Data for this study were obtained from multiple databases linked through collaborative agreements between the National Cancer Institute (NCI), the Centers for Medicare and Medicaid Services (CMS), and the American Medical Association (AMA).

Surveillance, Epidemiology and End Results (SEER) Program

(Specific aims 1, 2a, and 2b)

The NCI's Surveillance, Epidemiology, and End Results (SEER) program is an epidemiologic surveillance system collecting demographic information, clinical and tumor characteristics, initial surgical and radiation treatment, vital status, and cause of death for all individuals who are diagnosed with cancer and reside within one of the 17 SEER regions shown in Figure 3.1 below. These sites were selected based upon achieving the highest level of quality case ascertainment and reporting, and for their diverse sub-populations, making it one of the most relied-upon sources of national incidence and survival estimates. This program currently covers about 28% of the United States (US) and is comparable to the general US population across levels of poverty and education, but is slightly more urban and includes a greater proportion of foreign born residents.[80,81]

Patterns of Care (POC) studies

(Specific aim 1)

NCI supplements the standard SEER registry abstraction to obtain detailed information about treatment for a subset of SEER cases. This effort, known as the POC, was developed by NCI to investigate the dissemination of state-of-the-art cancer treatment into community practices. These studies selected a stratified random sample of individuals (proportionate registry size) from the SEER program 10, 12, and 13 cancer registries which covered up to 14% of the United States

population.[82] All individuals were aged ≥20 years with a histologically confirmed cancer for selected sites, stages, and years. A listing of all cancers and stages examined by the POC are detailed elsewhere.[83] Patients were excluded if the cancer diagnosis was determined at autopsy or on the death certificate; the diagnosis was a second malignancy other than to a non-melanoma skin cancer; or if the individual was simultaneously diagnosed with another cancer. Individuals were sampled by gender with oversampling of African-Americans and Hispanics in all years and Asian/Pacific Islanders and American Indians/Alaskan Natives in 2005 only.

In addition to the standard SEER abstraction, the POC studies supplemented information on initial course of treatment by asking physicians (via mailed questionnaire) to verify the treatments delivered to patients; reviewing a unified medical record (inpatient and outpatient); and in some cases SEER registrars visited doctors' offices to abstract data. Requested information included whether radiation, chemotherapy or immunotherapy was received as part of the initial course of treatment, identifying the specific agents delivered and the dates of first administration (2005 studies only).

Surveillance, Epidemiology and End Results Program (SEER)–Medicare linked database

(Specific aims 1, 2a, and 2b)

The SEER-Medicare database consists of a linkage of two large population-based data sources providing detailed clinical and healthcare utilization information on Medicare beneficiaries diagnosed with cancer.[4] The SEER data (described

above) have been linked to Medicare enrollment and Part A (Hospital insurance) and B (Medical insurance) claims data. Approximately 93% of all elderly cancer patients in SEER have been matched to Medicare enrollment files with an established algorithm, resulting in a linked database that includes over 3.3 million elderly individuals (age ≥ 65 years).[46] Nearly all Medicare beneficiaries are eligible for Part A and close to 93% opt to enroll in the Part B.[47]

AMA Physician Masterfile

(Specific aim 2b)

The AMA Physician Masterfile data contain current and historical information on over one million residents and physicians in the United States.[84] To obtain characteristics of physicians providing services to patients in the SEER-Medicare database, we used the Universal Physician Identification Number (UPIN) to link claims from Medicare to the AMA data.[85,86]

These data sources are uniquely situated for this research because of their large, longitudinal population-based structure and detailed data capture regarding patient-level demographic, tumor, and clinical characteristics, general healthcare utilization, receipt of specific chemotherapeutic agents, and physician- and hospital-level characteristics. Figure 3.2 below provides a visual display of the study population created for *Specific Aim 1*.

B. METHODS COMMON TO BOTH SPECIFIC AIMS

i) SEER-Medicare data structure

For Medicare-eligible individuals with fee-for-service coverage and an incident cancer diagnosis in a SEER region, Medicare claims are organized into files including the Patient Entitlement and Diagnosis Summary File (PEDSF) and claims for inpatient hospitalizations (MEDPAR), durable medical equipment (DME), outpatient hospital services (OUTSAF), and physician and other provider services (NCH).[49] The PEDSF includes one record for all individuals with a cancer diagnosis in a SEER area who have been matched with Medicare enrollment data. This file also includes basic demographic, clinical, tumor, and area level socioeconomic status measures. The claims files encompass a multitude of information on specific service dates, diagnoses, procedures, and agents delivered during medical encounters using various medical coding systems. Diagnoses and procedures on hospital claims are reported using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) codes. ICD-9 CM diagnosis and procedure codes can be used to identify chemotherapy administration, but not specific agents. DME claims contain National Drug Codes (NDCs) that can be used to identify specific oral chemotherapeutic agents that are equivalent to other Medicare-covered intravenously administered chemotherapy agents.[4] Physician and outpatient claims include ICD-9 CM diagnosis codes and Healthcare Common Procedure Coding System (HCPCS) codes. HCPCS can be used to identify chemotherapy and specific agents. Outpatient claims include revenue center codes which serve as another means of identifying chemotherapy administration.

In addition, the NCI produces the Hospital file which reports descriptive information for hospitals that are part of the SEER-Medicare database.[87] Hospital

data is derived from two sources maintained by CMS. Every year, hospitals that bill to Medicare are required to file an annual report called the Healthcare Cost Report (HCRIS). In addition, CMS occasionally requires hospitals to complete the Provider of Service (POS) survey.

Additional information about these files as well as the numerous tables containing data summarizations and variable values will be discussed as relevant and can be found on the SEER-Medicare website (http://healthservices.cancer.gov/seermedicare/).

ii) Data acquisition

Through cooperation with the NCI, SEER registries, IMS, Inc., and Medical Marketing Solutions, Inc., we requested and received the following research files:

Specific Aim 1

a) POC study data for in-situ or early stage breast cancer diagnosed in 2000 and 2005, stage II or III CRC in 2000 and 2005, NSCLC in 2005, and ovarian cancer in 2002. This included a unique encrypted identifier that could be matched to the SEER-Medicare data;
b) SEER-Medicare files (PEDSF, DME, MEDPAR, NCH, and OUTSAF) for the year prior, the year of, and the year following the POC study year for each cancer site listed above.

Specific Aim 2

a) SEER-Medicare files (PEDSF, DME, MEDPAR, NCH, and OUTSAF) for all CRC patients diagnosed between 1999 and 2007, including claims files through 2008.

b) SEER-Medicare hospital files from 1996, 1998, and 2000-2009.

c) AMA Physician Masterfile data for specified physicians treating patients with chemotherapy (discussed in detail below).

iii) Definition of variables common to both Specific Aims

- **Age at diagnosis** is reported as a continuous variable, but was categorized for analysis 65-69, 70-74, 75-79, 80-84, and 85+ years.
- **Diagnosis date** is reported only as the month and year. No day of diagnosis is reported by SEER. Therefore, we assumed that all individuals were diagnosed on the first day of the month reported by SEER.
- **Sex** is reported as male or female.
- **Race/ethnicity** was reported by Medicare and will be categorized as follows: White Non-Hispanic, Black Non-Hispanic, Other Non-Hispanic, and Hispanic.
- **Marital status** will be classified as either married, single, other (separated, divorced, widowed), or unknown.
- **Median household income (census tract)** was reported by a linkage between the SEER data and the Census summary files for the year 2000 and will be reported in quartiles and with an unknown category.
- **Percentage living below the poverty line (census tract)** was reported by a linkage between the SEER data and the Census summary files for the year 2000 at the census-tract level and was categorized in quartiles.
- **Educational attainment (census tract)** was reported by a linkage between the SEER registry data and the census summary files for the year 2000 and was

categorized as the percentage of individuals in a census tract receiving a high school education or higher.

- **Metropolitan county of residence** was defined as either metropolitan or non-metropolitan according to the SEER data.
- **Region** reflected the census regions of Northeast, Midwest, South and West.
- **Year of diagnosis** was reported from the SEER registry program.
- **Cancer site** was defined as breast, colon, rectum, non-small cell lung, or ovary as reported by SEER data.
- **Tumor stage** was reported according to the American Joint Commission on Cancer collaborative staging scheme 3rd Edition for cases diagnosed from 2000-2003 and 6th Edition for cases diagnosed from 2004-2007.
- **Histological grade** was grouped as well-differentiated/moderately differentiated, poorly/undifferentiated, or unknown, based upon pathology reports from the initial biopsy confirming the cancer diagnosis in the SEER data.
- **Tumor extent** was reported as T1-T2, T3, or T4 based upon SEER data.
- **Tumor size** was reported as < 2 cm, 2-3 cm, 3-4 cm, and >4 cm based upon SEER data.
- **Number of positive lymph nodes** was reported for stage III patients only and be classified as none, 1-3 nodes, ≥ 4 nodes, positive but number unknown, or unknown or not stated.
- **Number of lymph nodes examined** was classified as <12 nodes, ≥12 nodes, or unknown as reported by SEER.

- **Metastasis** was classified as Yes or No based on information obtained from the SEER data.
- **Comorbid conditions** were captured by the using the ICD-9 codes associated with the 19 conditions included in the Charlson comorbidity scale, a weighted index measure of comorbidity that predicts 1-year all-cause mortality.[76] The Klabunde adaptation was used to assess comorbidities in the 365 days prior to the diagnosis date.
- **Initial chemotherapeutic treatment regimen received** will be defined using multiple claims files and their associated diagnosis, procedure, and drug codes and service dates. If a claim for a general chemotherapy procedure code, a diagnosis code for chemotherapy administration, or HCPCS code or NDC for a specific agent was found, the individual was defined as having received chemotherapy during the specified post-diagnosis period (2-12 months). The receipt of specific chemotherapy agents were defined similarly by identifying at least one claim with a HCPCS code or NDC for the specific agent during the post-diagnosis period. Appendix A lists all of the codes used to identify chemotherapy treatment in the Medicare claims.

iii) Other methods common to both Specific Aims

Analyses were conducted using SAS software version 9.2 (SAS Institute Inc, Cary, NC, USA).

C. METHODS - SPECIFIC AIM 1

i) Study group definition

The cancer sites, stages, and years of diagnoses were selected based on availability of the POC data and included in-situ or early stage breast cancer diagnosed in 2000 and 2005, stage II or III CRC in 2000 and 2005, NSCLC in 2005, and ovarian cancer in 2002. All POC patients were required to be age ≥65 at cancer diagnosis; and have POC treatment information verified through physician confirmation or a unified medical record review. Patients identified as being enrolled in a clinical trial were excluded because Medicare only covers routine costs associated with federally funded clinical trials (e.g, office visits and medical tests), and may not cover the cost of the agents themselves.[70]

This study included eligible patients in the POC data who were matched to the SEER-Medicare data. Using the Medicare files, we required that all individuals were continuously enrolled in Medicare Parts A and B for the 2-, 4-, 6-, 8-, 10-, or 12-month periods following diagnosis (the post-diagnosis periods); were never enrolled in a health maintenance organization (HMO) during the associated post-diagnosis periods; did not have a subsequent cancer diagnosis (as reported by SEER) in the year following the qualifying POC cancer diagnosis; and had at least one Medicare claim during the specified post-diagnosis period. These criteria ensured that detailed claims for all individuals in the study were reported to Medicare and were not attributable to the treatment of a subsequent cancer. Due to the time-varying nature of these criteria, the number of individuals eligible for analysis in each post-diagnosis period decreased over time. Details of the 6-month post-diagnosis cohort exclusions are listed in the Appendix B.

ii) Definition of variables

Receipt of chemotherapy (POC data): For this analysis, the POC cohort was considered the gold standard measure for the receipt of any chemotherapy and for specific agents. Individuals were defined in POC as receiving any chemotherapy if a physician verified or a unified medical record identified that the individual was administered any chemotherapeutic agent. The receipt of specific agents was identified in POC through the same mechanism. For the POC studies conducted in 2005, the date of first administration was collected for each specific agent delivered. Therefore, the analysis defined the initial course of treatment as the diagnosis date (set to the first day of the month, as only month of diagnosis is reported by SEER) to 365 days following the diagnosis date. If treatment was received outside of the year following diagnosis, it was not considered part of the initial course of chemotherapy.

Receipt of chemotherapy (SEER-Medicare data): Identifying the receipt of any chemotherapy and specific agents in Medicare claims required an examination of multiple claims files and their associated diagnosis, procedure, and drug codes and service dates. If a claim for a general chemotherapy procedure code, a diagnosis code for chemotherapy administration, or HCPCS code or NDC for a specific agent was found, the individual was defined as having received chemotherapy during the specified post-diagnosis period. The receipt of specific chemotherapy agents were defined similarly by identifying at least one claim with a HCPCS code or NDC for the specific agent during the post-diagnosis period.

iii) Analysis

Reporting of the agreement between the two data sources and the validity of chemotherapy captured in Medicare claims was examined at interval periods using

the 2, 4, 6, 8, 10 and 12-month post-diagnosis cohorts. Specifically, we estimated the Kappa and corresponding 95% CIs to assess concordance between the two data sources, as well as the sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) and their corresponding 95% CIs of the Medicare claims definitions using the POC as the gold standard.

We selected the specific chemotherapeutic agents to be validated based on their frequency of use in the 6-month post-diagnosis period. Using sample size calculations, we maximized the accuracy of the Se and Sp estimates to have a minimal acceptable lower confidence limit that is less than 10% from the point estimate.[88] Based upon this sample size calculation, we included only specific chemotherapeutic agents where the POC reported that there were 37 or more individuals receiving the treatment. Due to the small number of in situ and early stage breast cancer patients receiving chemotherapy, the 2000 and 2005 POC data were combined for analysis.

While the POC studies were considered the gold standard, they may be subject to measurement error in their reporting of initial chemotherapy treatment. Therefore, beyond reporting the Kappa to assess concordance between the two sources, we also conducted a sensitivity analysis to examine the impact of potential misclassification of the gold standard (i.e., the POC),[89] focusing on an example of oxaliplatin receipt among stage II or III CRC patients diagnosed in 2005.

D. METHODS – SPECIFIC AIM 2

i) Study group definition – Prevalence of treatment and trends, 2000-2007

To examine trends in the utilization of specific chemotherapeutic agents, we first identified all patients in SEER diagnosed at age ≥66 with their first primary stage II or III cancer of the colon or rectum. SEER staging was based on the American Joint Commission on Cancer (AJCC), 3rd edition from January 1, 2000-December 31, 2003 or AJCC 6th edition from January 1, 2004-December 31, 2007. The diagnosis date was set to the first day of the month, as SEER does not report the day of diagnosis. Diagnoses identified at autopsy or death certificate only were excluded, resulting in a cohort of 55,549 individuals. All individuals were required to have continuous Medicare Part A and B enrollment and no HMO enrollment for the 12-months before and 8-months after diagnosis to ensure complete capture of healthcare utilization and treatment information. We excluded all individuals missing their month of diagnosis. As a result of these criteria, 32,278 individuals were eligible for further analysis. To examine the utilization of various chemotherapeutic agents, we restricted the cohort to individuals who had a claim for at least one specific chemotherapeutic agent in the 8-months following diagnosis, limiting our final cohort to 12,839 patients (Figure 4.1).

ii) Study group definition – Oxaliplatin analysis, 2004-2007

To identify patient, physician, and hospital characteristics associated with the receipt of oxaliplatin, we first imposed identical SEER and Medicare criteria to construct the oxaliplatin cohort, limiting the diagnosis date to January 1, 2004–December 31, 2007, the period where oxaliplatin began to disseminate among stage II and III CRC patients. This cohort included 15,694 patients.

Next, to identify characteristics of the hospital where cancer surgery was performed, we further restricted this cohort to individuals with a surgical claim (i.e., colectomy or proctectomy) in the inpatient (MEDPAR) or outpatient hospital (OUTSAF) files in the 6-months following diagnosis. These files include the provider number necessary to identify the hospital where treatment was received. If a patient had surgical claims from multiple hospitals, the first hospital was retained for analysis. We then linked the cohort to the SEER-Medicare Hospital file by the provider number and year of diagnosis for each patient. Hospitals that did not match and patients without claims for surgery during the 6-months post-diagnosis were excluded from analysis. The resulting cohort included 14,418 individuals and 1,022 hospitals.

Lastly, to identify characteristics of physicians providing chemotherapy services, we required all patients to have at least one claim for a specific chemotherapeutic agent in the physician (NCH) or the OUTSAF claims files during the 8-months following their diagnosis. For all patients, we obtained the performing and attending provider reported by the NCH and OUTSAF files, respectively.[90] The physician with the most chemotherapy-related claims during the 8-month period post-diagnosis was considered the treating physician. UPINs that did not match to the AMA Physician Masterfile or contained all missing values were excluded from analysis. As a result, 4,819 patients, 795 hospitals, and 1,579 physicians were included in the final oxaliplatin analysis (Figure 4.2).

iii) Definition of variables

Patient demographic characteristics: We obtained demographic characteristics of patients including year of diagnosis, sex, age at diagnosis (66-69, 70-74, 75-79, 80-84, or 85+), race/ethnicity (White Non-Hispanic, Black Non-Hispanic, Other Non-Hispanic, Hispanic, or Unknown), marital status (married, single, other (divorced, separated, widowed), or unknown), and region of residence (Northeast, South, Midwest, or West) from SEER. County-level metropolitan area was defined as metropolitan or non-metropolitan. SEER-Medicare does not report individual-level socioeconomic (SES) information. Therefore, we used the percentage of residents living below the federal poverty level, an aggregated measure of SES at the census tract level (Census 2000). Previous studies have shown that the census tract poverty variable may be the best proxy measure of economic status for elderly Medicare beneficiaries.[91,92] This variable was categorized into quartiles: ≤4%, 4.01-≤8%, 8.01-≤15%, and >15% (i.e., the tract with the highest percentage of people living below the poverty level).

Tumor and clinical characteristics: We also obtained clinical characteristics from SEER, including cancer site (colon or rectum), AJCC stage (II or III), histologic grade (well/moderately differentiated, poorly/undifferentiated, or unknown), tumor size (<2cm, 2-<3cm, 3-<4cm, ≥4cm, or unknown), and number of lymph nodes examined (<12 nodes, ≥12 nodes, or unknown). The Charlson Comorbidity Index was measured from the 365 days of Medicare inpatient and outpatient claims prior to diagnosis using the methodology developed by Klabunde et al.[77]

Hospital characteristics: We retrieved characteristics of hospitals where patients received colorectal cancer surgery from the SEER-Medicare Hospital file. Hospital

characteristics included NCI center designation (none, clinical, or comprehensive), NCI cooperative membership group count (0 or ≥1), teaching hospital status (yes or no), type of hospital (non-profit, private, or government), and total bed size, measured in quartiles (<204 beds, 204-343 beds, 344-487 beds, or 488+ beds).

Physician characteristics: We obtained characteristics of physicians who treated patients with chemotherapy from the AMA Physician Masterfile and included medical degree (Medical Doctor (MD) or Doctor of Osteopathy (DO)), whether the physician was trained in the US (yes or no), year of medical school graduation (<1981 or ≥1981), primary specialty (oncology, hematology/oncology, hematology, internal medicine, or other), and sex.

Measurement of specific chemotherapeutic agents for the treatment of CRC: We categorized patients as receiving any chemotherapy treatment using International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis, ICD-9-CM procedure, Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS), and revenue center codes. Because we were concerned with identifying initial treatment with 5-FU, capecitabine, oxaliplatin, irinotecan, and bevacizumab, specifically, we excluded patients with administration codes only, as we were unable to identify the agents they received. Initial treatment with these agents was defined using the two month period of claims data following the first chemotherapy claim for each patient. The administrative codes used to identify any chemotherapy, the specific agents, and their measures of validity using previously published methods[49,93] are listed in the Appendix C.

v) Analysis

We estimated the prevalence (and its 95% confidence interval (CI) of 1) any chemotherapy use among all eligible stage II and III CRC patients and 2) specific agents among all patients treated with chemotherapy (and having at least one specific agent claim) by year, cancer site, and stage. All analyses were performed on the chemotherapeutic agent-level so that individuals could be counted more than once in a given year (e.g., if they received both oxaliplatin and 5-FU). Therefore, the percentages do not sum to 100%. We present results for specific agents with ≥5% prevalence in at least one year. Logistic regression models stratified by cancer site and year were used to test for trends in the utilization of any chemotherapy from 2000-2007 and for specific agents from 2004-2007. All models included patient age in 5-year categories (66-69, 70-74, 75-79, 80-84, 85+) to control for changes to the US population age structure over time, and diagnosis year to assess time trends.

Trends in the replacement of 5-FU with capecitabine were estimated by measuring the proportion of capecitabine use among all users of fluoropyrimidines by year, cancer site, and stage. Individuals receiving both 5-FU and capecitabine in the 2-months following their first chemotherapy claims were excluded from the analysis (n=83). Because the administrative definition for identifying capecitabine in Medicare claims has a very low sensitivity (47%), but high specificity (98%), we sought to estimate the proportion of patients receiving capecitabine that were missed by Medicare claims. The following equation was used to calculate the additional number of patients receiving capecitabine:

$$N_{cap\_corr} = (N_{cap} - (1 - Se_{cap}) * (N_{yr\_tot} - N_{5fu\_tot}) / (Se_{cap} + Sp_{cap} - 1)$$ [94]

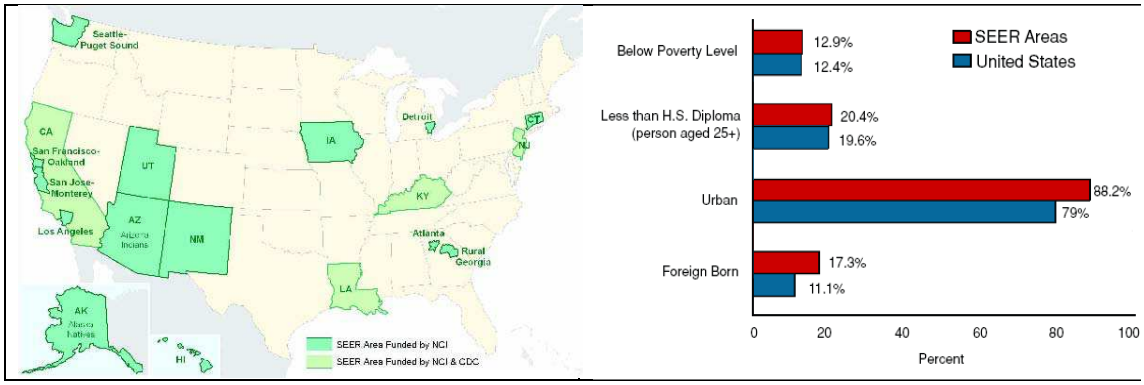
Where N_{cap_corr} is the number of capecitabine users, corrected for the misclassification in Medicare claims, N_{cap} is the number of capecitabine users identified by Medicare claims, N_{yr_tot} is the total number of individuals in site/stage patient group, N_{5fu_tot} is the total number of 5-FU users in site/stage patient group, and Se_{cap} and Sp_{cap} are the sensitivity and specificity of the administrative definitions used to identify capecitabine in Medicare claims.

These additional patients were added to the total number of 5-FU and capecitabine users and the proportion of patients receiving 5-FU, capecitabine (as measured by claims), and capecitabine (as imputed using validation data) were graphed.

We estimated the proportion of patients receiving any chemotherapy and oxaliplatin, specifically, across patient demographic and clinical variables and calculated univariate prevalence ratios for the receipt of oxaliplatin for each patient, physician, and hospital characteristic.

Patient observations for the oxaliplatin cohort were clustered within hospitals and physicians in a non-nested manner. Miglioretti and Heagerty have developed a generalized estimating equation (GEE) strategy that can be used to adjust for the correlation among observations within non-nested multi-level data and provide estimates of marginal (population-averaged) associations.[95] We used this strategy to account for the correlations of oxaliplatin receipt among patients who were treated with chemotherapy by the same physician and/or underwent surgery at the same hospital. The patient was the unit of analysis and the hospital's provider number and the physician's UPIN were the clustering variables.

We estimated prevalence ratios for patient, physician and hospital variables using multivariate Poisson models with a log link and an independent GEE working matrix. Separate analyses for on- and off-label indications were performed, as the influence of the selected characteristics may vary by indication. Finally, we assessed the contribution of the measured patient, physician, and hospital characteristics on the explained variation in the receipt of oxaliplatin by calculating and comparing the c-statistic for four models, including: 1) all patient, physician and hospital variables, 2) patient-level variables only, 3) physician-level variables only, and 4) hospital-level variables only.



Source: National Cancer Institute, NIH Publication No. 05-4772 September 2005.

Figure 3.1. Surveillance, Epidemiology and End Results (SEER) reporting areas and regions (left) and demographic comparison with the general population of the United States in 2000 (right)

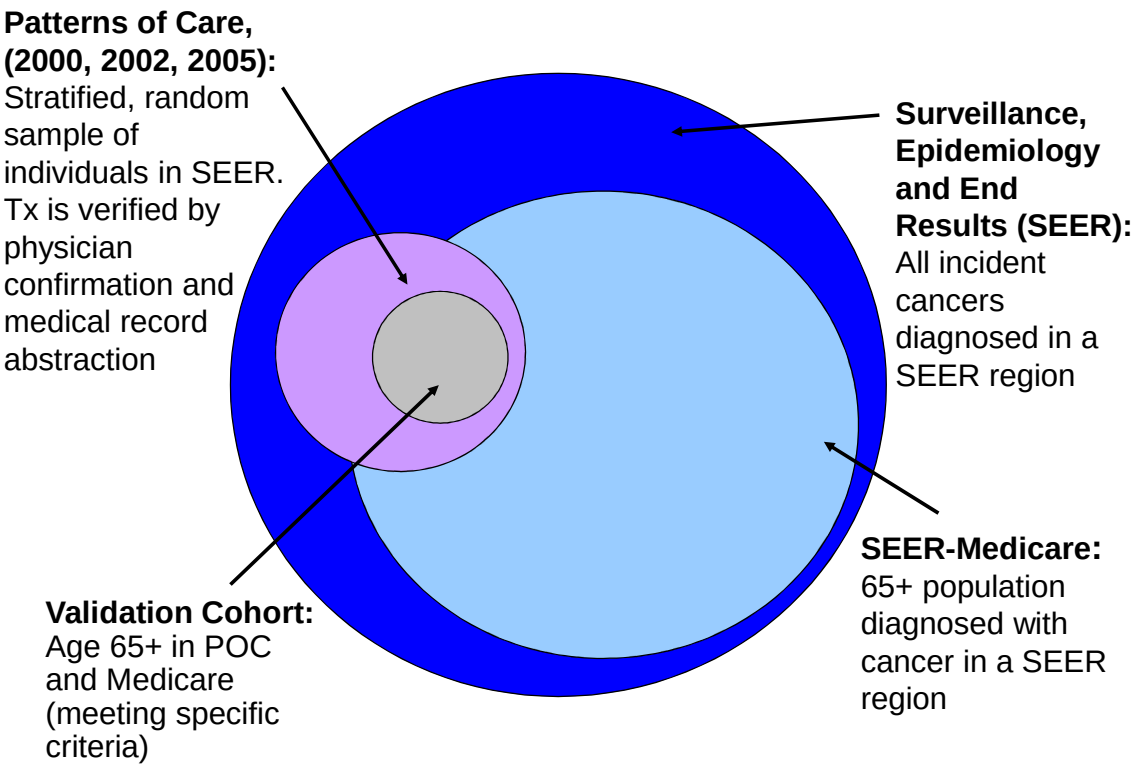


FIGURE 3.2 • Data sources utilized for chemotherapy validation study

Figure 3.3: Flow chart for specific chemotherapeutic agent analysis

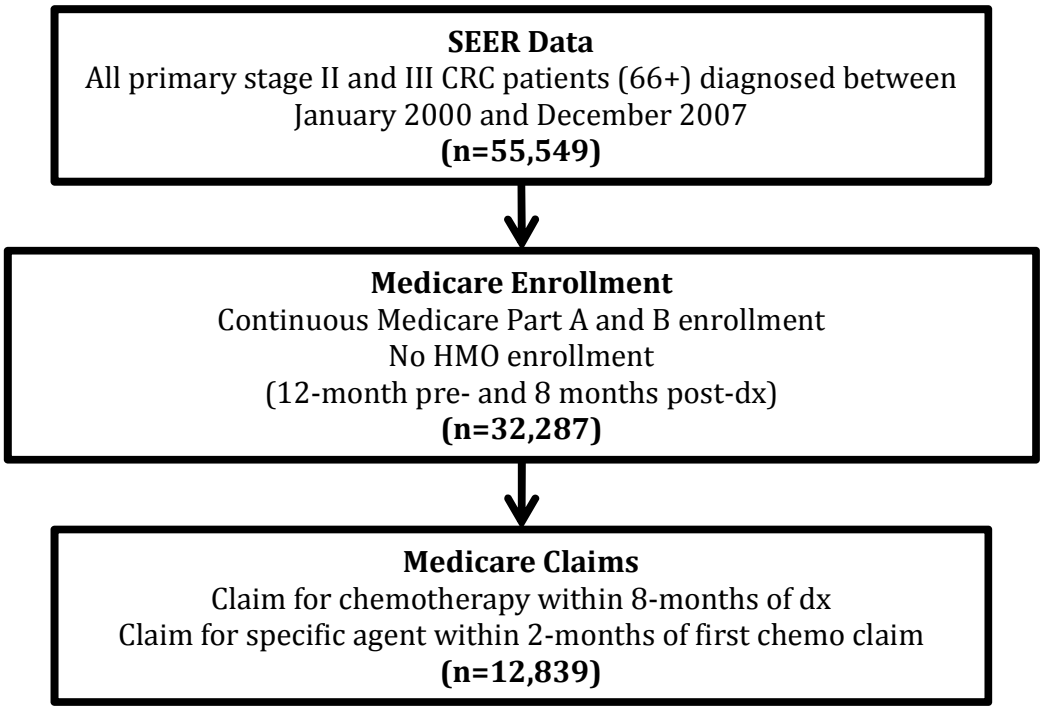
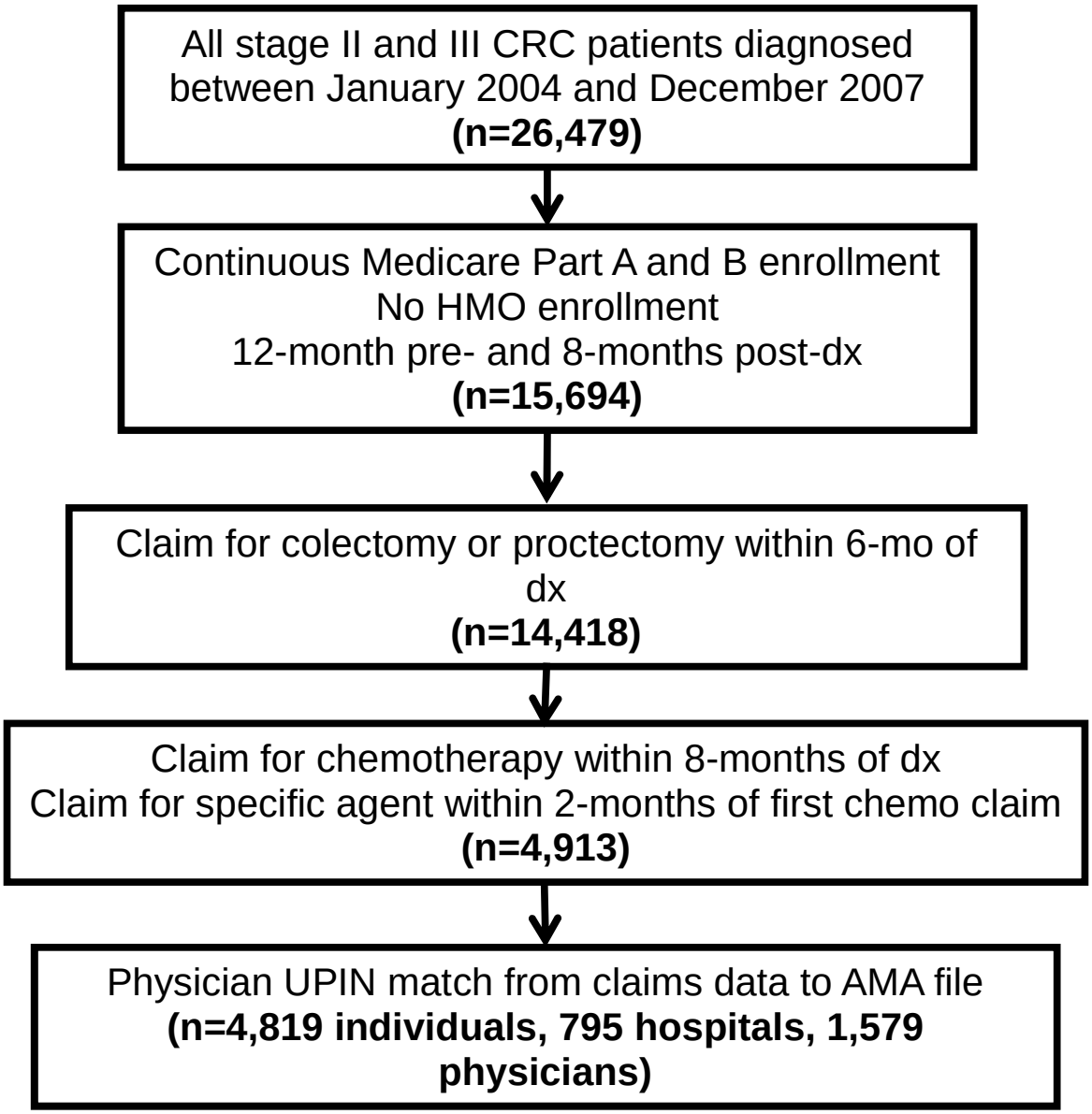


Figure 3.4: Flow chart for oxaliplatin analysis cohort



CHAPTER 4

RESULTS: Identifying specific chemotherapeutic agents in Medicare data: a validation study[1]

A. INTRODUCTION

Chemotherapy represents an integral part of the treatment plan for many individuals diagnosed with cancer, as it decreases the risk of recurrence and mortality in many settings. Randomized controlled trials have documented the efficacy of chemotherapeutic agents used to treat a variety of cancers. To examine the translation of this evidence into the routine clinical setting, large healthcare databases, such as the Surveillance, Epidemiology, and End Results (SEER) program-Medicare linked database, are increasingly used to conduct non-experimental studies evaluating the uses, benefits, and harms of these treatments among individuals excluded from trials, including older adults, those with multiple co-morbidities, and those treated off-label.[63,74,96-119]

The validity of these studies relies upon a variety of issues, including the ability of claims data to accurately capture treatment(s) of interest, study endpoint(s), and other important design and clinical issues.[48] Measurement error in the assessment of chemotherapy could lead to biased study results. Prior research supports the validity of claims data to identify intravenously administered

[1] The results in this chapter have been accepted by *Medicare Care* on Sep 12, 2011. Authors include the committee members listed on the title page and Dr. Linda C. Harlan of the Applied Research Program at the National Cancer Institute.

chemotherapy treatment for a variety of cancer sites,[49-53] but does not address more recently approved or orally administered agents, or changes in validity using multiple claims windows following diagnosis.

We conducted a validation study to assess the utility of Medicare claims for capturing the receipt of any chemotherapy and specific agents delivered to patients diagnosed at age ≥65 with stage II or III colorectal cancer (CRC), in situ or early stage breast, non-small cell lung cancer (NSCLC), or ovarian cancer. This assessment 1) evaluated the validity of selected single agent chemotherapies, including an orally-administered agent and 2) described the variation in measures of validity for any chemotherapy and specific treatments over multiple follow-up periods and across cancer sites.

B. METHODS

Data sources

We used the National Cancer Institute (NCI)'s data from the Patterns of Care studies (POC) as the gold standard for identifying chemotherapy and the linked SEER-Medicare data as the test source for identifying chemotherapy. The SEER program of cancer registries collects demographic information, clinical and tumor characteristics, vital status, and cause of death for all incident cancers reported for individuals who reside in one of the registries' defined geographic areas.[2]

NCI supplements the standard SEER registry abstraction to obtain detailed information about treatment for a subset of SEER cases. This effort, known as the

POC, was developed by NCI to investigate the dissemination of state-of-the-art cancer treatment into community practices. These studies selected a stratified random sample of individuals (proportionate registry size) from the SEER program 10, 12, and 13 cancer registries which covered up to 14% of the United States population.[82] All individuals were aged ≥20 years with a histologically confirmed cancer for selected sites, stages, and years. A listing of all cancers and stages examined by the POC are detailed elsewhere.[83] Patients were excluded if the cancer diagnosis was determined at autopsy or on the death certificate; the diagnosis was a second malignancy other than to a non-melanoma skin cancer; or if the individual was simultaneously diagnosed with another cancer. Individuals were sampled by gender with oversampling of African-Americans and Hispanics in all years and Asian/Pacific Islanders and American Indians/Alaskan Natives in 2005 only.

In addition to the standard SEER abstraction, the POC studies supplemented information on initial course of treatment by asking physicians (via mailed questionnaire) to verify the treatments delivered to patients; reviewing a unified medical record (inpatient and outpatient); and in some cases SEER registrars visited doctors' offices to abstract data. Requested information included whether radiation, chemotherapy or immunotherapy was received as part of the initial course of treatment, identifying the specific agents delivered and the dates of first administration (2005 studies only).

The SEER-Medicare data arise from a linkage of persons in the SEER data with their Medicare enrollment, Part A (Hospital insurance) and B (Medical insurance) claims data. These data include approximately 3.3 million elderly

individuals (age ≥ 65 years) diagnosed with cancer in one of the SEER areas or regions.[46] Approximately 94% of all elderly individuals included in SEER have been matched to the Medicare enrollment file with an established matching algorithm. Virtually 100% of all beneficiaries are eligible for Part A and 93% will opt to enroll in Part B.[47]

For Medicare-eligible individuals with fee-for-service coverage, Medicare claims are organized into files including claims for inpatient hospitalizations, durable medical equipment (DME), outpatient hospital services, and physician and other provider services [49]. These claims encompass a multitude of information on specific service dates, diagnoses, procedures, and agents delivered during medical encounters using various medical coding systems. Diagnoses and procedures on hospital claims are reported using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) codes. ICD-9 CM diagnosis and procedure codes can be used to identify chemotherapy administration, but not specific agents. DME claims contain National Drug Codes (NDCs) that can be used to identify specific oral chemotherapeutic agents that are equivalent to other Medicare-covered intravenously administered chemotherapy agents.[4] Physician and outpatient claims include ICD-9 CM diagnosis codes and Healthcare Common Procedure Coding System (HCPCS) codes. HCPCS can be used to identify chemotherapy and specific agents. Outpatient claims include revenue center codes which serve as another means of identifying chemotherapy administration. The codes used in our analysis are presented in the Appendix.

Study sample and eligibility criteria

The cancer sites, stages, and years of diagnoses were selected based on availability of the POC data and included in-situ or early stage breast cancer diagnosed in 2000 and 2005, stage II or III CRC in 2000 and 2005, NSCLC in 2005, and ovarian cancer in 2002. All POC patients were required to be age ≥65 at cancer diagnosis; and have POC treatment information verified through physician confirmation or a unified medical record review. Patients identified as being enrolled in a clinical trial were excluded because Medicare only covers routine costs associated with federally funded clinical trials (e.g, office visits and medical tests), and may not cover the cost of the agents themselves.[70]

This study included eligible patients in the POC data who were matched to the SEER-Medicare data. Using the Medicare files, we required that all individuals were continuously enrolled in Medicare Parts A and B for the 2-, 4-, 6-, 8-, 10-, or 12-month periods following diagnosis (the post-diagnosis periods); were never enrolled in a health maintenance organization (HMO) during the associated post-diagnosis periods; did not have a subsequent cancer diagnosis (as reported by SEER) in the year following the qualifying POC cancer diagnosis; and had at least one Medicare claim during the specified post-diagnosis period. These criteria ensured that detailed claims for all individuals in the study were reported to Medicare and were not attributable to the treatment of a subsequent cancer. Due to the time-varying nature of these criteria, the number of individuals eligible for analysis in each post-diagnosis period decreased over time. Details of the 6-month post-diagnosis cohort exclusions are listed in the Appendix.

Identification of receipt of chemotherapy and specific agents in POC and SEER-Medicare

For this analysis, the POC cohort was considered the gold standard measure for the receipt of any chemotherapy and for specific agents. Individuals were defined in POC as receiving any chemotherapy if a physician verified or a unified medical record identified that the individual was administered any chemotherapeutic agent. The receipt of specific agents was identified in POC through the same mechanism. For the POC studies conducted in 2005, the date of first administration was collected for each specific agent delivered. Therefore, the analysis defined the initial course of treatment as the diagnosis date (set to the first day of the month, as only month of diagnosis is reported by SEER) to 365 days following the diagnosis date. If treatment was received outside of the year following diagnosis, it was not considered part of the initial course of chemotherapy.

Identifying the receipt of any chemotherapy and specific agents in Medicare claims required an examination of multiple claims files and their associated diagnosis, procedure, and drug codes and service dates. If a claim for a general chemotherapy procedure code, a diagnosis code for chemotherapy administration, or HCPCS code or NDC for a specific agent was found, the individual was defined as having received chemotherapy during the specified post-diagnosis period. The receipt of specific chemotherapy agents were defined similarly by identifying at least one claim with a HCPCS code or NDC for the specific agent during the post-diagnosis period.

Comparison of chemotherapy reported in POC and SEER-Medicare

Reporting of the agreement between the two data sources and the validity of chemotherapy captured in Medicare claims was examined at interval periods using the 2, 4, 6, 8, 10 and 12-month post-diagnosis cohorts. Specifically, we estimated the Kappa and corresponding 95% CIs to assess concordance between the two data sources, as well as the sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) and their corresponding 95% CIs of the Medicare claims definitions using the POC as the gold standard.

We selected the specific chemotherapeutic agents to be validated based on their frequency of use in the 6-month post-diagnosis period. Using sample size calculations, we maximized the accuracy of the Se and Sp estimates to have a minimal acceptable lower confidence limit that is less than 10% from the point estimate [88]. Based upon this sample size calculation, we included only specific chemotherapeutic agents where the POC reported that there were 37 or more individuals receiving the treatment. Due to the small number of in situ and early stage breast cancer patients receiving chemotherapy, the 2000 and 2005 POC data were combined for analysis.

While the POC studies were considered the gold standard, they may be subject to measurement error in their reporting of initial chemotherapy treatment. Therefore, beyond reporting the Kappa to assess concordance between the two sources, we also conducted a sensitivity analysis to examine the impact of potential misclassification of the gold standard (i.e., the POC),[89] focusing on an example of oxaliplatin receipt among stage II or III CRC patients diagnosed in 2005.

All analyses were conducted in SAS 9.2 (SAS Institute, Cary, NC). This study was reviewed by the University of North Carolina at Chapel Hill Institutional Review Board (IRB) and was determined to be exempt from IRB approval.

C. RESULTS

The final validation cohort included 1,187 individuals diagnosed with a primary cancer of the breast in 2000 (n=156) or 2005 (n=155), colon or rectum in 2000 (n=171) or 2005 (n=338), lung (non-small cell only) in 2005 (n=195), and ovary in 2002 (n=170) (Table 1). The percentage of patients receiving any chemotherapy in this cohort was 17% for in-situ/early stage breast cancer diagnosed in 2000 and 20% in 2005; 61% for stage II/III CRC diagnosed in 2000 and 52% in 2005; 78% for ovarian cancer diagnosed in 2002; and 49% for NSCLC diagnosed in 2005.

Figure 4.1 displays the sources of chemotherapy claims found in the Medicare files (hospital, physician, outpatient, DME, or multiple files) for all individuals included in the validation studies by cancer site and year of diagnosis. The large majority of individuals receiving chemotherapy only had claims reported in the physician file with very few individuals having claims identified in the hospital file only (< 3%). However, variation by cancer site and year of diagnosis was evident, reflecting different settings in which treatment was delivered by site and over time. For example, the approval of capecitabine in 2005 for CRC increased the percentage of individuals with claims identified using the DME file in 2005, as bills for orally administered agents appear primarily in the DME file. Chemotherapy

claims for breast cancer were largely identified by physician claims in both 2000 and 2005.

The comparisons of any chemotherapy identified by the POC and Medicare claims for the post-diagnosis periods for each cancer site/year are reported in Table 4.2. Individuals receiving chemotherapy according to each data source is reported. Overall, the measures of agreement and validity for identifying the receipt of any chemotherapy were high for all cancer sites and post-diagnosis periods, except for the 2- and 4-month periods. Excluding those periods, Kappa estimates of concordance ranged from 77% - 87%; Se ranged from 84% - 97%, Sp ranged from 78% - 97%, PPVs ranged from 87% - 96%, and NPVs ranged from 81% - 96%. The Sp estimates for the receipt of any chemotherapy for women diagnosed with ovarian cancer in 2002 were low in the later post-diagnosis periods. Due to the small number of women not receiving chemotherapy in the later post-diagnosis periods, the Sp estimates are unstable. Although the confidence intervals are wide, these intervals include Sp ranges that are consistent with estimates across other cancer sites. Across all cancer sites and year, the Sp and Se estimates for the receipt of any chemotherapy did not vary by patient characteristics (data not shown).

Table 4.3 describes the measures of agreement and validity for the Medicare claims definitions used to identify the receipt of specific chemotherapeutic agents during the 6-month post-diagnosis period. For all intravenous agents administered to patients diagnosed with CRC and NSCLC, the measures of concordance and validity were high: Kappa ranged from 71% - 95%; Se ranged from 75% - 95%; Sp ranged from 90% - 99%; PPV ranged from 85% - 99%; and NPV ranged from 81% -

97%. Consistently, these measures (Kappa, Se, and PPV) were lowest for oxaliplatin. The measures of agreement and validity for identifying capecitabine, an orally administered agent equivalent to the intravenously administered 5-fluorouracil (5-FU) for CRC, in Medicare claims was poor with Kappa and Se of only 55% and 47%, respectively.

For breast cancer, the Se estimates for cyclophosphamide and doxorubicin were lower than other cancer site-agents at 75% and 73%, respectively; however, the 95% confidence intervals included values consistent with other sites. For ovarian cancer, the Sp estimates for carboplatin and paclitaxel were low at 78% and 74%, respectively. The Sp estimates for the specific ovarian cancer agents were lower than agents used to treat other cancer sites across all post-diagnosis periods (data not shown). Evidence of variation was seen when comparing the above measures for the same agents across different cancer sites. The Kappa, Se, and Sp for the receipt of paclitaxel and carboplatin were higher among patient treated for NSCLC as compared to those treated for ovarian cancer.

Figure 4.2 illustrates how the use of multiple post-diagnosis periods changes the Se and Sp estimates for specific chemotherapeutic agents used to treat individuals diagnosed with stage II and III CRC in 2005. Generally, the Se for specific treatments reach their maximum close to the 8-month post-diagnosis period, with the exception of oxaliplatin for which Se continues to climb up to the 12-month post-diagnosis period. The Se of capecitabine is approximately 50% lower than the Se for all other CRC agents and remains steady over time. The Sp of Medicare

claims for identifying patients who did not receive specific CRC chemotherapy agents was > 93% for all post-diagnosis periods.

We conducted a sensitivity analysis to assess the impact that potential misclassification of the gold standard (i.e., the POC studies) could have on our results, using the specific example of oxaliplatin treatment for CRC patients in 2005. We identified 10 individuals diagnosed with CRC in 2005 who had 2 or more claims for oxaliplatin during the 12-months post-diagnosis, but were not identified by POC as having received oxaliplatin as part of the initial course of treatment. Because physicians would not likely submit claims to Medicare for administering oxaliplatin (an expensive treatment) unless it was actually delivered, we assumed that these patients were misclassified by the POC studies. We varied the percentage of oxaliplatin-treated patients that were missed by the 2005 CRC POC study from 0% to 60% (or 0 to 6 individuals) and assessed the changes in Se, Sp, and PPV. Over the range of values, the PPV increased the most from 84% to 94%, while the Se and Sp remained nearly constant, increasing only from 89% to 90% and 96% to 98%, respectively (data not shown).

D. DISCUSSION

We found that utilizing 6, 8, 10, or 12 months of Medicare claims following a primary diagnosis of in situ or early stage breast, stage II or III colorectal, non-small cell lung, or ovarian cancer can accurately identify whether an individual received any chemotherapy as part of their initial course of treatment. However, the ability of

Medicare claims to identify the receipt of specific chemotherapeutic agents appeared to vary by the agent, cancer site, and mode of administration. Medicare claims used to identify intravenously administered agents for CRC and NSCLC generally had a high Se, Sp, PPV, and NPV; although the Se tended to increase using longer post-diagnosis periods for more recently approved agents (i.e., oxaliplatin). The Se and Sp estimates for identifying any chemotherapy treatment among individuals diagnosed with breast and ovarian cancers were generally lower than those for CRC and NSCLC. Across cancer sites, Medicare claims performed best when identifying specific agents used to treat NSCLC (i.e., carboplatin and paclitaxel) with all measures of agreement and validity exceeding 90%.

Our findings update a prior study by Warren et al[49] utilizing POC data (1991, 1995, and 1996) to assess the utility of Medicare claims data for identifying the receipt of chemotherapy among individuals diagnosed with in situ or early stage breast, stage II or III CRC, and ovarian cancer. We found remarkably similar Kappa and Se estimates for identifying the receipt of any chemotherapy across cancer sites, with all confidence intervals encompassing the prior study estimates. However, our Kappa and Se estimates of Medicare claims for identifying specific chemotherapeutic agents are higher than those reported by Warren and colleagues. For example, in our study the Se of claims to identify the receipt of cyclophosphamide for the treatment of ovarian cancer was 75% (Table 3) compared with only 47% in the earlier study. It is possible that coding and reporting behavior improved over time, especially with the rising cost of chemotherapy.[120] These updated measures further confirm the utility of Medicare claims to identify these

agents and provide the relevant information that may be used to correct for misclassification.

Our study extended the Warren study by examining the chemotherapeutic agents that were not included in the original study, such as doxorubicin for breast cancer, oxaliplatin and capecitabine for CRC, and paclitaxel for breast and NSCLC. Another study examined the validity of Medicare claims for identifying specific agents in comparison to two different clinical trials among breast (1995-1997) and lung (1998-2000) cancer patients. The study reported the Se and Sp for doxorubicin as 91% (95% CI: 79%, 98%) and 100%, and for paclitaxel as 86% (79%, 92%) and 100%, consistent with our findings.[50]

This is the first study to examine the validity of Medicare claims to identify oxaliplatin for individuals diagnosed with stage II and III CRC. The Se of Medicare claims to identify oxaliplatin increases with the length of the claims window post-diagnosis. A temporary HCPCS code was available for oxaliplatin (C9205) in 2005, while starting January 1, 2006, a permanent HCPCS code (J9263) was established. It is possible that physician coding improved after the permanent code was available, leading to better capture of oxaliplatin in later post-diagnosis periods.

There have been no prior validation studies examining the reporting of capecitabine in the Medicare data. We observed consistently low Se estimates for capecitabine in the Medicare claims for all post-diagnosis periods. One possible explanation for its poor Se is that patients who cannot afford their copayments received the drug through pharmacy assistance programs sponsored by the pharmaceutical company. It may also be that patients had prescription drug

insurance that covered oral medications and the patient or the provider did not submit a claim for capecitabine to Medicare. Capecitabine is covered under Medicare Part B, as it is an oral alternative to an intravenous medication (5-FU). Chemotherapeutic agents that are only in oral form would be covered under Medicare's Part D prescription drug coverage, which was implemented in 2006. Using Part D data to identify use of oral chemotherapies is limited as only 52% of Medicare beneficiaries have Part D enrollment.[121] Our findings, taken together with limited Part D enrollment among Medicare beneficiaries, suggest that the reporting of oral chemotherapeutic agents in the Medicare data may be incomplete. However, additional validation of oral chemotherapeutic agents in the Medicare data is needed. Two possible approaches to further explore the frequency of capecitabine claims in the outpatient drug setting would be to link: 1) Medicare dually-eligible individuals to their Medicaid prescription drug claims or 2) poor, elderly individuals that meet state pharmacy assistance program thresholds to their outpatient drug claims. These two groups are particularly unique and therefore results from these analyses may not be generalizable to the larger Medicare population.

This study has a number of strengths. Through cooperation with the NCI and SEER registries, we linked verified treatment data obtained through physician confirmation or unified medical record review to Medicare claims for a large number of individuals aged ≥65 years and diagnosed with one of four different cancers. The detailed POC data collection allowed us to assess the validity of Medicare claims to identify specific agents that have not previously been validated. We examined and reported variation in measures of validity across different post-diagnosis periods,

whereas prior studies primarily used one or two broad post-diagnosis time windows.[49,51,53]

Our study is not without limitations. There may be patients in the study who received treatment from another healthcare payer (e.g., the Veterans Health Administration). These claims would not be captured in this analysis. Therefore, our results may be viewed as minimum thresholds which could be improved by combining information from other payers. Furthermore, approximately 26% of individuals in the POC studies lacked physician confirmation or unified medical record review and were therefore excluded from analysis. We also excluded individuals who had any HMO enrollment during the post-diagnosis periods, as detailed claims data were not reported to Medicare for these individuals. These exclusions along with our focus on individuals 65+ years limit the overall generalizability of our findings. This analysis examined the receipt of chemotherapy as part of the initial course of treatment, but did not distinguish between adjuvant and neoadjuvant treatment; we would not expect results to differ based on the receipt of therapy before or after surgery, however. Similarly, we cannot be sure that claims appearing later in the post-diagnosis period still relate to the initial course of treatment, or whether they are actually linked to treatment of recurrent or progressive cancer.

In conclusion, we assessed the utility of Medicare claims to identify the receipt of any chemotherapy and specific agents. Generally, Medicare claims can accurately identify the receipt of any chemotherapy and most specific agents administered intravenously. Medicare claims in combination with clinical data from

cancer registries may be a valuable resource for health services research focused on evaluating treatment-related issues. Additionally, these results may be useful to assess the potential impact of treatment misclassification in future studies.

Table 4.1. Characteristics of individuals aged 65 and older included in the Patterns of Care Studies* who were not enrolled in a clinical trial and had Medicare fee-for-service coverage only in the 6-month period following cancer diagnosis

Characteristic	Breast (2000)	Breast (2005)	Colo-rectal (2000)	Colo-rectal (2005)	Ovary (2002)	Non-Small Cell Lung (2005)
	(%) n=156	(%) n=155	(%) n=171	(%) n=338	(%) n=170	(%) n=197
Demographics						
Gender						
Male	0.0	0.0	46.8	43.5	0.0	50.8
Female	100	100	53.2	56.5	100	49.2
Age at diagnosis (mean, SD)	75 (7)	74 (7)	75 (7)	76 (8)	75 (7)	74 (6)
65 - 69	23.7	31.0	24.6	21.3	25.9	24.9
70 - 74	24.4	22.6	25.2	24.6	24.1	31.5
75 - 79	32.7	26.5	22.2	20.4	26.5	24.4
80 - 84	10.3	9.7	16.4	18.6	15.9	15.2
85+	9.0	10.3	11.7	15.1	7.7	4.1
Race						
White Non-Hispanic	53.2	42.6	54.4	50.3	70.0	46.2
Black Non-Hispanic	21.2	24.5	14.6	17.8	16.5	23.4
Hispanic	13.5	18.1	13.5	14.8	4.1	12.7
Other	12.2	13.6	17.5	17.2	9.4	16.8
Unknown	0.0	1.3	0.0	0.0	0.0	1.0
Marital status						
Married	43.6	43.2	53.8	54.7	54.1	53.3
Other	53.2	54.8	45.0	44.1	44.1	46.2
Unknown	3.2	1.9	1.2	1.2	1.8	0.5
Median household income†						
≤ $30,000	26.3	21.9	16.96	26.0	26.5	17.3
$30,001 - $45,000	31.4	25.8	32.75	26.3	26.5	36.0
$45,001 - $60,000	25.0	28.4	24.56	21.3	22.9	21.8
≥ $60,001	17.3	23.9	25.73	26.3	24.1	24.9
High school education†						
≤ 70%	17.3	22.58	22.22	24.3	16.5	21.3
71 - 80%	18.6	20.65	16.37	14.2	18.8	18.8
81 - 90%	40.4	29.68	32.75	32.3	34.1	37.6
> 90%	23.7	27.1	28.65	29.3	30.6	22.3
County of residence in metro areas size†						
Over 1 million population	42.3	61.3	63.2	63.3	48.2	52.3
250,000 - 1 million population	25.0	23.9	20.5	15.4	23.5	28.4
All other counties	32.7	14.8	16.4	21.3	28.2	19.3
Tumor characteristics at diagnosis						
Histologic grade						
Well-differentiated	16.0	18.7	2.9	5.9	5.9	4.6

Moderately differentiated	36.5	43.9	67.3	66.9	12.9	23.4
Poorly/undifferentiated	32.1	27.1	28.3	26.2	48.8	32.5
Unknown	15.4	10.3	1.2	1.2	32.4	39.6
Tumor extent						
Tis	23.1	23.9	0.0	0.0	0.0	0.0
T1	48.1	41.9	1.2	2.1	25.3	24.9
T2	24.4	29.0	5.3	5.0	18.8	32.0
T3	2.6	4.5	75.4	79.0	34.7	8.1
T4	0.0	0.0	18.1	13.9	0.0	24.4
Unknown	1.9	0.7	0.0	0.0	21.2	10.7
Metastasis						
No	100.0	100	100	100	78.8	70.1
Yes	0.0	0.0	0.0	0.0	21.2	29.4
Unknown	0.0	0.0	0.0	0.0	0.0	0.5
Number of positive lymph nodes						
None	50.0	43.9	40.4	52.4	25.3	27.4
1 - 3 nodes	10.3	23.2	36.3	30.8	8.2	5.6
≥ 4 nodes	8.3	9.1	15.8	11.2	0.6	2.6
Positive but number unknown	0.0	0.0	1.2	0.0	0.6	1.5
Unknown or nodes not examined	31.4	23.9	6.4	5.6	65.3	63.0

* POC studies in 2000, 2002, and 2005 include the SEER 10, SEER 12, and SEER 13 registries, respectively.

† Median household income, percentage of census tract with a high school education, and county of residence in metro area size are linked from 2000 Census data.

Table 4.2: Comparison of any chemotherapy identified by SEER POC data and Medicare claims during various post-diagnosis periods for selected cancer sites and year

	Source reporting receipt of chemotherapy								
	POC=Yes, Med=Yes	POC=No, Med=No	POC=Yes, Med=No	POC=No, Med=Yes	Kappa (%) (95% CI)	Se (%) (95% CI)	Sp (%) (95% CI)[†]	PPV (%) (95% CI)	NPV (%) (95% CI)
Breast (2000, 2005)									
2 months	11	259	46	2	27 (7, 46)	19 (10, 32)	99 (97, 100)	85 (55, 98)	85 (80, 89)
4 months	45	252	13	6	79 (70, 88)	78 (65, 87)	98 (95, 99)	88 (76, 96)	95 (92, 97)
6 months	48	247	9	7	83 (74, 91)	84 (72, 93)	97 (94, 99)	87 (76, 95)	96 (93, 98)
8 months	48	245	7	7	84 (77, 92)	87 (76, 95)	97 (94, 99)	87 (76, 95)	97 (94, 99)
10 months	48	240	7	8	83 (75, 92)	87 (76, 95)	97 (94, 99)	86 (74, 94)	97 (94, 99)
12 months	49	240	6	8	85 (77, 93)	89 (78, 96)	97 (94, 99)	86 (74, 94)	98 (95, 99)
Colorectal (2000)									
2 months	45	78	61	3	36 (23, 49)	42 (33, 52)	96 (90, 99)	94 (83, 99)	56 (47, 65)
4 months	90	66	15	6	76 (66, 86)	86 (78, 92)	92 (83, 97)	94 (87, 98)	81 (71, 89)
6 months	92	60	12	7	77 (67, 87)	88 (81, 94)	90 (80, 96)	93 (86, 97)	83 (73, 91)
8 months	93	53	8	8	79 (69, 89)	92 (85, 97)	87 (76, 94)	92 (85, 97)	87 (76, 94)
10 months	91	50	7	8	79 (69, 89)	93 (86, 97)	86 (75, 94)	92 (85, 96)	88 (76, 95)
12 months	88	48	7	10	76 (65, 87)	93 (85, 97)	83 (71, 91)	90 (82, 95)	87 (76, 95)
Colorectal (2005)									
2 months	70	172	115	3	36 (26, 45)	38 (31, 45)	98 (95, 100)	96 (88, 99)	60 (54, 66)
4 months	145	157	34	8	76 (69, 83)	81 (74, 86)	95 (91, 98)	95 (90, 98)	82 (76, 87)
6 months	154	151	23	10	81 (74, 87)	87 (81, 92)	94 (89, 97)	94 (89, 97)	87 (81, 91)
8 months	153	145	19	10	82 (76, 88)	89 (83, 93)	94 (88, 97)	94 (89, 97)	88 (83, 93)
10 months	148	144	17	10	83 (77, 89)	90 (84, 94)	94 (88, 97)	94 (89, 97)	89 (84, 94)
12 months	147	140	15	9	85 (79, 90)	91 (85, 95)	94 (89, 97)	94 (89, 97)	90 (85, 94)
Non-Small Cell Lung (2005)									
2 months	61	149	60	5	50 (39, 60)	50 (41, 60)	97 (93, 99)	92 (83, 97)	71 (65, 77)
4 months	95	111	17	6	80 (72, 88)	85 (77, 91)	95 (89, 98)	94 (88, 98)	87 (80, 92)
6 months	89	95	8	5	87 (80, 94)	92 (84, 96)	95 (89, 98)	95 (88, 98)	92 (85, 97)
8 months	77	87	8	5	85 (78, 93)	91 (82, 96)	95 (88, 98)	94 (86, 98)	92 (84, 96)
10 months	70	76	6	4	87 (79, 95)	92 (84, 97)	95 (88, 99)	95 (87, 99)	93 (85, 97)
12 months	64	72	5	6	85 (76, 94)	93 (84, 98)	92 (84, 97)	91 (82, 97)	94 (85, 98)

Ovary (2002)*									
2 months	96	45	48	3	46 (33, 59)	67 (58, 74)	94 (83, 99)	97 (91, 99)	48 (38, 59)
4 months	129	36	9	6	77 (66, 88)	93 (88, 97)	86 (71, 95)	96 (91, 98)	80 (65, 90)
6 months	125	32	5	5	83 (72, 93)	96 (91, 99)	86 (71, 95)	96 (91, 99)	86 (71, 95)
8 months	119	26	6	6	76 (64, 89)	95 (90, 98)	81 (64, 93)	95 (90, 98)	81 (64, 93)
10 months	112	25	5	6	77 (64, 90)	96 (90, 99)	81 (63, 93)	95 (89, 98)	83 (65, 94)
12 months	109	21	3	6	78 (65, 92)	97 (92, 99)	78 (58, 91)	95 (89, 98)	88 (68, 97)

POC = Patterns of Care, Med=Medicare, Se = Sensitivity, Sp = Specificity, PPV = Positive predictive value, NPV = Negative predictive value

* Three ovarian cancer patients did not report any chemotherapy treatment data in POC and were removed from analysis.

† Exact binomial 95% confidence intervals are rounded to the nearest digit. Therefore, none of the upper limits is exactly 100%.

Table 4.3: Comparison of specific chemotherapeutic agents identified by SEER POC data and Medicare claims during the 6-month post-diagnosis period for selected cancer sites and years*

	Source reporting receipt of specific agent				Kappa (%) (95% CI)	Se (%) (95% CI)	Sp (%) (95% CI)†	PPV (%) (95% CI)†	NPV (%) (95% CI)
	POC=Y Med=Y	POC=N Med=N	POC=Y Med=N	POC=N Med=Y					
Breast (2000 and 2005)									
Cyclophosphamide	39	249	13	4	83 (73, 92)	75 (61, 86)	98 (96, 100)	91 (78, 97)	95 (92, 97)
Doxorubicin	27	266	10	3	78 (67, 90)	73 (56, 86)	99 (97, 100)	90 (73, 98)	96 (93, 98)
Colorectal (2000)									
5-Fluorouracil (5-FU)	87	62	15	5	76 (66, 86)	85 (77, 92)	93 (83, 98)	95 (88, 98)	81 (70, 89)
Colorectal (2005)									
5-Fluorouracil (5-FU)	114	192	14	11	83 (77, 89)	89 (82, 94)	95 (91, 97)	91 (85, 96)	93 (89, 96)
Capecitabine	22	279	25	5	55 (39, 70)	47 (32, 62)	98 (96, 99)	81 (62, 94)	92 (88, 95)
Oxaliplatin	51	254	17	9	73 (63, 82)	75 (63, 85)	97 (94, 98)	85 (73, 93)	94 (90, 96)
Non-Small Cell Lung (2005)									
Carboplatin	77	112	4	1	95 (90, 99)	95 (88, 99)	99 (95, 100)	99 (93, 100)	97 (91, 99)
Paclitaxel	61	123	7	2	90 (83, 96)	90 (80, 96)	98 (94, 100)	97 (89, 100)	95 (89, 98)
Ovary (2002)									
Carboplatin	110	35	11	10	68 (56, 81)	91 (84, 95)	78 (63, 89)	92 (85, 96)	76 (61, 87)
Paclitaxel	100	39	13	14	62 (49, 75)	88 (81, 94)	74 (60, 85)	88 (80, 93)	75 (61, 86)

POC = Patterns of Care, Med=Medicare, Se = Sensitivity, Sp = Specificity, PPV = Positive predictive value, NPV = Negative predictive value

* Individuals lacking treatment data for the specific agent of interest were excluded from analysis.

† Exact binomial 95% confidence intervals are rounded to the nearest digit. Therefore, none of the upper limits is exactly 100%.

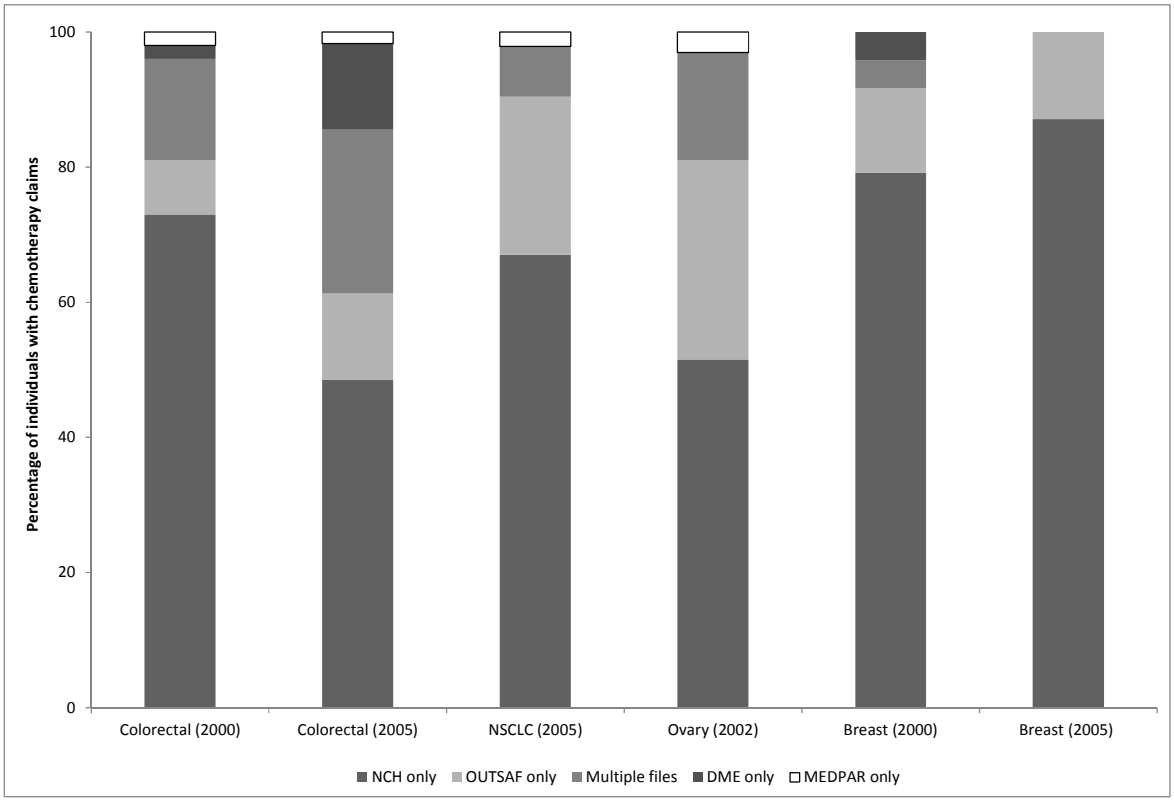


Figure 4.1. Sources of chemotherapy claims for the year following diagnosis reported by Medicare for all individuals aged ≥65 years in the POC studies, by selected cancer site and year of diagnosis.

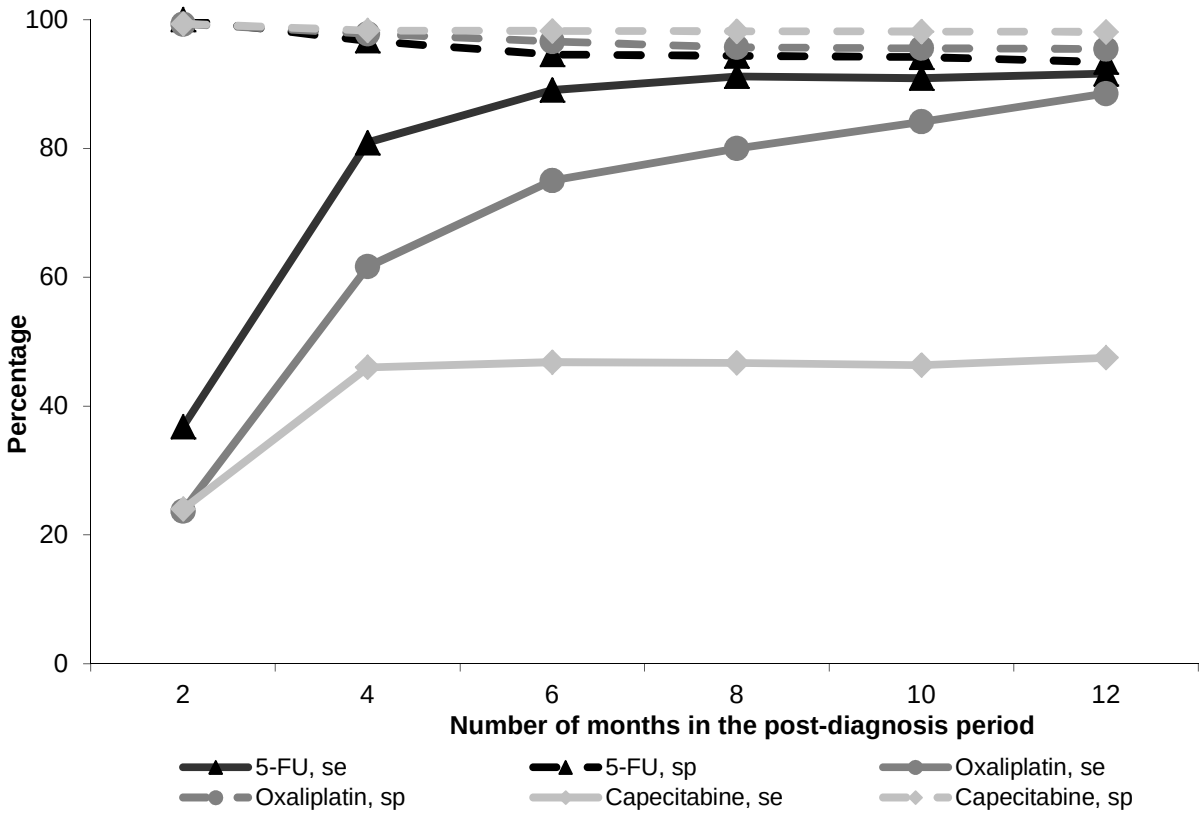


Figure 4.2. Sensitivity and specificity of Medicare claims for identifying the receipt of specific agents by post-diagnosis period, Colorectal cancer, 2005.

CHAPTER 5

RESULTS: Influence of patient, physician, and hospital characteristics on the receipt of oxaliplatin among elderly stage II and III colorectal cancer patients[2]

A. INTRODUCTION

In 2010, there were an estimated 142,570 newly diagnosed cases and 51,370 deaths attributable to colorectal cancer (CRC) in the United States (US), leading to approximately $8.9 billion in spending on cancer care.[2,3] Almost 50% of these cases were diagnosed at stage II or III, representing a large portion of the overall disease burden.[8] Treatment guidelines for stage II and III CRC have changed over time, incorporating new evidence on therapies evaluated in randomized controlled trials (RCTs).[122]

Chemotherapy represents an integral part of the treatment plan for many individuals diagnosed with CRC as it is proven to decrease the risk of disease recurrence and overall mortality.[12-19] Until the early 2000's, the National Comprehensive Cancer Network (NCCN) recommended that stage III colon and stage II and III rectal cancer patients receive a chemotherapy regimen of 5-fluorouacil (5-FU) plus leucovorin (LV). However, RCTs in the mid-2000's sought to establish the efficacy of a number of new chemotherapeutic agents used to treat CRC. In particular, three RCTs demonstrated that adding oxaliplatin to 5-FU/LV significantly improved disease-free and overall survival for individuals diagnosed

[2] This chapter will be submitted the journal, *Cancer*. Authors include those listed on the title page.

with stage III, but not stage II colon cancer.[13,23,24,41] Clinically significant toxicities of oxaliplatin treatment included neutropenia and sensory neuropathy. Based on an evaluation of the evidence on benefit and harm, the Food and Drug Administration (FDA) approved oxaliplatin for the treatment of stage III colon cancer in November 2004[34] and it has now become the standard of care in this group.[10]

While many stage II CRC patients receive chemotherapy, the benefits of treatment are controversial. Although RCTs of chemotherapy in stage II disease have shown a trend towards efficacy of 5-FU/LV treatment alone[36] and in combination with oxaliplatin,[13,23,41] the differences have not lead to significant survival benefits. Among high-risk stage II colon cancer patients, such as those with T4 tumor penetration, poorly differentiated histology, bowel obstruction, bowel perforation, or fewer than 12 lymph nodes examined, studies suggest that adjuvant therapy with 5-FU/LV (alone or in combination with oxaliplatin) may be beneficial.[13,123] RCT evidence is lacking on the benefits of oxaliplatin for stage II and III rectal cancer in preoperative chemoradiotherapy regimens; however, results from colon cancer are often extrapolated to support its use in patients with rectal cancer.

Despite this uncertainty in the benefit of newer chemotherapeutic agents, particularly among the elderly who were underrepresented in RCTs, few studies have examined the utilization patterns of specific chemotherapeutic agents in stage II and III CRC or the translation of the trial evidence on oxaliplatin into routine clinical practice. Similarly, little is known about the off-label use of oxaliplatin in patients diagnosed with stage II colon or stage II or III rectal cancers. The objectives of the current study were to describe trends in the utilization of specific chemotherapeutic

agents for the treatment of stage II and III CRC (5-flurouracil, capecitabine, oxaliplatin, irinotecan, and bevacizumab) from 2000-2007 and identify patient, physician, and hospital characteristics associated with the receipt of oxaliplatin from 2004-2007. We examined the influence of these characteristics overall and separately for on- and off-label indications. In light of the clinical trial evidence, our findings highlight areas of potential overuse and underuse of specific chemotherapeutic agents and may be helpful in developing targeted interventions to encourage more evidence-based and equitable dissemination of effective treatments.

B. METHODS

Data sources

Data for this study were obtained from multiple databases linked through collaborative agreements between the National Cancer Institute (NCI), the Centers for Medicare and Medicaid Services (CMS), and the American Medical Association (AMA).

Surveillance, Epidemiology and End Results Program (SEER)–Medicare database

The SEER-Medicare database consists of a linkage of two large population-based data sources providing detailed clinical and healthcare utilization information on Medicare beneficiaries diagnosed with cancer.[4] The SEER registries collect demographic, clinical and tumor characteristics, vital status, and cause of death for

all incident cancers reported for individuals who reside in one of the registries' defined geographic areas, currently covering approximately 28% of the US population.[45] These data have been linked to Medicare enrollment and Part A (Hospital insurance) and B (Medical insurance) claims data. Approximately 93% of all elderly cancer patients in SEER have been matched to Medicare enrollment files with an established algorithm, resulting in a linked database that includes over 3.3 million elderly individuals (age ≥ 65 years).[46] Nearly all Medicare beneficiaries are eligible for Part A and close to 93% opt to enroll in the Part B.[47]

In addition, the NCI produces the Hospital file which reports descriptive information for hospitals that are part of the SEER-Medicare database.[87] Hospital data is derived from two sources maintained by CMS. Every year, hospitals that bill to Medicare are required to file an annual report called the Healthcare Cost Report (HCRIS). Additionally, CMS periodically requests institutions to complete the Provider of Service (POS) survey for certification purposes. NCI has extracted selected variables from the two data sources from 1996, 1998, and 2000-2009 for inclusion in the Hospital File. Medicare inpatient and outpatient hospital claims can be linked to the Hospital file using the provider number on the claim.

AMA Physician Masterfile

The AMA Physician Masterfile data contain current and historical information on over one million residents and physicians in the United States.[84] To obtain characteristics of physicians providing services to patients in the SEER-Medicare database, we used the Universal Physician Identification Number (UPIN) to link claims from Medicare to the AMA data.[85,86]

Study cohorts

Specific agent trends cohort

To examine trends in the utilization of specific chemotherapeutic agents, we first identified all patients in SEER diagnosed at age ≥66 with their first primary stage II or III cancer of the colon or rectum. SEER staging was based on the American Joint Commission on Cancer (AJCC), 3rd edition from January 1, 2000-December 31, 2003 or AJCC 6th edition from January 1, 2004-December 31, 2007. The diagnosis date was set to the first day of the month, as SEER does not report the day of diagnosis. Diagnoses identified at autopsy or death certificate only were excluded, resulting in a cohort of 55,549 individuals. All individuals were required to have continuous Medicare Part A and B enrollment and no HMO enrollment for the 12-months before and 8-months after diagnosis to ensure complete capture of healthcare utilization and treatment information. We excluded all individuals missing their month of diagnosis. As a result of these criteria, 32,278 individuals were eligible for further analysis. To examine the utilization of various chemotherapeutic agents, we restricted the cohort to individuals who had a claim for at least one specific

chemotherapeutic agent in the 8-months following diagnosis, limiting our final cohort to 12,839 patients.

Oxaliplatin cohort

To identify patient, physician, and hospital characteristics associated with the receipt of oxaliplatin, we first imposed identical SEER and Medicare criteria to construct the oxaliplatin cohort, limiting the diagnosis date to January 1, 2004–December 31, 2007, the period where oxaliplatin began to disseminate among stage II and III CRC patients. This cohort included 15,694 patients.

Next, to identify characteristics of the hospital where cancer surgery was performed, we further restricted this cohort to individuals with a surgical claim (i.e., colectomy or proctectomy) in the inpatient (MEDPAR) or outpatient hospital (OUTSAF) files in the 6-months following diagnosis. These files include the provider number necessary to identify the hospital where treatment was received. If a patient had surgical claims from multiple hospitals, the first hospital was retained for analysis. We then linked the cohort to the SEER-Medicare Hospital file by the provider number and year of diagnosis for each patient. Hospitals that did not match and patients without claims for surgery during the 6-months post-diagnosis were excluded from analysis. The resulting cohort included 14,418 individuals and 1,022 hospitals.

Lastly, to identify characteristics of physicians providing chemotherapy services, we required all patients to have at least one claim for a specific chemotherapeutic agent in the physician (NCH) or the OUTSAF claims files during the 8-months following their diagnosis. For all patients, we obtained the performing

and attending provider reported by the NCH and OUTSAF files, respectively.[90] The physician with the most chemotherapy-related claims during the 8-month period post-diagnosis was considered the treating physician. UPINs that did not match to the AMA Physician Masterfile or contained all missing values were excluded from analysis. As a result, 4,819 patients, 795 hospitals, and 1,579 physicians were included in the final oxaliplatin analysis.

Patient characteristics

We obtained demographic characteristics of patients including year of diagnosis, sex, age at diagnosis (66-69, 70-74, 75-79, 80-84, or 85+), race/ethnicity (White Non-Hispanic, Black Non-Hispanic, Other Non-Hispanic, Hispanic, or Unknown), marital status (married, single, other (divorced, separated, widowed), or unknown), and region of residence (Northeast, South, Midwest, or West) from SEER. County-level metropolitan area was defined as metropolitan or non-metropolitan. SEER-Medicare does not report individual-level socioeconomic (SES) information. Therefore, we used the percentage of residents living below the federal poverty level, an aggregated measure of SES at the census tract level (Census 2000). Previous studies have shown that the census tract poverty variable may be the best proxy measure of economic status for elderly Medicare beneficiaries.[91,92] This variable was categorized into quartiles: ≤4%, 4.01-≤8%, 8.01-≤15%, and >15% (i.e., the tract with the highest percentage of people living below the poverty level).

We also obtained clinical characteristics from SEER, including cancer site (colon or rectum), AJCC stage (II or III), histologic grade (well/moderately differentiated, poorly/undifferentiated, or unknown), tumor size (<2cm, 2-<3cm, 3-

<4cm, ≥4cm, or unknown), and number of lymph nodes examined (<12 nodes, ≥12 nodes, or unknown). The Charlson Comorbidity Index was measured from the 365 days of Medicare inpatient and outpatient claims prior to diagnosis using the methodology developed by Klabunde et al.[77]

Hospital characteristics

We retrieved characteristics of hospitals where patients received colorectal cancer surgery from the SEER-Medicare Hospital file. Hospital characteristics included NCI center designation (none, clinical, or comprehensive), NCI cooperative membership group count (0 or ≥1), teaching hospital status (yes or no), type of hospital (non-profit, private, or government), and total bed size, measured in quartiles (<204 beds, 204-343 beds, 344-487 beds, or 488+ beds).

Physician characteristics

We obtained characteristics of physicians who treated patients with chemotherapy from the AMA Physician Masterfile and included medical degree (Medical Doctor (MD) or Doctor of Osteopathy (DO)), whether the physician was trained in the US (yes or no), year of medical school graduation (<1981 or ≥1981), primary specialty (oncology, hematology/oncology, hematology, internal medicine, or other), and sex.

Measurement of specific chemotherapeutic agents for the treatment of CRC

We categorized patients as receiving any chemotherapy treatment using International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis, ICD-9-CM procedure, Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS), and revenue center

codes. Because we were concerned with identifying initial treatment with 5-FU, capecitabine, oxaliplatin, irinotecan, and bevacizumab, specifically, we excluded patients with administration codes only, as we were unable to identify the agents they received. Initial treatment with these agents was defined using the two month period of claims data following the first chemotherapy claim for each patient. The administrative codes used to identify any chemotherapy, the specific agents, and their measures of validity using previously published methods[49,93] are listed in the Appendix C.

Statistical analysis

We estimated the prevalence (and its 95% confidence interval (CI) of 1) any chemotherapy use among all eligible stage II and III CRC patients and 2) specific agents among all patients treated with chemotherapy (and having at least one specific agent claim) by year, cancer site, and stage. All analyses were performed on the chemotherapeutic agent-level so that individuals could be counted more than once in a given year (e.g., if they received both oxaliplatin and 5-FU). Therefore, the percentages do not sum to 100%. We present results for specific agents with ≥5% prevalence in at least one year. Logistic regression models stratified by cancer site and year were used to test for trends in the utilization of any chemotherapy from 2000-2007 and for specific agents from 2004-2007. All models included patient age in 5-year categories (66-69, 70-74, 75-79, 80-84, 85+) to control for changes to the US population age structure over time, and diagnosis year to assess time trends.

Trends in the replacement of 5-FU with capecitabine were estimated by measuring the proportion of capecitabine use among all users of fluoropyrimidines

by year, cancer site, and stage. Individuals receiving both 5-FU and capecitabine in the 2-months following their first chemotherapy claims were excluded from the analysis (n=83). Because the administrative definition for identifying capecitabine in Medicare claims has a very low sensitivity (47%), but high specificity (98%), we sought to estimate the proportion of patients receiving capecitabine that were missed by Medicare claims. The following equation was used to calculate the additional number of patients receiving capecitabine:

$$N_{cap\_corr} = (N_{cap} - (1 - Se_{cap}) * (N_{yr\_tot} - N_{5fu\_tot}) / (Se_{cap} + Sp_{cap} - 1)$$ [94]

Where N_{cap_corr} is the number of capecitabine users, corrected for the misclassification in Medicare claims, N_{cap} is the number of capecitabine users identified by Medicare claims, N_{yr_tot} is the total number of individuals in site/stage patient group, N_{5fu_tot} is the total number of 5-FU users in site/stage patient group, and Se_{cap} and Sp_{cap} are the sensitivity and specificity of the administrative definitions used to identify capecitabine in Medicare claims.

These additional patients were added to the total number of 5-FU and capecitabine users and the proportion of patients receiving 5-FU, capecitabine (as measured by claims), and capecitabine (as imputed using validation data) were graphed.

We estimated the proportion of patients receiving any chemotherapy and oxaliplatin, specifically, across patient demographic and clinical variables and calculated univariate prevalence ratios for the receipt of oxaliplatin for each patient, physician, and hospital characteristic.

Patient observations for the oxaliplatin cohort were clustered within hospitals and physicians in a non-nested manner. Miglioretti and Heagerty have developed a generalized estimating equation (GEE) strategy that can be used to adjust for the correlation among observations within non-nested multi-level data and provide estimates of marginal (population-averaged) associations.[95] We used this strategy to account for the correlations of oxaliplatin receipt among patients who were treated with chemotherapy by the same physician and/or underwent surgery at the same hospital. The patient was the unit of analysis and the hospital's provider number and the physician's UPIN were the clustering variables. We estimated prevalence ratios for patient, physician and hospital variables using multivariate Poisson models with a log link and an independent GEE working matrix. Separate analyses for on- and off-label indications were performed, as the influence of the selected characteristics may vary by indication. Finally, we assessed the contribution of the measured patient, physician, and hospital characteristics on the explained variation in the receipt of oxaliplatin by calculating and comparing the c-statistic for four models, including: 1) all patient, physician and hospital variables, 2) patient-level variables only, 3) physician-level variables only, and 4) hospital-level variables only. All statistical analyses were conducted using the SAS Version 9.2 (SAS Institute, Inc., Cary, NC).

C. RESULTS

Specific agent trends cohort

We identified 32,287 patients diagnosed with stage II or III colorectal cancer who met all SEER and Medicare eligibility criteria. The left columns of Table 5.1 report the demographic and clinical characteristics of this cohort. Percentages are calculated across rows to reflect the proportion of the specified group receiving chemotherapy. Overall, 41% of patients received chemotherapy.

The prevalence of chemotherapy receipt among this cohort is illustrated in Figure 5.1 by year, cancer site, and stage. Treatment with any chemotherapy was highest among stage III rectal and colon cancer patients. The utilization of chemotherapy in stage II rectal cancer increased over the time period ($p=0.006$) while utilization in stage II colon cancer decreased ($p<0.0001$).

Among those receiving chemotherapy, we identified 12,839 patients who had at least one Medicare claim for a specific chemotherapeutic agent. Our analysis of the prevalence of specific agents and their associated 95% CIs was limited to this group and is pictured by year, cancer site and stage in Figure 5.2a-d**,** noting the number of individuals included in the analysis for each year. For all cancer site and stage combinations, the utilization of 5-FU significantly decreased from 2000-2007 across all cancer sites and stages ($p<0.0001$), with prevalence close to 100% for all site and stage combinations in 2000 and dropping to around 70% by 2007. Accordingly, Capecitabine utilization increased from 2004-2007 in all groups ($p< 0.0001$), but was most noticeable in patients diagnosed with stage II rectal cancer with a prevalence of 38% in 2007. The utilization of oxaliplatin increased substantially from 2004-2007 (stage II colon: $p<0.0001$; stage III colon: $p< 0.001$; stage II rectum: $p=0.006$; stage III rectum: $p=0.0003$) and was highest among

patients diagnosed with stage II and III colon cancers. Bevacizumab use was minimal in stage II and III colon cancer over the study period, but increased to a prevalence of almost 10% by 2007 (stage II colon: p=0.002; stage III colon: p<0.0001). Irinotecan was used in less than 10% of stage III colon and rectal cancer patients during the entire time period. Use of irinotecan in stage III colon cancer decreased slightly from 2004-2007 (p=0.05), but the same was not true for stage III rectal cancer (p=0.99).

Trends in the replacement of 5-FU with capecitabine are illustrated in Figure 5.3a-d. Relying upon Medicare claims alone may understate the use of capecitabine. Therefore, we estimated the additional proportion of patients using capecitabine that were missed by claims relying upon the previous validation study methods[93] starting in 2005, the year that capecitabine was approved for use in stage III colon cancer. The share of individuals using capecitabine steadily increased after 2005 and is most pronounced in the stage II colon and rectal cancer groups, likely due to more frequent substitution in the single-agent setting. By 2007, almost 70% of all individuals treated with chemotherapy in the stage II rectal cancer group were treated with capecitabine, after accounting for misclassification.

Oxaliplatin cohort

We identified 4,819 patients diagnosed with stage II or III colorectal cancer who met all SEER, Medicare, surgery, and chemotherapy eligibility criteria for inclusion in the analysis examining the influence of patient, physician, and hospital characteristics on the receipt of oxaliplatin. The right columns of Table 5.1 report the demographic and clinical characteristics of this cohort.

Table 5.2 summarizes the characteristics of the physicians (n=1,579) and hospitals (n=795) included in the oxaliplatin analysis and the number and percentage of patients receiving oxaliplatin for each group. The majority of physicians were male (82%), MDs (97%), US-trained (67%), medical school graduates ≥1981 (56%) and had a primary specialty of oncology or hematology/oncology (76%). Most hospitals in the analysis were lacking NCI cancer center designation (97%) and cooperative group memberships (51%). About 40% were teaching hospitals and over 60% were non-profit entities. In univariate analyses, patients who were treated by MDs and US-trained physicians were more likely to receive oxaliplatin. Patients undergoing CRC surgery at non-profit and teaching hospitals were less likely to receive oxaliplatin treatment.

Overall, 2,183 patients (52%) received oxaliplatin as part of the initial course of treatment, reflecting a prevalence of on- and off-label treatment of 56% and 29%, respectively. Table 5.3 reports the unadjusted overall, adjusted overall, and on- and off-label adjusted prevalence ratios (PRs) for the receipt of oxaliplatin across patient, physician, and hospital characteristics. In the overall adjusted analysis, older age (e.g., 85+ vs. 66-69: aPR =0.24, 95% CI: (0.12, 0.48)), other marital status (separated, divorced, or widowed vs. married: aPR =0.89, 95% CI: (0.78, 1.01)), and earlier year of diagnosis (e.g., 2004 vs. 2007: aPR =0.42, 95% CI: (0.31, 0.51)) were associated with a lower prevalence of oxaliplatin treatment. Patients diagnosed with colon vs. rectal cancer were more likely to receive oxaliplatin (aPR=2.28, 95% CI: (1.74, 2.98)), whereas those diagnosed with stage II vs. III disease were less likely (aPR= 0.65, 95% CI: (0.56, 0.76)). There were (statistically non-significant) trends in

the associations between higher Charlson comorbidity scores (e.g., 2+ vs. 0: aPR=0.88, 95% CI: (0.71, 1.08)) and higher percentage of the census tract living under the poverty level (e.g., 4th vs. 1st: aPR=0.91, 95% CI: (0.77, 1.09)), and a lower prevalence of oxaliplatin treatment.

In general, the influences of patient, physician, and hospital characteristics on the receipt of oxaliplatin in the on- and off-label settings were similar to the overall cohort. In the off-label analysis patients diagnosed with stage II rectal cancer were substantially less likely to receive oxaliplatin than those diagnosed with stage II colon cancer (aPR=0.39, 95% CI: (0.28, 0.54)).

The overall Poisson model including all patient, physician, and hospital variables had a c-statistic (or area under the receiver operating curve) of 77.6%. Patient-level characteristics accounted for almost all of the explained variation (c-statistic=77.5%), while physician-level and hospital-level characteristics did not explain receipt of oxaliplatin (c-statistic=53.1% and 53.5%, respectively). Thus, after conditioning upon the receipt of any chemotherapy, the explainable variation in the receipt of oxaliplatin appears to be almost exclusively driven by patient-level factors.

D. DISCUSSION

In this population-based analysis among patients who received chemotherapy treatment, there were substantial shifts in the utilization of specific chemotherapeutic agents used to treat stage II and III CRC patients diagnosed from 2000–2007. For all cancer site and stage combinations, the utilization of capecitabine and oxaliplatin

increased substantially from 2004-2007, while 5-FU decreased. Use of bevacizumab in stage II and III colon cancer significantly increased, while irinotecan use remained relatively constant among stage III CRC patients, likely because data on its lack of efficacy were not reported until 2007.[25,26] After receiving FDA approval for stage III colon cancer in 2005, the proportion of patients treated with capecitabine (in place of 5-FU) increased over time, particularly in stage II CRC where single agent use is common.

Measured patient-level characteristics appeared to drive most of the explainable variation in receipt of oxaliplatin among individuals diagnosed with stage II or III CRC between 2004 and 2007. In particular, patients who were younger, female, married, and diagnosed in later study years were more likely to receive oxaliplatin. Those patients diagnosed with cancer of the colon, stage III disease, and having no comorbidities (measured by the Charlson comorbidity score) were also more likely to receive oxaliplatin. In multivariate analyses, DOs and physicians trained outside of the US were less likely to treat patients with oxaliplatin; however, these associations were not statistically significant. The primary specialty of the physician treating the patient did not appear to influence the prevalence of treatment with oxaliplatin. In general, the characteristics of hospitals where patients received their CRC surgery did not have a strong influence on a patient's receipt of oxaliplatin after adjustment for other factors and clustering.

Few studies have examined trends in treatment with specific chemotherapeutic agents over time among stage II and III CRC patients. Ferro and colleagues[57] conducted a cross-sectional study of 115 ambulatory centers in the US

to examine the utilization of 8 of the most commonly prescribed chemotherapeutic regimens by 421 individuals diagnosed with primarily metastatic CRC (mCRC) between 2002 and 2005. In line with our results, utilization of oxaliplatin substantially increased after FDA approval for mCRC, late in 2004 while 5-FU decreased. A more recent study by Hsiao et al[58] drew upon the SEER-Medicare database and reported the utilization of three regimens, 5-FU/LV alone, irinotecan-based regimens, and oxaliplatin-based regimens for stage III colon cancer patients by year of diagnosis from 2002-2005. Similar levels of utilization were reported for oxaliplatin of approximately 35% in 2004 and 57% in 2005.

A number of studies have examined associations between patient and physician characteristics and the receipt of any chemotherapy among stage II and III CRC patients. In general, age, sex, race/ethnicity, region, area-level SES, cancer site, nodal status, and number of comorbidities have been shown to influence the receipt of initial chemotherapy treatment.[55,61,64,66,70,72] Physician characteristics, such as younger age and receipt of US-based training, have also been shown to predict the receipt of chemotherapy overall.[71]

However, our study focused on a population of stage II and III CRC patients receiving chemotherapy and attempted to distinguish the patient, physician, and hospital characteristics associated with the receipt of oxaliplatin, specifically. After conditioning upon chemotherapy receipt, the influence of access to care-related variables appeared to diminish. The associations between race/ethnicity and metropolitan county area status and oxaliplatin receipt are no longer seen. Hsiao[58] and Kahn[70] reported that among patients receiving chemotherapy, elderly patients

and those with more comorbidity were less likely to receive oxaliplatin treatment, which are consistent with the results of our study. The apparent age barrier to the receipt of oxaliplatin is in stark contrast to the evidence about lack of differences in the efficacy,[73] effectiveness,[124] and safety[70] of oxaliplatin in older stage III colon cancer patients.

A study by Becker et al[79] examined patient and physician predictors of oxaliplatin use in stage III colon cancer patients diagnosed from September 2004-December 2005. The authors found that without conditioning on chemotherapy receipt, younger age, white race, being married, having fewer comorbidities, urban location, having a poorly/undifferentiated tumor, and having a younger physician were associated with increased odds of oxaliplatin receipt. A recent study by Abrams et al[59] performed a cross-sectional study using an outpatient chemotherapy ordering system in the US. This study identified patients receiving adjuvant chemotherapy between 2004 and the beginning of 2010. In 2004, 39% of stage III colon cancer patients received oxaliplatin with a fluoropyrimidine, but by 2007, this percentage increased to 90%. Stage II colon cancer patients also experienced a rapid increase in oxaliplatin use, reaching 79% by 2008. Older age was again associated with decreased receipt of oxaliplatin in both stage II and III colon cancer patients. Our study expands upon these findings by 1) including stage II and III rectal cancer patients, 2) seeking to estimate trends in replacement of 5-FU with capecitabine, and 3) augmenting our predictive analysis with additional data (i.e., hospital-level characteristics).

This study has multiple strengths. First, the data are derived from population-based cancer registry and healthcare utilization resources, providing a “real world” context for studying patterns of chemotherapy use in the community setting. In addition, this is one of the first studies to examine the extent of on- and off-label use of a number of specific chemotherapeutic agents in routine practice over time. Lastly, through further linkages to the AMA Masterfile and SEER-Medicare hospital file, we were able to construct a rich multilevel data source to examine the influence of patient, physician, and hospital characteristics on the receipt of oxaliplatin.

Our study is not without limitations, however. The SEER-Medicare data provide information on many important patient and tumor characteristics that may be associated with treatment patterns, but unobserved factors such as patient preference or comorbidities not assessed through the Charlson Comorbidity Index may also influence treatment receipt. The physician and hospital data were somewhat limited; therefore other unmeasured physician and hospital factors may help to explain the variation in oxaliplatin treatment. Additionally, cohort entry was restricted by multiple criteria in order to ensure full healthcare utilization, treatment capture, and linkage to the two additional data sources. These criteria included having continuous Medicare Parts A and B enrollment (with no HMO enrollment), a claim for CRC surgery within 6-months from diagnosis at a hospital matched to the Hospital file, and a claim for a specific chemotherapeutic agent within 8-months of diagnosis, which may reduce the generalizability of our findings.

In conclusion, the utilization of capecitabine and oxaliplatin has increased markedly among stage II and III CRC patients receiving chemotherapy from 2004-

2007. After conditioning on the receipt of chemotherapy, 52% of all stage II and III CRC patients received oxaliplatin from 2004-2007. Much of this use was attributable to patients with off-label indications, for which RCT evidence is lacking or has shown little to no benefit. Patient characteristics appeared to drive most of the explainable variation in the receipt of oxaliplatin for both on- or off-label use. Off-label use of specific chemotherapeutic agents in stage II and III CRC is relatively common in routine practice; however, clinicians deciding to treat patient off-label should carefully weigh the unknown or minimal benefits of treatment against potentially serious side effects.

Table 5.1. Characteristics of elderly stage II or III colorectal cancer patients by cohort and treatment*

	2000-2007 cohort				2004-2007 cohort†			
Patient characteristics	**No chemo**		**Chemo**		**Chemo without oxaliplatin**		**Chemo with oxaliplatin**	
	n=18,951	%	n=13,336	%	n=2,636	%	n=2,183	%
Demographic characteristics								
Gender								
Male	7,555	55	6,259	45	1,289	56	1010	44
Female	11,396	62	7,077	38	1,347	53	1173	47
Age at diagnosis (mean, SD)	79.7 (7.1)		74.3 (5.6)		74.7 (5.7)		72.8 (4.8)	
65 - 69	1,784	36	3,200	64	598	46	697	54
70 - 74	3,075	43	4,056	57	753	51	713	49
75 - 79	4,174	54	3,535	46	716	56	553	44
80 - 84	4,880	71	1,955	29	434	69	199	31
85+	5,038	90	590	10	135	87	21	13
Race								
White Non-Hispanic	15,712	59	10,822	41	2,132	55	1766	45
Black Non-Hispanic	1,408	61	891	39	159	54	135	46
Hispanic	885	52	803	48	176	57	135	43
Other Non-Hispanic	898	53	796	47	166	54	142	46
Unknown	48	67	24	33	3	38	5	63
Marital status								
Married	8,071	51	7,739	49	1,514	52	1,387	48
Single	1,586	63	925	37	173	54	148	46
Other	8,476	67	4,185	33	868	60	570	40
Unknown	818	63	487	37	81	51	78	49
County of residence in metro areas size								
Metropolitan	15,709	58	11,173	42	2,188	54	1,871	46
Non-metropolitan	3,240	60	2,163	40	448	59	312	41
Missing	2	100	-	0	-	0	-	0
Percentage living below poverty level‡								
≤ 4%	4,090	57	3,076	43	591	51	561	49
4-8%	5,189	58	3,736	42	718	53	644	47
8-15%	4,742	60	3,212	40	653	57	490	43
>15%	4,930	60	3,312	40	674	58	488	42
Year of diagnosis								
2000	2,302	57	1,712	43	na	-	na	-
2001	2,430	58	1,730	42	na	-	na	-
2002	2,386	57	1,774	43	na	-	na	-
2003	2,420	57	1,839	43	na	-	na	-
2004	2,528	61	1,640	39	1,026	75	341	25
2005	2,409	59	1,670	41	718	56	554	44
2006	2,307	61	1,448	39	487	44	621	56
2007	2,169	59	1,523	41	405	38	667	62
Region								
Northeast	4,741	59	3,301	41	671	58	489	42
South	3,437	57	2,547	43	533	57	409	43
Midwest	2,998	59	2,107	41	458	60	301	40
West	7,775	59	5,381	41	974	50	984	50

Tumor characteristics at diagnosis									
Cancer site									
Colon	17,344	62	10,765	38	1,959	49	2,023	51
Rectum	1,607	38	2,571	62	677	81	160	19
AJCC/Derived AJCC stage								
II	13,534	76	4,266	24	930	69	419	31
III	5,417	37	9,070	63	1,706	49	1,764	51
Histologic grade								
Well/moderately-differentiated	14,582	61	9,520	39	1,887	56	1,511	44
Poorly/undifferentiated	3,855	54	3,315	46	644	51	616	49
Unknown	514	51	501	49	105	65	56	35
Tumor size								
<2 cm	600	51	569	49	153	60	104	40
2-<3 cm	1,935	59	1,348	41	270	51	259	49
3-<4 cm	3,423	59	2,337	41	472	54	397	46
≥4 cm	11,712	60	7,716	40	1488	54	1266	46
Unknown	1,281	48	1,366	52	253	62	157	38
Number of lymph nodes examined								
<12 nodes	8,613	58	6,172	42	1106	62	688	38
>12 nodes	10,063	59	6,927	41	1495	51	1464	49
Unknown or nodes not examined	275	54	237	46	35	53	31	47
Charlson Comorbidity Index								
0	11,957	56	9,247	44	1717	53	1507	47
1	4,477	61	2,904	39	655	57	492	43
2+	2,517	68	1,185	32	264	59	184	41

* Cases obtained from the SEER 17 registries were included in this analysis.

† The 2004-2007 cohort includes 4,219 individuals who received chemotherapy treatment (with a specific agent claim), had surgery performed at a hospital identified in the Hospital file, and were treated with chemotherapy by a physician included in the AMA Physician Masterfile.

‡ Percentage of census tract living below the poverty line and county of residence in metro area size are linked from 2000 Census data.

Table 5.2. Characteristics of the physician and hospitals providing care for elderly stage II and III colorectal cancer patients who were diagnosed from 2004-2007 and received treatment with specific chemotherapy agents

Characteristic	Physicians/ hospitals included in analysis		Patients receiving chemotherapy with oxaliplatin	
	N	%	N	%
Physician characteristics (n=1,579)				
Degree				
MD	1,526	96.6	2,118	45.7
DO	53	3.4	65	36.1
US-Trained				
Yes	1,054	66.8	1,464	46.4
No	525	33.2	719	43.2
Medical School Graduation				
<1981	697	44.1	995	44.3
≥1981	882	55.9	1,188	46.1
Primary specialty				
Oncology	710	45.0	1,079	45.9
Hematology/Oncology	484	30.7	635	44.4
Hematology	484	30.7	237	46.7
Internal Medicine	139	8.8	180	43.5
Other specialty	78	4.9	52	44.4
Gender				
Male	1,289	81.6	1,882	45.5
Female	290	18.4	301	44.3
Hospital characteristics (n=795)*				
NCI center designation				
None	849	97.1	2,113	45.3
Clinical	4	0.5	9	50.0
Comprehensive	21	2.4	61	43.6
NCI cooperative group membership count				
None	447	51.1	696	44.9
1+	427	48.9	1,487	45.5
Teaching hospital				
Yes	346	39.6	1,087	43.1
No	521	59.6	1,093	47.7
Unknown	7	0.8	3	33.3
Type of hospital				
Non-profit	543	62.1	1,661	44.4
Private	166	19.0	262	48.6
Government	158	18.1	257	48.5
Unknown	7	0.8	3	33.3
Total bed size				
< 204 beds	402	46.0	558	46.5
204 - 343 beds	209	23.9	549	45.6
344 - 487 beds	143	16.4	564	47.0
488+ beds	120	13.7	512	42.2

NCI=National Cancer Institute

*All hospital information was obtained from the year of patient diagnosis with exception of the NCI cancer center designation and cooperative group count which are reported for the year 2002. The total number of hospitals repored here (n=874) is greater than the total number of unique hospitals because some of the hospital characteristics changed over time and are reported here according to year of the patient's cancer diagnosis.

Table 5.3. Unadjusted and adjusted prevalence ratio estimates for the associations between patient, physician, and hospital characteristics and the receipt of oxaliplatin

	Overall	Overall	On-Label	Off-Label
	Unadjusted	Adjusted*	Adjusted*	Adjusted*
Characteristics	**PR (95% CI)**	**PR (95% CI)**	**PR (95% CI)**	**PR (95% CI)**
N	4,219	4,219	2,939	1,880
% receiving oxaliplatin	51.74	51.74	55.84	28.83
Demographic characteristics				
Gender				
Male	1.00	1.00	1.00	1.00
Female	1.06 (1, 1.13)	1.07 (0.95, 1.19)	1.03 (0.91, 1.16)	1.17 (0.9, 1.53)
Age category				
65 - 69	1.00	1.00	1.00	1.00
70 - 74	1.11 (1.04, 1.18)	0.91 (0.81, 1.03)	0.88 (0.77, 1)	0.97 (0.73, 1.28)
75 - 79	0.95 (0.88, 1.02)	0.76 (0.67, 0.88)	0.76 (0.66, 0.88)	0.72 (0.51, 1.02)
80 - 84	0.66 (0.59, 0.75)	0.55 (0.43, 0.7)	0.53 (0.41, 0.68)	0.6 (0.36, 1.02)
85+	0.29 (0.19, 0.43)	0.24 (0.12, 0.48)	0.25 (0.12, 0.52)	0.22 (0.03, 1.44)
Race/ethnicity				
White Non-Hispanic	1.00	1.00	1.00	1.00
Black Non-Hispanic	1.02 (0.89, 1.15)	1.05 (0.83, 1.32)	1.07 (0.84, 1.36)	0.96 (0.52, 1.78)
Other Non-Hispanic	1.02 (0.9, 1.16)	0.94 (0.71, 1.25)	0.9 (0.69, 1.19)	1.04 (0.61,1.8)
Hispanic	0.96 (0.84, 1.09)	0.97 (0.77, 1.21)	0.98 (0.78, 1.25)	0.95 (0.57, 1.58)
Marital status				
Married	1.00	1.00	1.00	1.00
Single	1.02 (0.9, 1.16)	0.94 (0.76, 1.16)	0.95 (0.75, 1.19)	0.83 (0.51, 1.36)
Other (separated, widowed, divorced)	0.83 (0.77, 0.9)	0.89 (0.78, 1.01)	0.88 (0.76, 1)	0.89 (0.67, 1.19)
County of residence in metro areas size				
Metropolitan	1.12 (1.02, 1.23)	1.13 (0.93, 1.37)	1.12 (0.92, 1.37)	1.12 (0.74, 1.71)
Non-metropolitan	1.00	1.00	1.00	1.00
Percent living below poverty level†				
≤ 4%	1.00	1.00	1.00	1.00
4-8%	1.06 (0.99, 1.14)	0.99 (0.87, 1.13)	1 (0.86, 1.15)	0.98 (0.72, 1.33)
8-15%	0.93 (0.86, 1)	0.93 (0.79, 1.09)	0.91 (0.76, 1.07)	1 (0.71, 1.41)
>15%	0.91 (0.84, 0.98)	0.91 (0.77, 1.09)	0.94 (0.79, 1.13)	0.84 (0.56, 1.27)
Year of diagnosis				
2004	0.47 (0.42, 0.52)	0.42 (0.34, 0.51)	0.47 (0.38, 0.58)	0.29 (0.18, 0.45)
2005	0.95 (0.88, 1.02)	0.73 (0.64, 0.84)	0.8 (0.69, 0.92)	0.84 (0.54, 1.29)
2006	1.33 (1.25, 1.42)	0.95 (0.84, 1.08)	0.98 (0.86,1.11)	0.88 (0.57, 1.36)
2007	1.00	1.00	1.00	1.00
Region				
East	0.91 (0.84, 0.98)	0.86 (0.7, 1.05)	0.87 (0.71, 1.05)	0.84 (0.54, 1.29)
South	0.95 (0.88, 1.03)	0.9 (0.74, 1.1)	0.91 (0.75, 1.09)	0.88 (0.57, 1.36)
Midwest	0.86 (0.78, 0.94)	0.87 (0.68, 1.11)	0.88 (0.69, 1.12)	0.84 (0.53, 1.33)
West	1.00	1.00	1.00	1.00

Tumor characteristics at diagnosis				
Cancer site				
Colon	2.66 (2.3, 3.07)	2.28 (1.74, 2.98)	-	-
Rectum	1.00	1.00	-	-
AJCC/Derived AJCC stage				
II	0.61 (0.56, 0.67)	0.65 (0.56, 0.76)	-	-
III	1.00	1.00	-	-
Cancer site and stage combination (off-label)				
Stage II Colon	-	-	-	1.00
Stage II Rectum	-			0.39 (0.28, 0.54)
Stage III Rectum	-	-	-	0.69 (0.38, 1.28)
Histologic grade				
Well/moderately-differentiated	0.91 (0.85, 0.97)	0.96 (0.86, 1.08)	0.98 (0.87, 1.11)	0.93 (0.7, 1.23)
Poorly/undifferentiated	1.00	1.00	1.00	1.00
Tumor size				
<2 cm	0.87 (0.75, 1.02)	0.92 (0.79, 1.07)	1 (0.77, 1.3)	0.7 (0.35, 1.41)
2-<3 cm	1.08 (0.98, 1.18)	1.01 (0.88, 1.15)	0.99 (0.85, 1.17)	1.11 (0.76, 1.63)
3-<4 cm	0.99 (0.92, 1.08)	0.96 (0.85, 1.08)	1 (0.87, 1.15)	0.83 (0.57, 1.21)
≥4 cm	1.00	1.00	1.00	1.00
Number of lymph nodes examined				
<12 nodes	1.00	1.00	1.00	1.00
>12 nodes	1.29 (1.2, 1.38)	1.08 (0.84, 1.39)	1.12 (0.98, 1.27)	0.98 (0.76, 1.28)
Charlson comorbidity score				
0	1.00	1.00	1.00	1.00
1	0.93 (0.86, 1)	0.92 (0.81, 1.04)	0.91 (0.8, 1.04)	0.95 (0.7, 1.28)
2+	0.9 (0.8, 1.01)	0.88 (0.71, 1.08)	0.81 (0.64, 1.04)	0.99 (0.67, 1.48)
Physician characteristics				
Degree				
MD	1.00	1.00	1.00	1.00
DO	0.79 (0.65, 0.96)	0.82 (0.52, 1.28)	0.83 (0.52, 1.32)	0.79 (0.33, 1.91)
US-Trained				
Yes	1.00	1.00	1.00	1.00
No	0.93 (0.87, 1)	0.94 (0.81, 1.09)	0.95 (0.83, 1.1)	0.93 (0.68, 1.28)
Medical School Graduation				
<1981	1.00	1.00	1.00	1.00
≥1981	1.04 (0.98, 1.11)	0.96 (0.84, 1.11)	0.99 (0.86, 1.14)	0.87 (0.66, 1.15)
Gender				
Male	1.00	1.00	1.00	1.00
Female	0.98 (0.89, 1.07)	0.99 (0.83, 1.19)	0.98 (0.82, 1.19)	1.03 (0.7, 1.52)
Specialty				
Oncology	1.00	1.00	1.00	1.00
Hematology/Oncology	0.97 (0.91, 1.04)	1.04 (0.88, 1.23)	1.03 (0.87, 1.22)	0.98 (0.7, 1.38)
Hematology	1.03 (0.94, 1.14)	1.02 (0.84, 1.23)	1.04 (0.85, 1.28)	1 (0.63, 1.57)
Internal Medicine	0.96 (0.85, 1.07)	1.02 (0.81, 1.27)	1.02 (0.83, 1.26)	0.99 (0.58, 1.7)
Other	0.98 (0.8, 1.2)	1.06 (0.7, 1.59)	0.94 (0.59, 1.51)	1.21 (0.65, 2.26)

Hospital characteristics				
NCI center designation‡				
None	1.00	1.00	1.00	1.00
Clinical	1.1 (0.7, 1.75)	1.16 (0.65, 2.04)	1.12 (0.63, 1.97)	1.22 (0.31, 4.71)
Comprehensive	0.96 (0.79, 1.16)	1.08 (0.75, 1.56)	1.21 (0.85, 1.71)	0.79 (0.31, 1.98)
NCI cooperative group membership count‡				
None	1.00	1.00	1.00	1.00
1+	1.01 (0.95, 1.08)	1.01 (0.85, 1.19)	0.97 (0.83, 1.14)	1.12 (0.79, 1.58)
Teaching hospital				
Yes	0.9 (0.85, 0.96)	0.95 (0.81, 1.12)	0.94 (0.8, 1.1)	0.99 (0.7, 1.4)
No	1.00	1.00	1.00	1.00
Type of hospital				
Non-profit	1.00	1.00	1.00	1.00
Private	1.08 (0.99, 1.19)	0.98 (0.81, 1.19)	1.03 (0.85, 1.24)	0.86 (0.53, 1.4)
Government	1.08 (0.98, 1.19)	1.05 (0.87, 1.27)	1.07 (0.88, 1.29)	0.98 (0.64, 1.5)
Total bed size				
< 204 beds	1.00	1.00	1.00	1.00
204 - 343 beds	1.01 (0.94, 1.08)	0.99 (0.83, 1.19)	1.06 (0.88, 1.28)	0.81 (0.56, 1.17)
344 - 487 beds	1.05 (0.98, 1.13)	0.99 (0.81, 1.21)	1.04 (0.85, 1.28)	0.83 (0.56, 1.22)
488+ beds	0.91 (0.84, 0.98)	0.95 (0.74, 1.22)	0.98 (0.76, 1.26)	0.85 (0.54, 1.33)

* Models are adjusted for all other covariates listed. Generalized estimating equations for non-nested clusters were utilized to estimate appropriate standard errors.

† Percentage of census tract living below the poverty line and county of residence in metro area size are linked from 2000 Census data.

‡ NCI cancer center designation and cooperative group count were reported as of the year 2002.

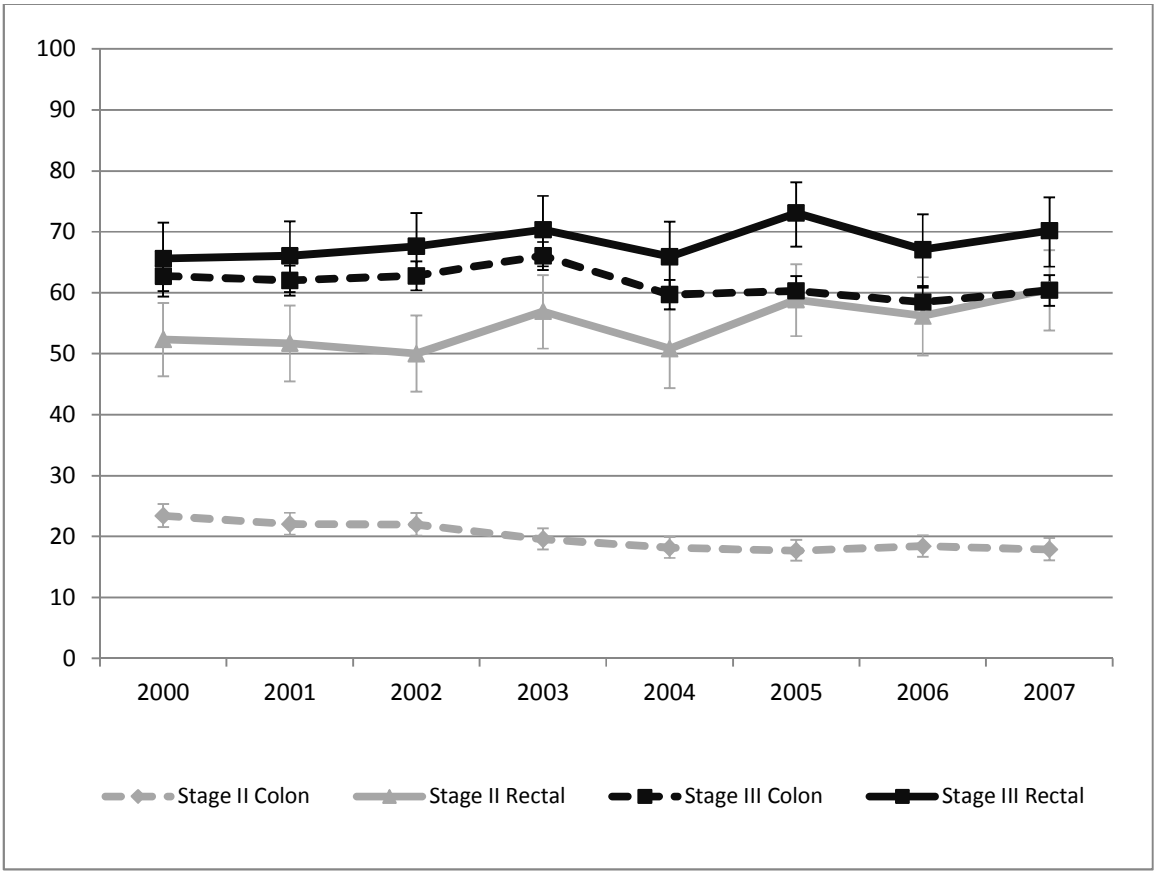
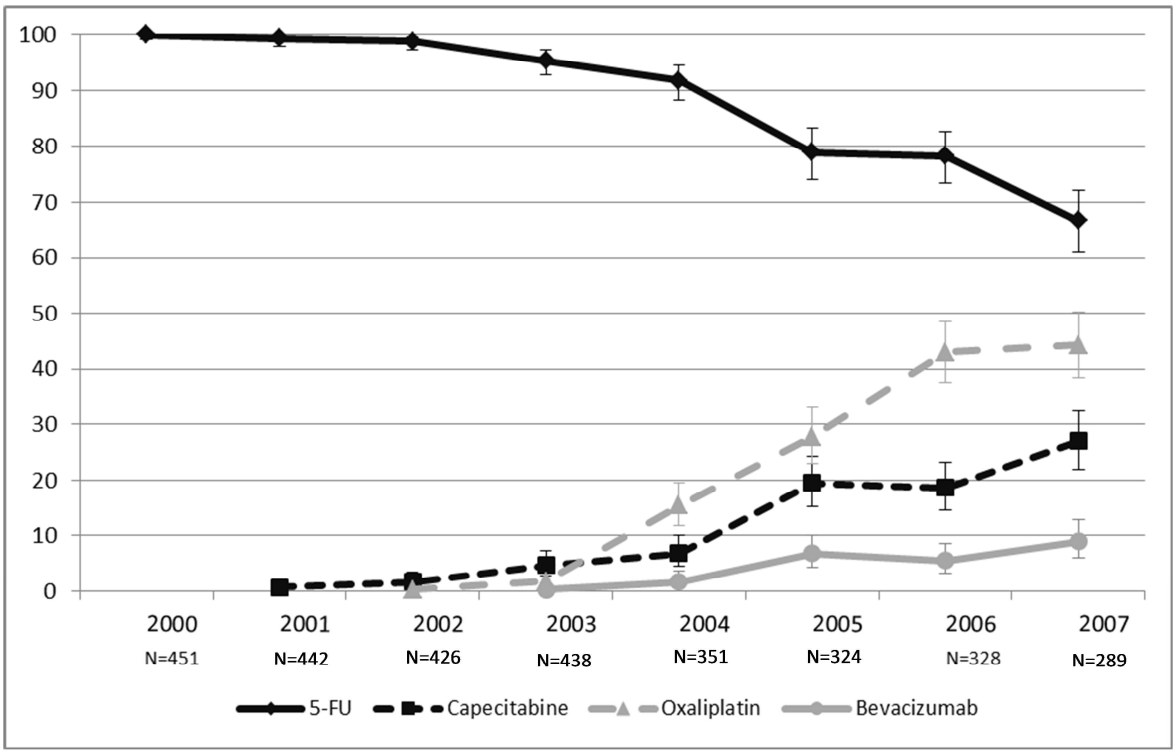
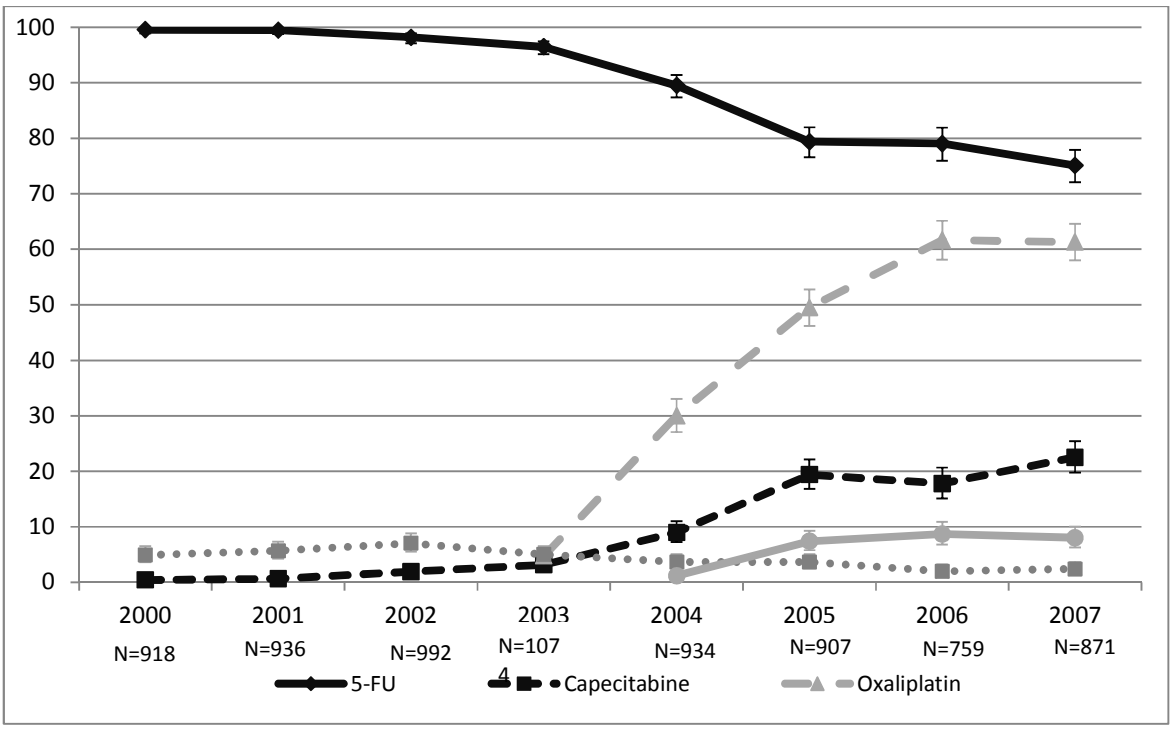


Figure 5.1. Prevalence of the receipt of any chemotherapy by cancer site, stage, and year of diagnosis, 2000-2007.

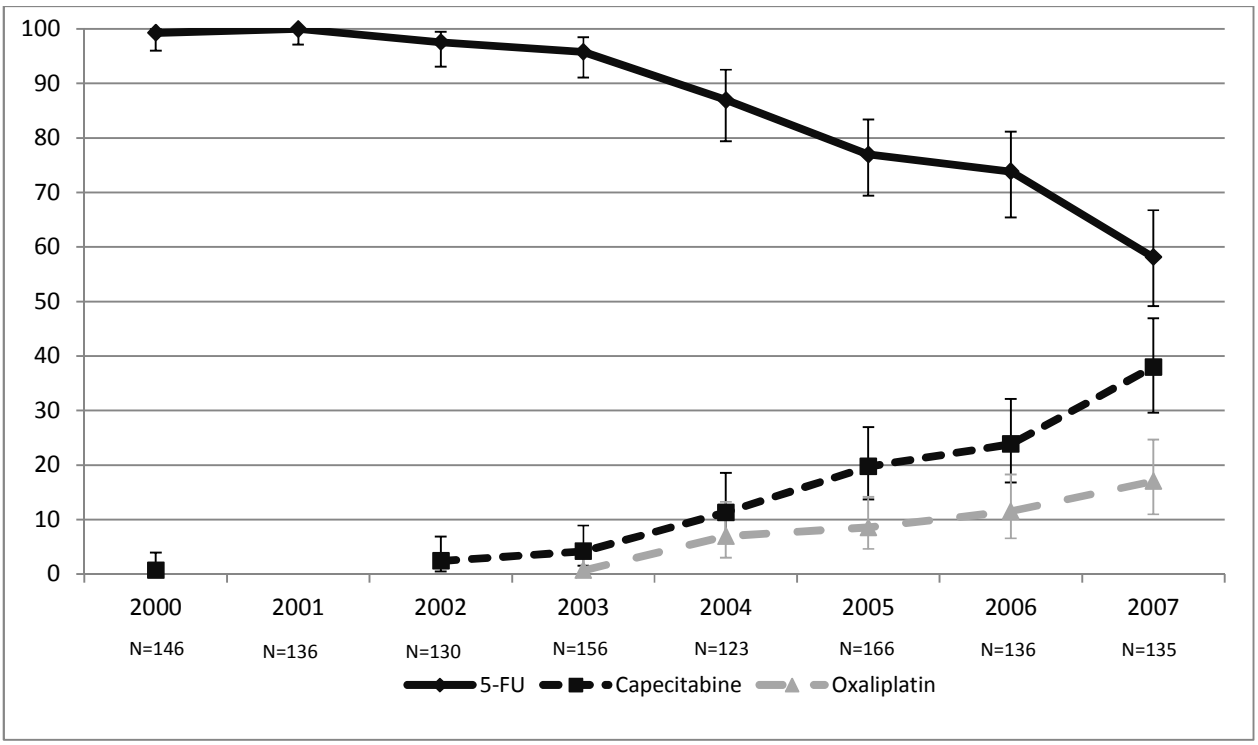
a) Stage II Colon Cancer



b) Stage III Colon Cancer



c) Stage II Rectal Cancer



d) Stage III Rectal Cancer

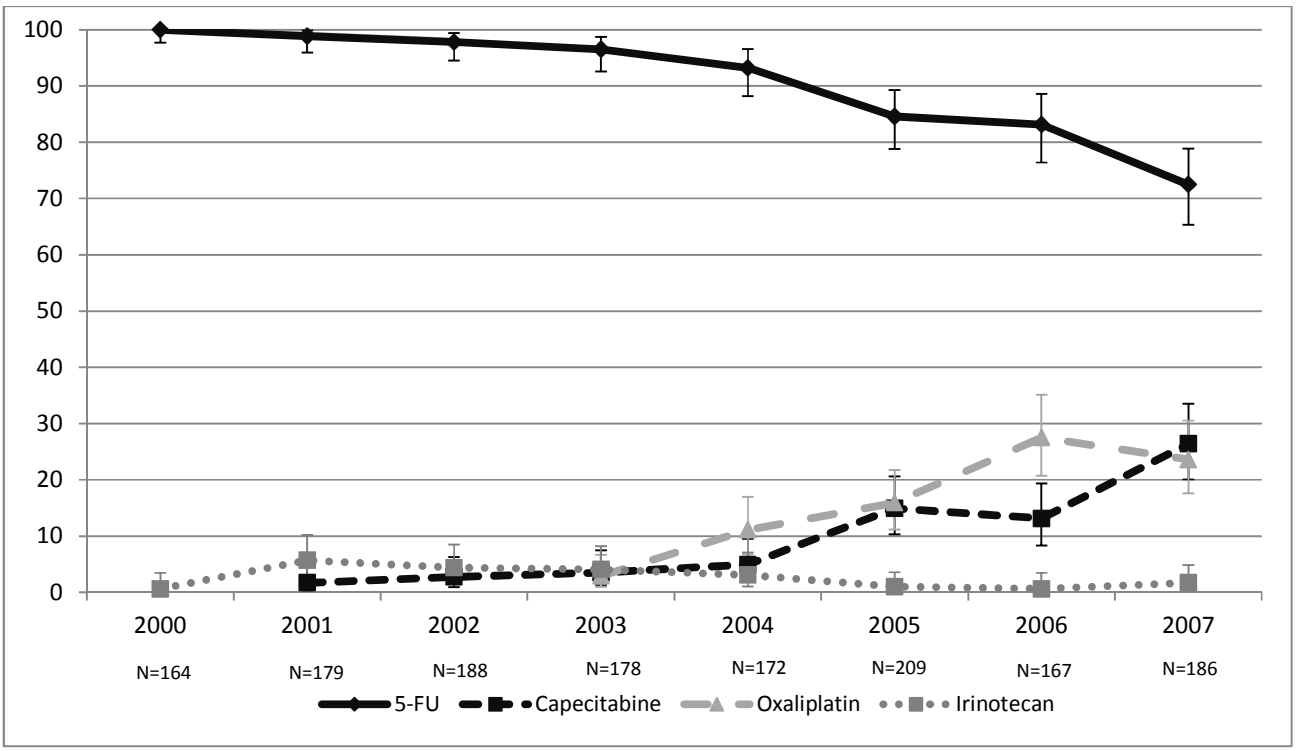


Figure 2a-d. Prevalence of treatment with specific chemotherapeutic agents by cancer site and stage, 2000-2007. Panels a, b, c, and d refer to stage II colon, stage III colon, stage II rectal, and stage III rectal cancers, respectively. Individuals could be counted multiple times if they received more than one agent within the two-months after the first chemotherapy claim (e.g., a patient receiving oxaliplatin and 5-FU).The total number of individuals included in the analysis is reported below the year of diagnosis. We included specific agents that had a prevalence of ≥5% in at least one year. Error bars represent exact binomial 95% confidence intervals.

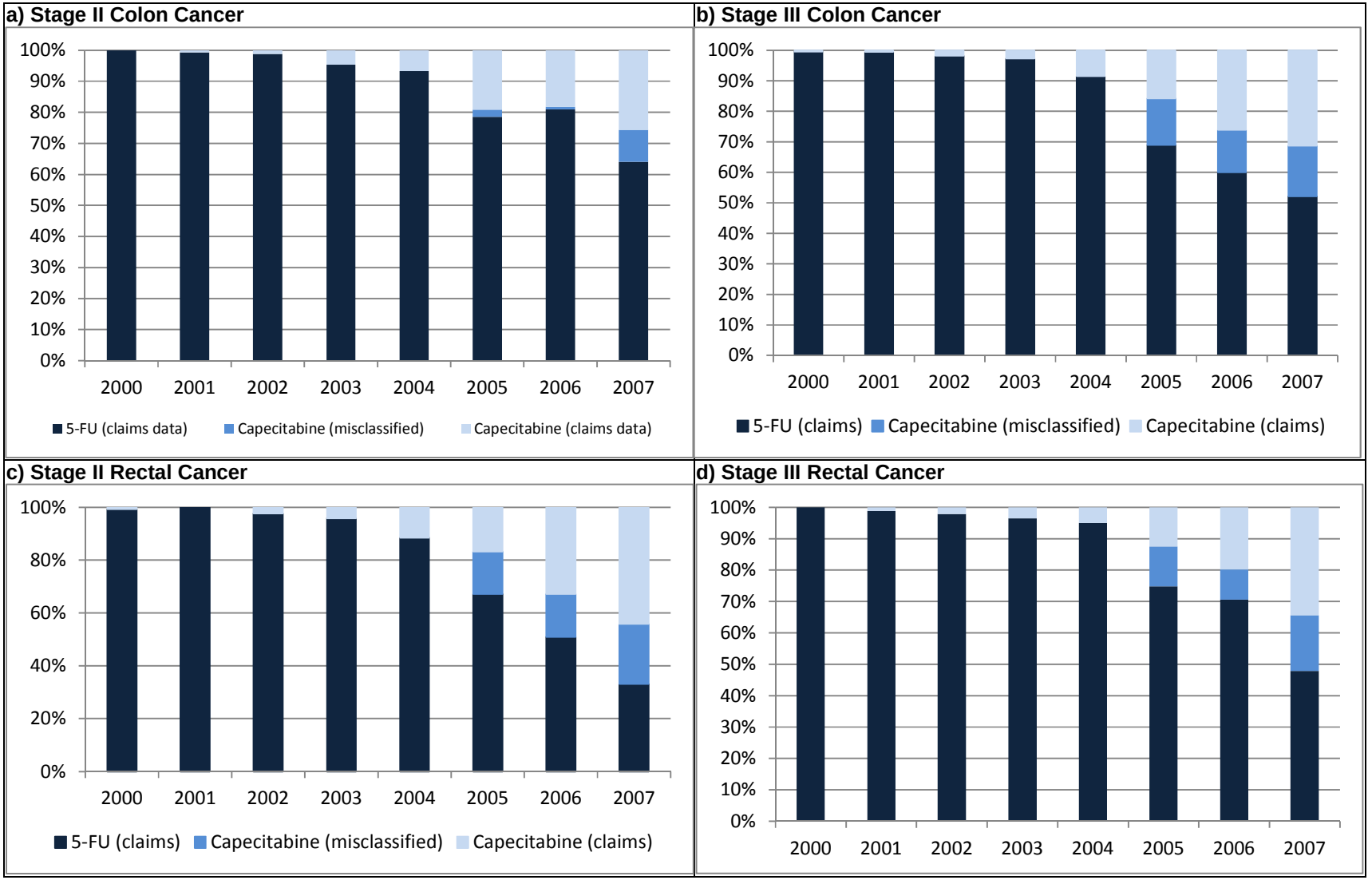


Figure 3a-d. Changes in the proportion of stage II and III colorectal cancer patients using capecitabine among all fluoropyrimidine users from 2000-2007 (n=12,540). The proportions in black represent 5-FU use and the proportions in light grey represent capecitabine use, as

measured directly from Medicare claims. The proportions in medium grey estimate capecitabine use that was missed based on a validation study by Lund et al and the calculation, $N_{cap\_corr} = (N_{cap} - (1 - Se_{cap}) * (N_{yr\_tot} - N_{5fu\_tot}) / (Se_{cap} + Sp_{cap} - 1)$, where N_{cap_corr} is the number of capecitabine users, corrected for the misclassification in Medicare claims, N_{cap} is the number of capecitabine users identified by Medicare claims, N_{yr_tot} is the total number of individuals in site/stage patient group, N_{5fu_tot} is the total number of 5-FU users in site/stage patient group, and Se_{cap} and Sp_{cap} are the sensitivity and specificity of the administrative definitions used to identify capecitabine in Medicare claims. Individuals were excluded if they received both 5-FU and capecitabine in the two months following their first chemotherapy claim (n=83).

CHAPTER 6

DISCUSSION

A. SUMMARY OF FINDINGS

This dissertation examined patterns of chemotherapeutic treatment among elderly stage II and III CRC patients through the linkage of data from administrative sources, population-based registries, and publicly available records. The research had two main objectives: 1) to assess the utility of Medicare claims to capture the receipt of any chemotherapy and specific agents delivered to patients diagnosed at age ≥65 with stage II or III colorectal cancer (CRC), in situ or early stage breast, non-small cell lung cancer (NSCLC), or ovarian cancer using various post-diagnosis claims windows (*Specific Aim 1)* and 2) to estimate the prevalence of specific chemotherapeutic agent use from 2000-2007 (*Specific Aim 2a*) and identify independent patient, physician, and hospital characteristics associated with the receipt of oxaliplatin (*Specific Aim 2b*) among elderly stage II and III CRC patients who receive chemotherapy.

To address the first objective, Medicare claims were compared to data from the POC studies (the gold standard) in order to estimate measures of agreement and validity for the receipt of chemotherapy and specific agents. Results showed that the receipt of chemotherapy and specific intravenous agents can be identified using Medicare claims, showing improvement from prior reports. Yet, variation in the validity of specific agents exists. Future studies should assess newly-approved

agents, regimens, and the impact of coverage decisions for these agents under the Medicare Part D program.

To address the second objective, the description of trends in the utilization of specific chemotherapeutic agents for the treatment of stage II and III CRC from 2000-2007 and identification of patient, physician, and hospital characteristics associated with the receipt of oxaliplatin from 2004-2007. There were substantial shifts in the utilization of specific chemotherapeutic agents used to treat stage II and III CRC patients diagnosed from 2000–2007. For all cancer site and stage combinations, the utilization of capecitabine and oxaliplatin increased substantially from 2004-2007, while 5-FU decreased. Use of bevacizumab in stage II and III colon cancer significantly increased, while irinotecan use remained relatively constant. Measured patient-level characteristics appeared to drive most of the explainable variation in receipt of oxaliplatin among individuals diagnosed with stage II or III CRC between 2004 and 2007; however a large portion of the variation remained unexplained. In particular, patients who were younger, married, living in a metropolitan area or low poverty level census tract, and diagnosed in later study years were more likely to receive oxaliplatin. Those patients diagnosed with cancer of the colon, stage III disease, and having no were also more likely to receive oxaliplatin. These findings 1) add support to the current literature confirming the accuracy of Medicare claims in identifying more recently approved chemotherapeutic agents, 2) contribute to the small but growing literature regarding the high levels of on- and off-label use of chemotherapeutic agents among stage II and III CRC patients, and 3) suggest that patient-level factors appear to drive the variation in

oxaliplatin use, underscoring the importance of weighing the potential benefits and harms when considering oxaliplatin treatment, particularly in the off-label setting.

The results from the first research aim had an important implication for the design and conduct of the second research aim; if any of the specific agents were measured with poor accuracy (either low Se or Sp), the measurement of specific agent utilization would be biased. The results of Specific Aim 1 confirmed that capecitabine required additional attention in Specific Aim 2 due to under-ascertainment of true use.

B. PUBLIC HEALTH IMPLICATIONS

The results of this dissertation research have several implications for public health and clinical practice. First, the finding that Medicare claims can accurately identify the receipt of any chemotherapy and specific intravenous agents will provide support to analyses seeking to examine patterns and effectiveness of chemotherapy treatment in elderly cancer patients. Because the elderly are often underrepresented in RCTs, evaluation of these agents in the diverse community setting is important to detect potential safety issues and over- or under-use of effective treatments.

Additionally, the utilization of many chemotherapeutic agents, including oxaliplatin, capecitabine, and bevacizumab, are increasing over time with a large proportion of the treated population receiving these agents off-label. These results will highlight the magnitude of off-label prescribing among stage II and III CRC patients and potentially catalyze further research efforts to examine the benefits and harms of treatment for non-approved indications.

Finally, patient-level factors were found to drive the majority of explainable variation in the receipt of oxaliplatin for elderly stage II and III CRC receiving chemotherapy. In addition, two physician factors were more weakly associated with oxaliplatin receipt. These factors, taken together, could serve as potential targets for interventions seeking to encourage evidence-based approaches and equitable dissemination of oxaliplatin treatment.

Chemotherapy treatment with combined oxaliplatin and fluoropyrimidine treatment has been shown to decrease disease recurrence and overall survival in stage III colon cancer patients. The results of this dissertation suggest that Medicare claims data can be used to accurately identify oxaliplatin and other specific chemotherapeutic agents for research studies evaluating patterns of care, effectiveness and safety among subgroups commonly excluded from RCTs. Early analysis in the Medicare data show that a substantial proportion of stage II colon and stage II and III rectal cancer patients receiving chemotherapy are treated with oxaliplatin. Tracking outcomes for these patients should help clarify the real world benefits and harms associated with oxaliplatin treatment.

C. STRENGTHS

Use of the linked SEER-Medicare and POC data (Specific Aim 1)

Through cooperation with the NCI and SEER registries, we linked verified treatment data obtained through physician confirmation or unified medical record review to Medicare claims for a large number of individuals aged ≥65 years and diagnosed with one of four different cancers. The detailed POC data collection

protocol allowed us to assess the validity of Medicare claims to identify specific agents that have not previously been validated. We examined and reported variation in measures of validity across different post-diagnosis periods, whereas prior studies primarily used one or two broad post-diagnosis time windows.[49,51,53]

Population-based examination of on- and off-label patterns of care in the elderly (Specific Aim 2)

Only one prior study has assessed on- and off-label use of specific chemotherapeutic treatments for colon cancer using an outpatient ordering system, which may not be entirely representative of the elderly US population. Other studies relying upon population-based resources (such as SEER-Medicare) have not examined the utilization and predictors of oxaliplatin receipt according to on- and off-label indication. The data for this dissertation were derived from a linkage between population-based cancer registries and administrative data from Medicare, providing a real world, population-based context for studying patterns of chemotherapy use among the elderly in routine clinical practice. This is one of the first studies to examine the extent of on- and off-label use of a number of specific chemotherapeutic agents, specifically among stage II and III rectal cancer patients.

Multi-level analysis of factors influencing oxaliplatin receipt (Specific Aim 2)

Lastly, through further linkages to the AMA Masterfile and SEER-Medicare hospital file, we were able to construct a rich multilevel data source to examine the influence of patient, physician, and hospital characteristics on the receipt of oxaliplatin among stage II and III CRC patients. Prior studies have primarily focused on the influence of patient factors and the receipt of oxaliplatin; however, the

interplay of multiple stakeholders in the treatment delivery process should be examined. We utilized a statistical approach developed by Miglioretti and Heagerty[95] that accounted for the non-nested clustering of patient observations at the physician and hospital levels.

D. LIMITATIONS

Misclassified gold standard treatment in the POC studies

The first aim of this dissertation relied upon gold standard treatment information obtained from the POC studies. However, it is possible that this information was measured with error (e.g., a physician incorrectly reported a specific agent received, treatments listed were for recurrence and not for initial chemotherapy treatment, etc.). Additionally, it is unlikely that Medicare would provide reimbursement for a treatment that was not actually administered (i.e., false-positive treatment reported by Medicare claims). Therefore, the validity of specific agent reporting in Medicare claims (and the receipt of chemotherapy overall) may be underestimated in our first aim. However, we conducted a sensitivity analysis using oxaliplatin as an example and found that despite the potential for POC treatment misclassification, the Se, Sp, and PPV only increased slightly.

Poor or unknown Se and Sp of specific agents in Medicare claims

The second aim of this dissertation examined the utilization of specific chemotherapeutic agents among stage II and III CRC patients over time. In our analysis, we included capecitabine, which from our first aim was shown to have consistently low Se estimates using the Medicare claims for all post-diagnosis

periods. In addition, we examined the use of two specific agents, irinotecan and bevacizumab, which were not included in the first validation aim due to the low number of individuals receiving these agents in the POC data. Therefore, it is uncertain how accurate the reporting of these agents are in the Medicare claims data. However, irinotecan and bevacizumab are both expensive chemotherapy treatments, ranging in cost for an 8-week course of close to $9,000 and $21,000, respectively.[125] Because of this high cost, physicians would be likely to submit claims for this agent and Medicare would be careful in appropriately reimbursing for this treatment. Therefore, we believe that the Se and Sp of Medicare claims to identify these treatments would be relatively high.

Trade-off between increased validity of treatment reporting and selection bias

In aims 2 and 3 of this dissertation, we were faced with handling a trade-off between increasing the validity of Medicare claims to identify chemotherapy treatment and inducing a selection bias based on requiring individuals to have continuous Medicare enrollment for the 8-months following diagnosis. From specific aim 1, we found that using an 8-month claims window post-diagnosis generally maximized the Se and Sp for identifying specific chemotherapeutic agents in Medicare claims. However, by using this window, we required all individuals diagnosed with stage II and III to survive at least 8-months after their diagnosis. Given that one-year overall survival for elderly stage II and III CRC is relatively high, the extent of selection may not have a large impact on this analysis. We believe that the associated increase in validity outweighs the decrease in generalizability of the findings to individuals surviving less than 8 months after diagnosis.

Generalizability of results from SEER-Medicare

All analyses were restricted by multiple criteria in order to ensure full healthcare utilization and treatment capture. Specifically, we required that all elderly individuals had at least 12 months pre- and 8-months post-diagnosis continuous enrollment in Medicare Parts A and B (and no HMO enrollment). Elderly individuals with HMO Medicare coverage may behave differently than those with Medicare fee-for-service coverage only due to plan incentives and competition. For Specific Aim 2, we further restricted entry into the cohort based on linkage requirements for the two additional data sources. These criteria included having a claim for CRC surgery within 6-months from diagnosis at a hospital matched to the SEER-Medicare Hospital file, and a claim for a specific chemotherapeutic agent within 8-months of diagnosis that matched a UPIN from the AMA Physician Masterfile. Taken together, these exclusions may reduce the generalizability of our findings to the US elderly population.

Influence of unmeasured factors in explaining oxaliplatin receipt

Our models examining the influence of patient, physician, and hospital characteristics on the receipt of oxaliplatin explained close to 78% of the overall variation. However, unmeasured factors such as patient preferences for or against treatment, comorbidities not captured by the Charlson Comorbidity Index, or other physician preferences and hospital characteristics lacking in our data would likely increase explanatory power.

E. FUTURE RESEARCH

Future research could build upon our findings and address some of the limitations mentioned above. First, further validation of capecitabine use should be undertaken in combination with the Medicare Part D data. It is likely that physician coding behavior for capecitabine will improve over time, as CMS continues to provide guidance on appropriate billing to providers and pharmacies. A longitudinal examination of the validity of capecitabine in Medicare claims (including Part D data) is indicated. Second, patterns of chemotherapy treatment among stage II and III CRC patients in private health insurance databases may shed light on the differences in patterns due to variation in insurance benefits and coverage. Third, the results from the multilevel analysis of factors associated with the receipt of oxaliplatin could be augmented or replicated in datasets with access to additional patient-level preference data. The Cancer Care Outcomes Research and Surveillance Consortium (CanCORs) collects information on patient reported outcomes and patient preferences and behaviors and may be an excellent resource for this analysis.

F. CONCLUSIONS

Validated Medicare definitions identified a substantial increase in oxaliplatin utilization from 2004-2007 for both on- and off-label indications. Patient characteristics were most influential in explaining the variation in oxaliplatin receipt among stage II/III CRC patients; however, future analysis should attempt to capture patient preferences. Off-label use of chemotherapeutic agents in stage II/III CRC was relatively common. In light of the RCT evidence, physicians should carefully

weigh the unknown/minimal benefits of treatment against potentially serious side effects when deciding whether to treat a patient off-label.

APPENDIX A

Table 1A. Administrative codes used to identify receipt of any chemotherapy from Medicare claims

Medicare claims field type	Codes of interest
ICD-9 diagnosis codes	V58.1, V66.2, V67.2
ICD-9 procedure codes	99.25
HCPCS	964xx, 965xx, J9000-J9999 (include J8520 and J8521 for CRC), G0355-G0362, Q0083-Q0085 (for 2005 only)
Revenue center codes	0331, 0332, and 0335
Specific agent codes	All HCPCS and NDCs listed for specific agents below

Table 1B: Administrative codes used to identify receipt of any chemotherapy from Medicare claims

Chemotherapeutic agent	Cancer sites[a]	HCPCS codes (2000, 2002, 2005)
5-FU	CR, Breast, Ovary	J9190
Capecitabine[b]	CR, Breast	J8520, J8521
Irinotecan	CR, NSCL	J9206
Oxaliplatin	CR	C9205, J9263
Bevacizumab	CR, Breast, NSCL	C9214, C9257, J9035, Q2024, S0116
Cetuximab	CR	C9215, J9055
Carboplatin	Breast, Ovary, NSCL	J9045
Cisplatin	Breast, Ovary, NSCL	C9418, J9060, J9062
Cyclophosphamide[c]	Breast, Ovary, NSCL	C9420, C9421, C9421, J8530, J9070 - J9097
Doxorubicin	Breast, Ovary, NSCL	C9415, J9000, J9001, J9010
Epirubicin	Breast	C1167, J9178, J9180
Trastuzumab	Breast	J9355
Methotrexate	Breast, NSCL	J8610, J9250, J9260
Paclitaxel	Breast, Ovary, NSCL	C9431, C9127, J9264, J9265, S1016
Docetaxel	Breast, NSCL	J9170, J9171
Etoposide	Ovary, NSCL	C9414, C9425, J8560, J9181, J9182
Ifosfamide	Ovary	C9427, J9208
Gemcitabine	Breast, NSCL	J9201
Alimta/Pemetrexed	NSCL	C9213, J9305
Iressa/Gefitnib	NSCL	J8565
Mitomycin C	NSCL	C9432, J9280, J9290, J9291
Vinblastine	NSCL	J9360
Vincristine	NSCL	J9370, J9375, J9380
Vinorelbine	NSCL	C9440, J9390

a CR= Colorectal, NSCL = Non-small cell lung
b To identify oral capecitabine in the DME files, we used the following National Drug Codes (NDCs): 00004110020, 00004110150, 00004110116, 00004110051, 00004110013, 00004110022, 00004110113, and 00004110151.
c To identify oral cyclophosphamide in the DME files, we used the following NDCs: 00015-0503-01, 00015-0503-02, 00015-0504-01, 00054-4129-25, 00054-4130-25, 00054-8089-25, 00054-8130-25.

APPENDIX B

Table 1. Sample size reductions for exclusion criteria, 6-month cohort by cancer site and diagnosis year

Cancer site	Dx year	Reason for exclusion	N excluded	% excluded	N Remaining
Breast	2005	Initial POC cohort	0	-	316
		Lacking verified treatment information	48	15.2	268
		Enrolled in a trial	20	6.3	248
		Lacking A+ B for 6-mo post-dx	21	6.6	227
		HMO coverage during 6-mo post-dx	69	21.8	158
		Subsequent cancer dx in <12 mo	1	0.3	157
		No claims in the 6-mo post-dx	2	0.6	**155**
		% of initial cohort remaining for analysis		**49.1**	
Breast	2000	Initial POC cohort	0	-	376
		Lacking verified treatment information	131	34.8	245
		Enrolled in a trial	6	1.6	239
		Lacking A+ B for 6-mo post-dx	18	4.8	221
		HMO coverage during 6-mo post-dx	60	16.0	161
		Subsequent cancer dx in <12 mo	3	0.8	158
		No claims in the 6-mo post-dx	2	0.5	**156**
		% of initial cohort remaining for analysis		**41.5**	
Colorectal	2000	Initial POC cohort	0	-	476
		Lacking verified treatment information	156	32.8	320
		Enrolled in a trial for 6-mo post-dx	7	1.5	313
		Lacking A+ B	49	10.3	264
		HMO coverage during 6-mo post-dx	89	18.7	175
		Subsequent cancer dx in <12 mo	2	0.4	173
		No claims in the 6-mo post-dx	2	0.4	**171**
		% of initial cohort remaining for analysis		**35.9**	
Colorectal	2005	Initial POC cohort	0	-	767
		Lacking verified treatment information	172	22.4	595
		Enrolled in a trial	36	4.7	559
		Lacking A+ B for 6-mo post-dx	97	12.6	462
		HMO coverage during 6-mo post-dx	118	15.4	344
		Subsequent cancer dx in <12 mo	5	0.7	339
		No claims in the 6-mo post-dx	1	0.1	**338**
		% of initial cohort remaining for analysis		**44.1**	

Non-Small Cell Lung	2005	Initial POC cohort	0	-	627
		Lacking verified treatment information	144	23.0	483
		Enrolled in a trial	28	4.5	455
		Lacking A+ B for 6-mo post-dx	165	26.3	290
		HMO coverage during 6-mo post-dx	77	12.3	213
		Subsequent cancer dx in <12 mo	3	0.5	210
		No claims in the 6-mo post-dx	15	2.4	195
		% of initial cohort remaining for analysis		**31.1**	
Ovary	2002	Initial POC cohort	0	-	446
		Lacking verified treatment information	122	27.4	324
		Enrolled in a trial	17	3.8	307
		Lacking A+ B for 6-mo post-dx	85	19.1	222
		HMO coverage during 6-mo post-dx	41	9.2	181
		Subsequent cancer dx in <12 mo	4	0.9	177
		No claims in the 6-mo post-dx	7	1.6	**170**
		% of initial cohort remaining for analysis		**38.1**	

APPENDIX C

Table 1. Comparison of specific chemotherapeutic agents identified by SEER POC data and Medicare claims during the 8-month post-diagnosis period using a 61 day window after first chemo claim to define receipt of specific agents*

	Source reporting receipt of specific agent								
Specific agents	**POC=Yes, Med=Yes**	**POC=No, Med=No**	**POC=Yes, Med=No**	**POC=No, Med=Yes**	**Kappa (%) (95% CI)**	**Se (%) (95% CI)**	**Sp (%) (95% CI)**	**PPV (%) (95% CI)**	**NPV (%) (95% CI)**
5-Fluorouracil	114	182	10	13	85 (79, 91)	92 (86, 96)	93 (89, 96)	90 (83, 94)	95 (91, 97)
Capecitabine	21	270	23	5	55 (40, 71)	48 (32, 63)	98 (96, 99)	81 (61, 93)	92 (88, 95)
Oxaliplatin	56	244	8	11	82 (74, 90)	88 (77, 94)	96 (92, 98)	84 (73, 92)	97 (94, 99)

POC = Patterns of Care, Med=Medicare, Se = Sensitivity, Sp = Specificity, PPV = Positive predictive value, NPV = Negative predictive value
* Individuals lacking treatment data for the specific agent of interest and those with POC administration dates >244 days from diagnosis were excluded from analysis.

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