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Opioid Prescribing and Opioid-Related Health Outcomes Among Cancer Survivors

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Opioid Prescribing and Opioid-Related Health Outcomes Among Cancer Survivors

by

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Dedication

For my mother, Veronica Gibson, my father, David Gibson, my grandfather, Hector Trevino, my grandmother, Guadalupe Trevino (1948-2019), and my partner, Claire Williamson.

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Opioid Prescribing and Opioid-Related Health Outcomes Among Cancer Survivors

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The US population of older long-term cancer survivors—Americans who are free of cancer 5-years post-cancer diagnosis and not receiving cancer treatment—is growing. The prevalence of pain among cancer survivors after curative treatment is approximately 40% and opioids are frequently prescribed to manage the pain. The purpose of this dissertation is to explore long-term opioid therapy and opioid-related harms in cancer survivors using Surveillance Epidemiology and End Results – Medicare linked datasets. First, we explored the temporal and geographical variation in long-term opioid therapy among cancer survivors in the United States. We found that long-term opioid therapy rates were highest in the south and lowest in the northeast and that long-term opioid therapy rates peaked in 2012 but declined until 2016. Second, we assessed if patient level pain conditions and provider specialties seen at outpatient visits by cancer were associated with long-term opioid therapy. We found that cancer survivors who had been diagnosed with chronic pain or noncancer pain conditions and who were treated by noncancer specialists were more likely to receive long-term opioid therapy. Third, we assessed if cancer survivors were more likely than noncancer controls—matched on age, gender, race, pain conditions, previous opioid use—to experience an opioid-related emergency department

visit or hospitalization. We found that the incidence of opioid-related adverse events were five times higher among cancer survivors who used opioids previously than opioid naïve cancer survivors. We found cancer survivors were as likely as persons without cancer to experience an opioid-related emergency department visit or hospitalization. In conclusion, we found high prevalence rates of long-term opioid therapy that differed by time and US geographical region and the risk of an opioid-related emergency department visit and hospitalization is comparable between cancer survivors and persons without a history of cancer. Our findings support the idea that policies and guidelines should continue to promote and incentivize the use of nonpharmacological and nonopioid interventions for managing pain among older adults.

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BACKGROUND

Opioids, Opioid Receptors, and Mechanism of Analgesia

Prescription opioids are predominately synthesized from opium alkaloids isolated from the Opium Poppy, *Papaver somniferum*.[1,2] There are three classes of opioids based on how the compound was synthesized – the natural opiates, synthetic opioids, and the semi-synthetic. Morphine, codeine, and thebaine are the three natural opiate alkaloids isolated from the opium of *P. somniferum*. Synthetic opioids are chemically manufactured compounds without the use of the natural opiates and have similar pharmacological effects as morphine.[1] Synthetic opioids include fentanyl, fentanyl derivatives (e.g. carfentanil) and non-fentanyl synthetic opioids which can be manufactured in pharmacological laboratories or synthesized in unregulated settings and distributed for sale alone or mixed with cocaine, amphetamines, or counterfeit medications.[1,22,214,215] Semi-synthetic opioids (e.g. hydrocodone, oxycodone, buprenorphine) are produced by chemically altering the opiate alkaloids – most commonly morphine's hydroxyl (-OH) side groups.[2] The semi-synthetic opioids are the most frequently prescribed drugs in the United States.[3] For example, of the top 200 prescribed drugs in the United States, Hydrocodone-acetaminophen was the 9th most prescribed medication.[3]

Prescription opioids are commonly absorbed by the gastrointestinal tract but some opioids can also be absorbed through the mucosal lining of the mouth or nose, into capillaries under the tongue, or through the skin.[2] Most opioid agonists and antagonists are metabolized in the liver by various cytochrome P450 enzymes (codeine, hydrocodone, oxycodone, methadone) or conjugation (morphine, oxymorphone, hydromorphone) producing active or inactive metabolites.[4] Prescription opioids and their associated metabolites are predominately eliminated by the kidney.[2] In older adults or persons with

renal or hepatic disease, reduced liver and/or renal functioning can lead to the accumulation of opioids and biologically active metabolites and increase the risk for an opioid adverse event, such as respiratory failure, sedation, seizures, hallucinations, and hypotension.[5-7]

There are three main opioid receptors in humans, the mu, delta, and kappa opioid receptors and are activated by endogenous opioids – endorphins, enkephalins, and dynorphins.[1,2,8] Endogenous opioids are biological compounds and are important for learning, behavior, and reward and the regulation of pain, body temperature, and multiple organ systems, including the cardiovascular and respiratory system.[9-11] All three opioid receptor types are distributed in the peripheral and central nervous system. Within the central nervous system, however, each receptor appears to be distributed in certain locations. The mu opioid receptor is distributed in the cerebral cortex, thalamus, in the dorsal horn of the spinal cord, and periaqueductal gray (PAG), while the kappa receptor is distributed to the hypothalamus and PAG, and the delta receptor is distributed throughout the basal ganglia.[216] As a result of the differential distribution of opioid receptors, activation of these receptors can produce different physiologic effects. For example, activation of kappa receptors can elicit feelings of dysphoria and sedation, while activation of delta receptors can reduce feelings of anxiety and is associated with convulsions and seizures.[8,216] All three opioid receptors are associated with analgesia.[8] The mu opioid receptors is responsible for most of the physiological effects associated with the use of prescription opioids, including euphoria and respiratory depression.[1,8] In general, activation of mu opioid receptors causes neurons to become hyperpolarized and inhibited by closing calcium channels and opening of potassium channels on pre- and post-synaptic neurons.[2,8]

Pain is defined as “An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage,” by the International Association for the Study of Pain.[12] Pain is transmitted from the periphery (e.g. your finger) to the central nervous through a series of neurons that synapse in the

dorsal root of the spinal cord. Pain fibers travel in the spinal cord as the *spinothalamic tract* which carry pain information to the thalamus and cerebral cortex.[13] Prescription opioids directly and indirectly inhibit the passing of pain signals from the peripheral nervous system to the central nervous system. The direct pathway involves inhibiting dorsal root neurons in the spinal cord by stimulation of mu opioid receptors, preventing the propagation of the pain signal from the peripheral nervous system to the central nervous system.[2] Indirectly, opioid agonists activate secondary neurons by inhibiting neurons in the PAG. The activated secondary neurons stimulate serotonergic neurons in the Dorsal Raphe nucleus and noradrenergic neurons in the Locus Ceruleus.[2,14] Neurons from these two brain areas project and inhibit spinal cord neurons by releasing serotonin and norepinephrine. It is important to understand the mechanism of analgesia for prescription opioids because opioids do not address the reason for pain but, instead, opioids stop the propagation of pain signals from the peripheral to the nervous system.

Tolerance to prescription opioids can result when mu opioid receptors are chronically stimulated.[2] Tolerance is a physiological state in which the body does not respond as it previously did to the same dose of a drug.[15] Therefore, higher doses will be required to achieve the same physiological effects. Opioid dependence and opioid use disorder – formerly known as opioid addiction – are different from tolerance. Opioid dependence is a physiological state in which the body has adapted to the use of prescription opioids.[15] Approximately 5% of individuals who initiate opioid therapy will develop dependence of prescription opioids.[16] If prescription opioids are withdrawn or the dose is reduced a person can experience abstinence symptoms including muscle aches, sweating, and diarrhea.[17] Opioid use disorder, or addiction to opioids, is a complex medical condition characterized by neuroanatomical and behavioral changes that lead to cravings, continued use of opioids despite a desire to stop, or impairment of an individual's personal, occupational, or social life.[17-19]

A Brief History of the Opioid Epidemic

On October 26, 2017, the opioid epidemic was declared a public health emergency and this declaration has been renewed every 90 days thereafter – as recently as October 8, 2020.[20,21] The opioid epidemic is an ongoing and evolving public health crisis characterized by three waves of increasing mortality rates associated with 1) natural and semisynthetic opioids, mostly prescription opioids (1999-2010), 2) heroin (2010-2016) and 3) fentanyl (2013-present day).[22,23] From 1999-2016, approximately 350,000 persons died from opioid-related causes.[24] The opioid epidemic has also been associated with billions of dollars in economic loss,[25,26] declines in life expectancy,[24,27] and increases in hospitalizations for drug overdoses.[28,29] While the macro-level costs of the opioid epidemic have been immense, the toll of the epidemic on individuals and their family are incalculable.

The opioid epidemic's origins are complex and can be briefly be described as changes in pain management attitudes,[30-35,43] aggressive pharmaceutical marketing,[36,37] and failure of regulatory oversight.[38] Historically, prescription opioids were used sparingly to manage all forms of pain, predominately due to the fear of causing addiction.[39] In the late 1990s, spurred by research demonstrating pain was undertreated,[40,41] the American Pain Society labelled pain as the 5th vital sign and recommended patient's intensity of pain should be elicited and recorded on a vital signs sheet.[33] This led to organizational recommendations that providers should screen all patients for pain and ask about pain severity. In 1999, The Veterans Health Administration required providers to measure and document all patient's pain intensity.[42] In 2000, the Joint Commission released pain management standards for accredited hospitals that included all patients be screened and treated for pain.[43]

Research was influential in changing the pain management behaviors of prescribers. Porter and Jick (1980) published a five-sentence letter in *New England Journal*

of Medicine (NEJM) reported 0.03% (4/11,882) of hospitalized patients who received an opioid who became addicted.[44] Most articles that referenced the Porter and Jick *NEJM* letter concluded prescription opioids were not addictive despite the lack of methodological details provided by the letter.[45] A second longitudinal observational study attempted to demonstrate that prescription opioids were safe in chronic pain patients. Portenoy and Foley (1986) followed 38 persons with noncancer pain on chronic opioid therapy – most receiving less than 50 MME/day – and found only 2 had exhibited aberrant behavior related to prescription opioids and both had known substance use disorders.[46] One person was found to be hoarding methadone sparking concerns of diversion and a second person increased their opioid consumption without medical approval.

In 1995, a controlled release formulation of oxycodone developed by Purdue Pharma received Federal Drug Administration approval for moderate to severe pain in December 1995.[36,37] Purdue Pharma aggressively marketed Oxycodone and minimized the risk of addiction by selectively reporting the findings by Porter and Jick. Later, Dr. Hershel Jick in an interview reported they were "mortified" with how opioid manufacturers used the letter to the *NEJM* editor to market prescription opioids as a non-addictive treatment for pain.[47] As the culture around pain management changed, and pharmaceutical companies increased marketing, the use of prescription opioids for treatment of pain began to be more common. Sales of prescription opioids and mortality rates due to prescription opioids increased.[48] In 2018 the mortality rate due to natural and semi-synthetic opioids was about 4 times higher than in 1999.[50]

Unfortunately, mortality rates due to heroin and synthetic opioids other than methadone have increased drastically since 2010 but recently, there are encouraging signs that mortality due to prescription opioids and heroin are declining.[56] Provisional data provided by the Centers for Disease Control and Prevention, however, suggests that the deaths due to fentanyl and other synthetic opioids fueled an increase in drug overdose mortality rates from June 2019 to May 2020, with the largest increase in drug overdose

deaths occurring from March 2020 to May 2020. This acceleration of opioid-related mortality corresponds to the period of nearly nationwide interventions to stop the spread of COVID-19.[57] The origins of these second and third waves of the opioid epidemic are not as well characterized as the first wave but increases in the use of heroin have been attributed to individuals shifting from prescription opioids to heroin,[51,52] and the availability and cost of heroin.[53-55]

In 2018, the rate of opioid-related mortality was 14.6 per 100,000 persons in the United States.[217] The opioid epidemic, however, was not limited to the United States but has also spread to its northern neighbor, Canada. Historically, Canada has had a high rate of opioid prescribing. From 1991 to 2007, opioid prescribing increased 30% in Canada from 458 to 591 prescriptions per 1000 individuals, largely driven by an increase in the use of long-acting oxycodone.[218] By 2010 Canada had the second highest consumption of prescription opioids.[91,219] Like the United States, the opioid-related mortality rate nearly doubled in Canada from 13.7 per million persons in 1991 to 27.1 per million persons in 2004.[218] In 2018, the opioid-related mortality rate in Canada was 12.0 per 100,000 persons (120 per million persons) which was largely driven by increases in deaths due to fentanyl.[220] However, there is evidence that most fentanyl-related deaths in Canada may be due to prescribed fentanyl; however, Canada does not collect data on the source of the fentanyl at the time of death.[221] One reason researchers in Canada are concerned about the influence of prescribed fentanyl is behind the high mortality rate due to opioids is because fentanyl opioid prescribing increased substantially following oxycodone's removal from Ontario's prescription drug formulary after oxycodone was linked to the majority of opioid-related deaths in the mid 2000s.[222]

Similarly to the United States and Canada, Australia appears to have been affected by the opioid epidemic. From 1990 to 2014, opioid dispensing in Australia increased four-fold, with oxycodone, buprenorphine, tramadol, fentanyl, and hydromorphone responsible for the rise in utilization after 2000.[223,224] The rise in opioid prescribing in Australia also

corresponds to an 1.6-fold increase in prescription opioid-related mortality from 2001 to 2012, (21.9 to 36.2 per million), mostly driven by accidental overdoses, while heroin-related mortality rate remained constant.[225]

Opioid prescribing and opioid-related morbidity and mortality also increased in Western Europe. Opioid prescribing in Western Europe was 2.5 times lower, on average, than opioid prescribing in Canada and 4 times lower than the United States, suggesting that the overall exposure to prescription opioids is lower.[226] One concerning sign is that oxycodone prescribing increased substantially in Norway, Sweden, Denmark, United Kingdom, Netherlands, and France, which has drawn comparisons to the beginning of the opioid epidemic in the United States.[227-230] In the Netherlands[229] and France,[230] opioid-related hospitalizations and mortality-rates have been shown to increase recently. These mortality rates, however, are substantially lower than in the United States and Canada. Deaths due to oxycodone and morphine, instead of heroin, are now the most common cause of opioid-related mortality in Norway.[231] Opioids used for the treatment of opioid use disorder (e.g. methadone and buprenorphine) have been implicated in many deaths in some European countries, but, evidence from Sweden suggests that the majority of persons who died from methadone and buprenorphine did not have a prescription for these medications.[232] Therefore, there is some concern about the diversion of medications for substance use disorder through unregulated settings.[232] In the United Kingdom, deaths due to methadone and tramadol have increased substantially.[233] Despite these increases in opioid-related morbidity and mortality, some have stated that Europe—excluding the United Kingdom—is not experiencing an opioid epidemic.[234] Overall, opioid prescribing is decreasing and the opioid-related mortality rates are approximately 13 times lower than the United States.[234] There is some concern about an opioid epidemic in the United Kingdom, particularly Scotland, where the opioid mortality rate is about 19 per 100,000.[234]

There are some significant differences between Western Europe and North America that may have protected Western Europe from a substantial rise in opioid-related deaths.

There is a lower exposure to prescription opioids in Europe which has resulted in lower rates of opioid-related morbidity and mortality. This may be cultural difference between North American and European healthcare providers as Fischer and colleagues (2013) note that North America has higher rates of prescribing of psychoactive compounds than other countries.[235] Further, there is no direct-to-consumer medical service marketing in Europe which may have kept demand for prescription opioids low.[226,235] Pharmaceutical companies are also restricted in their interactions with physicians and are, in general, prohibited from offering benefits to healthcare providers.[284] Fischer et al. (2013) also note that prescription opioids were more heavily regulated in European countries which limited opioid prescribing through days or amounts supplied, sites of dispensing, preventing pharmacist from correcting a technical error on a prescription, and more restrictive formularies.[235] Overall, Eastern Europe had more regulations than Western Europe, but a tougher regulatory environment may have prevented overuse of prescription opioids.[236] Furthermore, medication assisted treatment for heroin or opioid use disorder is more readily available in European countries than the United States which makes it more likely that individuals who need treatment for substance use disorder receive treatment.[226] Until recently, the opioid epidemic in North America has not affected Mexico. Historically, prescription opioid use was low in Mexico because of strong legislative laws that limited opioid prescribing.[237,238] Recently, however, Mexico has been left vulnerable to the spread of the opioid epidemic due to an aging population with more chronic health conditions. Deregulation and an increase in demand for opioids due to an aging population have increased opioid prescribing significantly, but the effects on opioid-related morbidity and mortality are not currently known.

Prescription Opioid Use and Opioid-Related Harms in Cancer Survivors

LONG-TERM OPIOID THERAPY

Persons who are diagnosed with cancer are living longer due to early detection and advancements in cancer treatment. Cancer mortality rates declined nearly 30% from 1991 to 2017.[58] It is expected that by 2040 there will be 26.1 million cancer survivors and nearly 75% will be 65 years or older.[59] Many cancer survivors will remain cancer-free for decades after initial treatment, yet, many will have chronic pain that jeopardizes their functioning and quality of life.[60-63]

Prescription opioids are frequently used to manage moderate to severe cancer related pain in persons undergoing cancer treatment.[195,196] The use of long-term opioid therapy to manage chronic pain in cancer survivors free of disease, however, is not recommended due to a lack of evidence of long-term efficaciousness and effectiveness in improving pain and function and known safety issues in the general population, including development of dependence and substance use disorder, and overdose.[64-67] One randomized controlled trial compared 12 month pain-related functioning between persons with chronic back pain or hip or knee osteoarthritis pain who randomly received opioids or nonopioids to manage pain.[199] After 1 year, opioid therapy did not result in better pain functioning compared to nonopioid analgesics. The findings of this study indicate that for some chronic pain conditions, opioid therapy should not be initiated because prescription opioids are not more efficacious and were associated with more medication-related symptoms than nonopioid therapy. Current guidelines recommend short trials of opioids in select cancer survivors only when all nonopioid and nonpharmacological pain management interventions have been tried.[64]

Short term trials of prescription opioids, however, are not without risk.[68-73] Use of a prescription opioid among breast cancer survivors was associated with an increased risk of experiencing a hospitalization and an overdose.[73] Long-term opioid therapy also

frequently follows small trials of opioid prescriptions,[68-72] and discontinuation rates for long-term opioid therapy are poor.[74] Common sequelae of long-term opioid therapy include constipation, dependence, overdose, sedation, hypotension, falls and fractures, and hypogonadism.[75-81] Use of prescription opioids for prolonged periods of time also increases the likelihood of opioid-related emergency department visits and hospitalizations.[82] Therefore, long-term opioid therapy is an important surrogate end-point and may even be considered an adverse event, due to a lack of evidence suggesting benefits in improvement of pain and function and because of its correlations with opioid-related adverse events.[83]

It is important to study patterns of opioid use and opioid-related adverse events in long-term cancer survivors because their opioid use, on a population level, and the risk of opioid-related harms has not previously been examined. Clinical guidelines addressing opioid prescribing have recommended opioids be used sparingly among cancer survivors not undergoing treatment and with no evidence of disease, with nonopioid analgesics being first line therapy for the management of chronic pain and improving function.[64-66] However, the initiation of opioid therapy and long-term opioid use have been shown to be common among cancer survivors, regardless of evidence of disease or treatment status.[97] Healthcare providers have reportedly been more likely to prescribe opioids to persons with a history of cancer, including in persons who do not have evidence of disease and are not undergoing treatment.[239] Cancer survivors also have a high prevalence of psychiatric comorbidities, like depression and anxiety, that may predispose this population to receive long-term opioid therapy which may translate into a higher rate of opioid-related harms.[240] Therefore, further examination of opioid prescribing and the consequences of opioid therapy is warranted in cancer survivors to inform guideline development and policy makers about potential opioid related harms that could be prevented.

TEMPORAL AND GEOGRAPHICAL VARIATION IN LONG-TERM OPIOID THERAPY

Opioid prescribing in the general population has been observed to vary by time and geographically.[84] The amount of prescription opioids dispensed peaked in 2010 and has slowly declined over the latter half of the decade following the implementation of state and federal opioid restricting policies.[84] The number of opioid prescriptions dispensed in the United States increased from 72.4 per 100 persons (2006) to 81.3 (2012) and then declined to 46.7 (2019).[85] However, the declines in opioid prescribing over time have not been constant across age groups, such that, the percentage of individuals with an opioid prescription from 2008 to 2018 declined the least among older adults.[86] Geography in the United States has shown to be an influential contextual factor for opioid prescribing. Research studies have been consistent with the finding that opioid prescribing in the U.S. is highest in southern and western geographical areas.[84,87-93]

Geographical and temporal patterning of long-term or chronic opioid therapy reflect similarities to opioid prescribing. Among Medicare beneficiaries, long-term opioid therapy rates are highest in the South-Eastern United States (Alabama, Georgia, Kentucky), and western states demonstrating that persons in Appalachia and the Southern regions are more likely to receive high-risk patterns of opioid therapy.[94-96] Long-term use of a Schedule II or II controlled substance rates among Medicare beneficiaries increased from 4.62% (2007) to 7.44% (2011).[82] Following the federal rescheduling of hydrocodone from Schedule III to the more restrictive Schedule II by the Drug Enforcement Administration in October 2014, long-term opioid therapy rates among older adults declined by 7% from 2013 to 2015.[95] Further, declines in long-term opioid therapy rates varied across states, such that, rates declined fastest in Alabama and slowest in North Dakota.

The average prevalence rate of long-term opioid therapy by cancer survivors is around 24%.[97] However, the rate of long-term opioid therapy among cancer survivors varies by the cancer diagnosis (colorectal, lung, prostate, breast, other), number of years

after diagnosis, post-surgical chemotherapy and radiation, and previous opioid use. Lee et al. (2017) found that about 10% of persons newly diagnosed with cancer who underwent curative surgery received long-term opioid therapy within the following year.[98] The authors[98] also found that long-term opioid therapy rates, in general, were highest among persons who received chemotherapy after their surgery, suggesting that treatment patterns may modify long-term patterns of opioid use. Shah et al. (2019) estimated the prevalence of long-term opioid therapy among opioid naïve cancer survivors who survived ≥5 years after a cancer diagnosis.[99] The prevalence rate was found to increase from 1.4% at 5 years after diagnosis to 7.1% at 18 years post-diagnosis and tended to be lowest among prostate cancer survivors and highest among lung cancer survivors.

One research gap in the survivorship literature is that national temporal and geographic trends in long-term opioid use among cancer survivors who lived ≥5 years after a cancer diagnosis have not been established. Shah et al. (2019) found a large increase in long-term opioid therapy in 2011 and a plateau until the study's end date in 2014 among older adults who lived 5 or more years after a cancer diagnosis. This pattern of long-term opioid use was similar between cancer survivors and the general Medicare population. This study, however, was limited to a single state (Texas) and was not able to assess how the trends in long-term opioid therapy among cancer survivors could have been influenced by federal rescheduling of hydrocodone combination products.

PROVIDER CHARACTERISTICS AND LONG-TERM OPIOID THERAPY

Even though the relationship between patient characteristics and receipt of long-term opioid therapy have been extensively studied, provider characteristics are thought to play a central role.[100,101] One narrative review conducted by Hooten et al. (2017) hypothesized that pain management training and attitudes and beliefs were prescriber characteristics that can be influential in treating patients with long-term opioid therapy.[100] Consistent with theoretical work, Barnett, Olenski, and Jena (2017) examined rates of long-

term opioid therapy among Medicare beneficiaries who were treated by emergency department physicians and found that older adults who were treated by providers with a high rate of opioid prescribing were more likely to receive long-term opioid therapy than persons treated by providers with low rates of opioid prescribing.[102]

Primary care providers – internal medicine and family medicine – write most of the opioid prescriptions dispensed in the United States.[103] Advanced practice providers – nurse practitioners and physician assistants – are responsible for approximately 20% of opioid prescriptions in the United States, but they have lower overall prescribing rates than primary care physicians.[103] Specialties with the highest rates of opioid prescribing are those who are more likely to care for patients with chronic pain, such as pain management and physical medicine and rehabilitation (PM&R) providers.[103-104] Even though opioid prescribing has declined for most medical and surgical specialties, opioid prescribing among providers that manage chronic pain and advanced practice providers has increased.[104,105]

Long-term cancer survivors receive multispecialty care, which may be important for receipt of preventive services, diagnosing and management of noncancer comorbidities, and monitoring for cancer recurrence.[106-109] Cancer survivors are frequently cared for by primary care physicians and oncologists, but, the physician specialties cancer survivors visit for treatment have been found to change as they progress through survivorship.[106] Care by multiple providers raises concerns about fragmentation of care and, potentially, overprescribing opioids to individuals placing them at higher risk for an overdose.[197,198] While primary care physicians have been observed to have moderate rates of opioid prescribing, oncologists write only a small percentage of total dispensed opioid prescriptions and, in general, have low opioid prescribing rates.[103,104,110] Moreover, opioid prescribing rates have declined among oncologists in recent years.[111]

Research findings have shown that opioid prescribing varies significantly across specialties and provider characteristics are associated with long-term opioid prescribing.

However, the relationship between provider specialty, type of pain and long-term opioid therapy in long-term cancer survivors has not previously been examined.

Opioid-Related Emergency Department Visits and Hospitalizations

Rates of opioid related ED visits and hospitalizations have been increasing in the United States, despite the implementation of state and federal policy and dissemination of opioid prescribing guidelines.[28,29] Among older adults, the increase in opioid-related hospitalizations and emergency department visits has been 74% and 34%, respectively.[29] Prescription opioids are one of the most common medications that drive adverse drug event related emergency department visits and hospitalizations among older adults.[112,113] The increase in utilization of health services by older adults are driven by the sequalae from therapeutic use of prescription opioids, such as, constipation.[114]

Consistent with trends observed in the general population, opioid-related emergency department visits and hospitalizations among cancer survivors have also been rising throughout the opioid epidemic. Jairam, Yang, Yu, and Park (2020) identified that opioid related emergency department visits among cancer survivors increased twofold from 15.7 to 32.3 per 100,000 cancer survivors from 2006 to 2015 which outpaced the increase for non-opioid related reasons.[115] Chua and colleagues (2019) found that the number of opioid-related hospitalizations increased slowly from 2006 to 2014 and were due mostly to increases in opioid poisoning rather than opioid abuse or heroin.[116] Both of these studies also highlighted that psychiatric comorbid conditions and substance use disorders were associated with adverse events.

Little is known about the comparative risk of an opioid-related ED visit and hospitalization between long-term cancer survivors and persons without cancer. Based on previous studies, cancer survivors have been found to have comparable or higher opioid use than the noncancer population.[117-121] Moreover, cancer survivors may be at a higher risk of being diagnosed with opioid use disorder or experiencing an overdose. Roberts et

al. (2020) matched older adults diagnosed with cancer to persons without cancer, and demonstrated that colorectal cancer survivors may be at a higher risk of opioid use disorder and overdose than noncancer controls within the first year after diagnosis.[122] More studies are needed to address the gap in knowledge on the potential harms of opioid-based pain management approaches in long-term cancer survivors and how these harms compare between persons with and without a history of a cancer diagnosis.

Definition of Cancer Survivorship

There is some variation among patients, researchers, and healthcare providers about the definition of cancer survivor. Cancer survivors are a heterogenous group of individuals with diverse health needs. The most common definition, created by the National Coalition for Cancer Survivorship, defines cancer survivors at the time of diagnosis and it extends to the end of their life.[123] In 1985, Dr. Fitzhugh Mullan wrote a personal reflection about his diagnosis with cancer and discussed how survivorship was a series of phases that began with diagnosis and acute survival and ended with permanent survival and discussed an individual's needs in each season.[124] Dr. Mullan implored that systematic investigations explore not only medical treatments to prevent or treat cancer but to explore interventions to manage the biological, psychological, and social concerns that arise during survivorship.[124]

Some have suggested that the National Coalition for Cancer Survivorship definition of cancer survivorship is too broad and does not acknowledge the heterogeneity in the treatment and healthcare needs of cancer survivors.[125-127] Instead, it may be more beneficial to focus on patient's needs during the phases or seasons of cancer survivorship. Surbone (2016) has argued that it is necessary to categorize survivorship based on the timing after diagnosis.[128] Even though the use of cancer survivor is common in research, it is important to acknowledge some individuals with a clinical history of a cancer diagnosis do not

identify with the term *cancer survivor* because it can provoke anxieties about cancer recurrence or thoughts about death.[129]

In the cancer survivorship literature concerning opioid prescribing, many different definitions have been applied that make it difficult to compare studies or make inferences based on findings. For example, Jones et al. (2020)[97] found that the prevalence of long-term opioid therapy among cancer survivors was 24%. However, this study included a broad population of cancer survivors, such as, individuals undergoing active cancer treatment, individuals who have lived 5 or more years after a cancer diagnosis, individuals diagnosed with lower stage tumors, and individuals diagnosed with more advanced cancer. Furthermore, this study also included cancers outside of the four most diagnosed cancers in the United States– breast, colorectal, lung, and prostate cancers – such as, head and neck, oral, melanoma, esophageal, and gynecological cancers, which may bias the prevalence estimate of long-term opioid therapy upward. Most studies investigating opioid use and related harms among cancer survivors have defined survivorship as beginning from the date of diagnosis.[73,97] Another definition defined cancer survivorship as beginning after cancer treatment.[181]

Two studies have examined opioid use[117] and opioid-related harms[122] by following individuals from the date of cancer diagnosis until long-term survivorship. Salz et al. (2019)[117] matched opioid naive individuals with incident cancer diagnoses to persons without a cancer history based on age, gender, race, Charlson comorbidity score, and geographical region and followed from the date of diagnosis until 6 years after the cancer diagnosis.[117] The authors defined opioid naïve as not having received chronic opioid therapy in the 12 months before follow up. Roberts et al. (2020)[122] matched cancer survivors to noncancer controls on the date of diagnosis based on age, gender, and geographical region and followed both cohorts for 12 months after the cancer diagnosis, but conducted a secondary analysis following cancer survivors and noncancer controls up to 6 years after diagnosis.

Several studies have specifically investigated opioid use in long-term cancer survivors. Shah et al. (2019)[99] examined receipt of long-term opioid therapy in persons who lived 5 or more years after a breast, colorectal, lung, or prostate cancer diagnosis. Sutradhar et al. (2017)[118] examined the rate of receipt of opioid prescriptions among persons who lived 5 or more years after a cancer diagnosis. Barbera et al. (2017)[121] compared opioid use between persons without cancer, newly diagnosed cancer patients, and long-term cancer survivors.

In the three middle chapters of the present dissertation, we use the term cancer survivors to refer to persons who are diagnosed with cancer and lived for ≥5 years after a cancer diagnosis. This is most consistent with the definition of long-term cancer survivors by Surbone (2016).[128] Our study differs from most of the survivorship literature by starting follow up at 5 years after diagnosis, excluded individuals for having received cancer treatment, and followed persons throughout their survivorship until the end of data availability (December 31, 2016). This definition is like the one employed by Shah et al. (2019)[99] and Sutradhar et al. (2017).[118] This study differs from Salz et al. (2019)[117] and Roberts et al. (2020)[122] as these studies begin at the date of diagnosis and followed some individuals up until long-term cancer survivorship. Therefore, our studies fill an important gap in the cancer survivorship literature by following long-term cancer survivors from diverse settings in the United States and examining geographical variation in and provider specialties associated with long-term opioid use, and identifying the rate of opioid-related adverse events that cancer survivors may experience relative to persons without cancer.

SPECIFIC AIMS

To summarize, our literature review identified the three research gaps in the cancer survivorship literature: 1) National temporal and geographical trends in receipt of long-term opioid therapy are unknown; 2) The influence of provider specialty and patient-level pain conditions on receipt of long-term opioid therapy has not been previously explored;

3) It is unknown whether cancer survivors are more likely than persons without a history of cancer are more likely to experience an opioid-related emergency department visits or a hospitalization compared to persons without cancer. Based on the three gaps in the survivorship literature, we developed three specific aims.

Aim 1. Assess the geographical and temporal trends in receipt of long-term opioid therapy by older adults who lived ≥5 years after a cancer diagnosis, have not been diagnosed with a secondary cancer, and are not currently being treated for cancer.

a. Persons diagnosed with cancer from 1991-2011 who lived 5 or more years after a cancer diagnosis will be followed from January 01, 2008 to December 31, 2016 to assess the annual prevalence of long-term opioid therapy. Trends will be stratified by U.S. census region and previous opioid use within the 1 year before follow up (opioid naïve, opioid non-naïve).

Aim 2. Determine the provider specialties from whom cancer survivors, ≥5 years after a cancer diagnosis, receive care from and how these provider specialties are associated with receipt of long-term opioid therapy.

a. This analysis will use the same analytical cohort as in Specific Aim 1.
b. Identify the prevalence of pain conditions in cancer survivors from 2012-2016 and assess the relationship between pain conditions and long-term opioid therapy.
c. Examine the pattern of specialty care for cancer survivors from 2012-2016 by calculating the percentage of cancer survivors who had 1 or more outpatient visit with each specialty group. Assess the relationship between provider specialties seen in a year by cancer survivors and the association with receipt of long-term opioid therapy.

Aim 3. Examine if cancer survivors, compared to non-cancer controls, are at an increased risk of experiencing OUD or an opioid related emergency department visit or inpatient stay.

a. Match persons without a history of a cancer diagnosis to cancer survivors diagnosed with cancer from 2003 to 2011 and lived ≥5 years after a cancer diagnosis. Persons will be matched on age, gender, race, pain conditions, and previous opioid use.
b. Assess if cancer survivors are more likely than noncancer controls to experience an opioid-related emergency department visit or hospitalization.

GENERAL METHODS

Below we detail general methods that were used in all specific aims. More detailed methodology for each specific aim can be found within the respective chapter (Chapters 2-4). Information that will be included within each chapter includes, but is not limited to, cohort inclusion and exclusion criteria, matching criteria, specific statistical analyses applied.

Datasets

The present study was performed using linked Surveillance, Epidemiology, and End Results (SEER)-Medicare data sets. SEER data is nationally representative of the United States population.[200] SEER is a program of cancer registries that began submitting cancer related information in 1973 from Connecticut, Iowa, New Mexico, Utah, Hawaii, and San Francisco. Over time, SEER has added Seattle-Puget Sound (1974), Georgia (1974), Alaska Native Tumor Registry (1999), Greater California (2001), Louisiana (2001), Kentucky (2001), Idaho (2018), New York (2018), and Massachusetts (2018) cancer registries, with many states providing data retrospectively. Detroit and New Jersey are no longer in the SEER program but were included in the 2018 release and their registry data was included in all analyses.

Medicare administrative claims datasets include insurance billing for health services for beneficiaries. Persons are eligible for benefits if they are 65 years or older, received Social Security Disability benefits for 24 months, or if they are diagnosed with End Stage Renal Disease or Amyotrophic Lateral Sclerosis. There are four Parts to Medicare, Part A (inpatient/hospital coverage), Part B (outpatient/medical coverage), Part C (Health Maintenance Organization alternative plans), and Part D (prescription drug coverage). Part A and B information is not routinely reported by Health Maintenance Organizations about health services received by their enrollees. For this reason, the current study will only include persons who have complete Part A, B, and D enrollment and have not been enrolled in Part C. We used the following Medicare administrative claims datasets: 1) Patient Entitlement and Diagnosis Summary File (PEDSF); 2) Prescription Drug Event (PDE) file; 3) Medicare Provider Analysis and Review (MEDPAR); 4) Carrier Claims; 5) Outpatient Claims (OUTSAF); 6) Durable Medical Equipment (DME); 7) Hospice data sets. Medicare administrative claims were linked to SEER data based on an encrypted patient identifier (**Table 1.1**).

Prescription opioids from the PDE file were identified with National Drug Codes from RedBook 2011, 2014, 2015, 2017. RedBook contains national drug codes and prescription formulary information for pharmacological agents that are classified as controlled substances Schedule II-IV. The Redbook contains the following prescription opioids: alfentanil, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levomethadyl, levorphanol, meperidine, methadone, morphine, opium in preparations, oxycodone, oxymorphone, pentazocine, remifentanil, sufentanil, tapentadol, and tramadol.

Software

Statistical Analysis Software (SAS) 9.4 (SAS Inc, Cary, NC) was used to perform all data management and statistical analysis. Proc Means and Proc Freq were used to calculate relevant descriptive statistics. Proc Genmod was used to perform generalized estimating equations (Aim 1 and 2). Proc Logistic was used to conduct multivariable logistic regression. Proc Lifetest and Proc Phreg was used to perform a Kaplan-Meier and Cox Proportional Hazards Model and Fine and Gray Model, respectively (Aim 3).

SAS code for all three specific aims is available upon request. This study used two macros available online. The first macro was used to calculate descriptive statistics, means and percentages stratified by groups, for all 3 aims.[130] The second macro was provided by National Cancer Institute to identify Charlson comorbidities in Medicare Claims.[131] However, these claims did not include ICD-10-CM diagnostic codes for the Charlson comorbidities. Therefore, these diagnostic codes were removed and replaced with ICD-9-CM and cross-walked ICD-10-CM codes provided by Quan et al. (2005).[132]

Appendix A

Table 1.1. SEER-Medicare Datafiles and Descriptions

Source/File	**Description**
Patient Entitlement and Diagnosis Summary File (PEDSF)	Details patient ID number and information on demographics, cancer diagnoses, state of residence, and Medicare entitlement enrollment (part A, B, D, Advantage) from 1991 to 2016. **Variables used:** patient id (used to link all files), SEER-Area, monthly part A, B, D, and HMO enrollment, age/sex/race, month/year of diagnosis, tumor site, stage, original reason for enrollment, state of residence.
Summarized Denominator File (SUMDENOM)	Non-cancer Medicare file. Details the patient ID, patient demographics, and Medicare Part A, B, D, and HMO enrollment information
Prescription Drug Event File (PDE)	Details drug utilization information includes name, date filled, quantity, refills, form, dosage, and limits/prior authorization status. **Variables used:** patient id number, part D event id number, prescription filled date, NDC, quantity dispensed, days supply, brand name, generic name, dosage form and strength
Medicare Provider Analysis and Review (MEDPAR)	Details Institutional Part A inpatient and skilled nursing facility claims received during the year. **Variables used:** patient id number, admission and discharge dates, ICD-9CM and ICD-10CM diagnosis codes
Outpatient Standard Analytical File (SAF)	Details Institutional Part B outpatient claims from hospitals, clinics, dialysis and rehabilitation facilities, and community mental health centers received during the year **Variables used:** patient id number, claim id number, claim dates, provider number, ICD-9CM and ICD-10CM diagnoses codes, revenue center date, revenue center healthcare common procedure coding system (HCPCS),
Carrier Claims (Physician/Supplier)	Details all provider/supplier bills and claims. **Variables used:** patient id number, claim dates, HCPCS code, principle claim diagnosis code
Hospice	Details claims for care received by Hospice providers. Hospice claims will be used to identify patients in the cohort who received hospice care during the cohort study period. Using patient id number, these individuals will be excluded from the analysis.

Chapter 2. Regional and Temporal Variation in Receipt of Long-Term Opioid Therapy Among Older Breast, Colorectal, Lung, and Prostate Cancer Survivors in the United States

Chapter 2 has been previously published as a full-length original manuscript in *Cancer Medicine* under a Create Commons Attribution License.

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ABSTRACT

Background: Older cancer survivors have high rates of long-term opioid therapy (≥90 days/year). However, the geographical and temporal variation in long-term opioid therapy rates for older cancer survivors is not known.

Methods: A retrospective cohort study was conducted using SEER-Medicare data. Persons aged ≥66 years, diagnosed with breast, colorectal, lung, or prostate cancer from 1991-2011, and alive ≥5 years after diagnosis were included. Persons were followed from 1/1/2008 until 12/31/2016. Persons were assigned to a census region in their state of residence each year. Individuals who were covered by an opioid prescription for at least 90 days in a calendar year were classified as having received long-term opioid therapy. Multivariable analysis was conducted using generalized estimating equations.

Results: Temporal trends significantly varied by region ($p<0.0001$) and opioid naïve status ($p<0.0001$). Compared to 2013, opioid naïve cancer survivors in the south and non-naïve survivors in the south and west experienced significant declines in long-term opioid therapy in 2015 and 2016. Significant declines were observed in 2016 for opioid naïve and

non-naïve cancer survivors residing in the northeast and among opioid naïve cancer survivors living in the Midwest.

Conclusion: The annual trends in the receipt of long-term opioid therapy significantly varied by region among older cancer survivors. Variation in a clinical practice suggests the need for more research and interventions to improve efficiency, process, cost, and quality of care.

INTRODUCTION

Approximately 67% of persons diagnosed with cancer are expected to live at least 5 years after their cancer diagnoses.[133] Chronic pain is common in patients and can last beyond the completion of cancer treatment.[134,135] Prescription opioids may be used to treat pain shortly after diagnosis but a substantial number of older adults use prescription opioids years after a cancer diagnosis.[99,121] For example, Salz et al. (2019) found that older persons diagnosed with cancer were more likely to experience chronic opioid years after their diagnosis compared to persons without cancer, but this relationship varied with respect to the cancer diagnosis.[117] Opioid therapy is associated with an increased risk of adverse events, such as falls and fractures,[75] hypogonadism,[77,78] and heart disease,[79] and utilization of prescription opioids for longer durations can increase the risk of adverse health outcomes particularly in older adults with a history of cancer.[81]

Previous studies have shown that opioid prescribing varies by time and geographical region in the United States.[86,88,90,91,94] In general, opioid prescribing rates, amount of opioids dispensed, days supplied, and long-term use are highest in Appalachia and the south. Furthermore, it appears prescription opioid prescribing peaked in 2010 and slowly declined until 2015.[90] Among older cancer-survivors residing in Texas, Shah et al. (2019) observed that the prevalence of receipt of long-term opioid therapy increased slowly from 2008 to 2010 but then increased sharply in 2011 and remained constant until 2014.[99] Previous studies have provided significant insight into the geographical and temporal

patterning of the utilization of prescription opioids, but national temporal and regional trends in receipt of long-term opioid therapy have not been examined specifically for older adult cancer survivors.

The purpose of this study was to examine how annual rates in the receipt of long-term opioid therapy changed across regions in the United States and by time for older persons with a history of breast, colorectal, lung, and prostate cancer diagnosis. We also examined if the temporal trends varied by opioid naivety given that patterns of opioid use are influenced by previous opioid use among older cancer survivors.[99] Understanding regional and temporal variations in long-term opioid therapy is important given the dissemination of opioid prescribing guidelines and implementation of state and federal policies that sought to regulate opioid prescribing over the previous decade.

METHODS

Data Source

A retrospective cohort study was performed using linked Surveillance, Epidemiology, and End Results (SEER)-Medicare data sets. SEER is a program of cancer registries that began submitting cancer related information in 1973 from states or regions within states. Medicare provides health coverage to approximately 96% of United States citizens aged 65 years and older. Persons are also eligible if they have received Social Security Disability benefits for 24 months or been diagnosed with End Stage Renal Disease (ESRD) or Amyotrophic Lateral Sclerosis. Fee for service Medicare includes Parts A and B, which cover inpatient hospital stays or outpatient services, respectively. Medicare Part D provides coverage for outpatient prescription drugs. The University of Texas Medical Branch Institutional Review Board (IRB) approved this study.

Study Cohort

Annual cohorts were constructed for each year of the study (2008-2016) using the same inclusion and exclusion criteria. Persons who were included were followed from January 1 to December 31 of a given year. Persons were eligible for inclusion in this study if they were diagnosed with a cancer of the breast, colorectum, lung, or prostate as their first cancer diagnosis anytime between January 1, 1991 to December 31, 2011. These four cancers were chosen because they are the most common cancers diagnosed in the United States. Persons were assigned an index date corresponding to at least 5 years post-cancer diagnosis, the date of survivorship. Individuals diagnosed with cancer before January 1, 2003 were assigned a date of survivorship of January 1, 2008 because they had survived greater than 5 years after cancer diagnosis and, therefore, were available on the first date of study.

Persons were excluded from the study if they were: 1) diagnosed at autopsy or on a death certificate, 2) had an unknown month of diagnosis or birth month or year, or 3) had been diagnosed with a second primary cancer. For each annual cohort, persons were excluded from the analysis if they were: 1) younger than 66 years of age on January 1 of the corresponding year, 2) had not been diagnosed for at least 5 years or the date of survivorship was later than January 1 of corresponding year (e.g. February 1, 20XX), 3) had noncontinuous Part A, B, and D enrollment or had enrollment in a Health Maintenance Organization (HMO) in the 12 months prior to January 1 of the corresponding year, 4) had a claim for hospice care, were deceased, or had received cancer treatment (**Table 2.1**) in the 12 months prior to January 1 of the corresponding year, or 5) had non-continuous enrollment in Part A, B, and D or enrollment in an HMO during the 12 months of follow up. Persons who died or had a claim for hospice care during a given year were censored at that date and were included in the study if they lived until April 1 of the corresponding year. The sample flowchart is presented in **Figure 2.1**

Prescription Opioid Outcomes (Long-Term Opioid Therapy)

National Drug Codes from RedBook were used to identify dispensed opioid prescriptions from the PDE file. The *cumulative* number of calendar days a person possessed an opioid prescription in a calendar year, from January 1 to December 31, was calculated. We assumed the prescription began on the date of dispensing and ended on the date of dispensing + days supplied – 1, accounting for the filled date as the first day of the opioid prescription. Persons who had an opioid prescription for ≥90 days in a calendar year were classified as having received long-term opioid therapy.

Covariates

Time invariant covariates were gender (male, female), race-ethnicity (non-Hispanic White, non-Hispanic Black, non-Hispanic other, Hispanic), diagnosis cohort, cancer diagnosis (breast, colorectal, lung, prostate), and original reason for Medicare entitlement (age related enrollment, or non-age related). Diagnosis cohort was the recategorization of the year of cancer diagnosis into 5 cohorts (1991-1994, 1995-1998, 1999-2002, 2003-2006, 2007-2011). Time varying covariates were the years post-cancer diagnosis, age at the beginning of a calendar year (66-74, 75-84, ≥85 years), metropolis status (metropolis, urban-rural), census region (west, northeast, Midwest, south), Medicaid eligibility, Charlson comorbidity score ≥ 1, depressive disorder, anxiety disorder, alcohol use disorder, drug use disorder, and opioid naïve status. Opioid naïve cancer survivors were persons who did not receive any prescription opioid in the previous 12 months prior to January 1 of a calendar year. Appropriate diagnostic and procedure ICD-9CM and ICD-10 codes were utilized to identify relevant Charlson comorbidities and mental health disorders.[132,136]

Statistical Analysis

Means (standard deviations) and Medians (Quartile 1, Quartile 3) were calculated for continuous variables and frequencies (percentages) were calculated for categorical

covariates. Descriptive analysis was conducted to examine the distribution of patient characteristics by calendar year to assess how the composition of the overall cohort changed over time. To assess crude regional differences in long-term opioid therapy we calculated prevalence rates for each calendar year by dividing the total number of persons who received long-term opioid therapy by the total number of person-years contributed for each calendar year. For each calendar year a person could contribute a minimum of 0.3 person-years to a maximum of 1.0 person-year.

Multivariable analysis estimating the adjusted odds ratio (aOR) of receipt of long-term opioid therapy within each calendar year was conducted utilizing generalized estimating equations (GEE)[137] with a binomial distribution, logit link function, and an autoregressive (AR1) correlation structure to account for repeated measures of persons. An offset statement was included for the person-years contributed to each calendar year. To assess if time trends differed across U.S. regions and opioid-naïve status we performed statistical interactions between the calendar year and census region and opioid naïve status by including each individual interaction-term into the main effects model. Since the statistical interactions between year and region and year and opioid naïve status were significant, we stratified the models by these variables to examine how the temporal trends in receipt of long-term opioid therapy varied by region and opioid naïve status. In the stratified analysis of opioid non-naive persons, the working correlation structure was specified as independent due to the non-convergence of the AR1 model for this subgroup. We chose 2013 as the reference year because this was the year before the enforcement of the federal rescheduling of hydrocodone.[138] All statistical tests were two-sided with $\alpha = 0.05$. All data management steps and analyses were performed with SAS version 9.4 (SAS Inc, Cary, NC).

RESULTS

Overall, there were 344,443 persons who contributed a total of 1,255,333.8 person-years. The minimum number of person-years contributed by a single individual was 0.3 and the maximum was 9.0, with an average of 3.6 person-years (Std=2.5) and median of 3.0 person-years (Q1, Q3 = 1.9, 5.0).

Table 2.2 demonstrated how the person characteristics changed at selected years during the study period. Overall, from 2008 to 2016, the sample became slightly younger. There were small increases in the percentage of persons diagnosed with depressive and anxiety disorders. From 2008 to 2016, there was a decline in the percentage of colorectal cancer survivors but an increase in the percentage of prostate cancer survivors. From 2008 to 2016, the percentage of northeastern and southern residents increased, while the percentage of midwestern and western residents decreased. However, the west comprised over 40% of the sample each year. One of the largest demographic changes during the study period was the composition of years of diagnosis. In 2008, most of the sample was comprised of persons diagnosed with cancer in 1999-2002 (59%). In 2016, no diagnosis cohort comprised a simple majority, but the 2007-2011 cohort comprised the largest percentage (35%). The 1991-1994 cohort and 1995-1998 cohort comprised 16% and 23% of the 2008 sample, respectively, but comprised 5% and 8% of the 2016 sample.

Overall, the rate of long-term opioid therapy increased from 8.0 persons with long-term opioid therapy per 100 person years in 2008 to 10.0 in 2012 and then decreased to 8.5 in 2016. **Figure 2.2** displays the rates of receipt of long-term opioid therapy stratified by region. Throughout, the study period the south had the highest prevalence rates, and the northeast had the lowest rates. The rates of long-term opioid therapy increased from 2008-2012 and declined from 2013-2016 across all regions. From 2008 to 2016 the rate of long-term opioid therapy increased in the west from 7.9 per 100 person-years (2008) to 8.1 (2016), increased in the Midwest from 8.9 (2008) to 9.9 (2016), and increased in the south

from 9.4 (2008) to 11.3 (2016), but decreased in the northeast from 5.5 (2008) to 5.3 per 100 person-years (2016).

After adjusting for patient demographics, cancer diagnosis, and comorbid conditions, the time trend in receipt of long-term opioid therapy was found to vary significantly by U.S. region (p=0.0002, not shown), therefore, we stratified our model assessing temporal trends of receipt of long-term opioid therapy by census regions (**Table 2.3**). After 2013, there was no statistically significant decline in the trend of long-term opioid therapy, overall, in the receipt of long-term opioid therapy in the west, northeast, and Midwest. Instead, a statistically significant increase was observed in the Midwest in 2014 (aOR = 1.05, 95% CI: 1.00, 1.10). A significant decline was noted in the south in 2015 (aOR = 0.93, 95% CI: 0.89, 0.98) but not in 2014 (aOR = 0.97, 95% CI: 0.94, 1.01) and 2016 (aOR = 0.97, 95% CI: 0.91, 1.03).

The time trend in the rate of long-term opioid therapy was found to vary significantly by opioid naïve status after adjusting for patient demographics, cancer diagnosis, and comorbid conditions (p<0.0001, not shown), therefore we stratified our models by U.S. census region and opioid naïve status. **Figure 2.3 and 2.4** present the annual rate of long-term opioid therapy in opioid naïve (**Figure 2.3**) and opioid non-naive (**Figure 2.4**). The annual time trend in the receipt of long-term opioid therapy stratified by opioid naïve status adjusted for patient demographics and clinical history is presented in **Table 2.4.** After 2013, statistically significant declines were observed in 2014 (aOR = 0.78, 95% CI: 0.64, 0.94), 2015 (aOR = 0.58, 95% CI: 0.47, 0.71) and 2016 (aOR = 0.57, 95% CI: 0.46, 0.71) among opioid naïve cancer survivors residing in the south. Similarly, statistically significant declines in long-term opioid therapy among opioid naïve cancer survivors were observed in the Midwest in 2016 (aOR = 0.63, 95% CI: 0.48, 0.82) and in the northeast in 2016 (aOR = 0.71, 95% CI: 0.53, 0.94). Among opioid non-naïve cancer survivors, statistically significant declines were observed in the west in 2015 (aOR = 0.91, 95% CI: 0.86, 0.95) and 2016 (aOR = 0.87, 95% CI: 0.82, 0.92), in the northeast in 2016

(aOR = 0.87, 95% CI: 0.78, 0.97), in the Midwest in 2015 (aOR = 0.92, 95% CI: 0.86, 1.00) and in the south in 2015 (aOR = 0.90, 95% CI: 0.85, 0.96) and 2016 (aOR = 0.88, 95% CI: 0.82, 0.95).

A sensitivity analysis in which observations with less than a full person year were removed was consistent with our results, except we did not observe a significant reduction in long-term opioid use in the Midwest in 2015 among opioid non-naïve persons (**Table 2.5**). We also performed a sensitivity analysis examining the temporal trends within region including only colorectal and lung cancer survivors and found strong declines among opioid naïve persons in the south but no significant differences in the other regions among opioid naïve and non-naïve individuals (**Table 2.6**). A separate sensitivity analysis exploring temporal trends in receipt of long-term opioid therapy within each cancer diagnosis group revealed no significant declines after 2013 in all cancer diagnosis groups (**Table 2.7**).

DISCUSSION

We observed that the time trends in the receipt of long-term opioid therapy among older cancer survivors significantly varied by U.S. region and prior opioid use. Overall, the prevalence of long-term opioid therapy was highest in the south and lowest in the northeast. After stratifying by previous opioid use, we observed statistically significant and sustained declines in the receipt of long-term opioid therapy for opioid naïve persons residing in the south and among opioid non-naïve persons in the south and west after 2013. This study builds upon the literature concerning opioid prescribing in older cancer survivors by identifying that time and place are influential contextual factors for receipt of long-term opioid therapy among older persons who lived 5 or more years after a cancer diagnosis.

In general, previous studies have indicated that opioid prescribing and long-term opioid therapy rates are lowest in the northeast but highest in the south and have declined substantially after 2010, particularly in the south.[82,86,88,90,91,94,95,139] Our study cohort was

comprised of persons who were diagnosed with cancer in a SEER state or region. SEER capture areas, however, cover approximately 35% of US residents with selected states in different regions.[140] The long-term opioid therapy rates among older cancer survivors presented in this study may underestimate actual regional prevalence rates. Most of our cancer survivor cohort in the west (California, Washington), northeast (New Jersey, Connecticut), Midwest (Michigan, Iowa), and south (Georgia, Kentucky, Louisiana) resided in states with lower rates of long-term opioid therapy compared to some regional non-SEER neighboring states, although some SEER states historically had high long-term use rates. There were fewer observations in our study from non-SEER states with observed high long-term opioid therapy rates. Despite these differences, our results on the geographical patterning of long-term opioid therapy rates among older cancer survivors is consistent with the findings of long-term opioid therapy in Medicare beneficiaries.[95]

Gender differences in the utilization of prescription opioids have been previously observed in older adults, with women more likely to receive long-term opioid therapy and men more likely to receive high-dose therapy, but this is debated. [82,95,141,142] Temporal trends in long-term opioid use have found larger absolute and relative reductions in the rates of long-term opioid use in women as compared to men.[95] Our study is consistent with Shah et al. (2019) which found that female cancer survivors are more likely to receive long-term opioid therapy than men.[99] We performed a sensitivity analysis examining the trends of long-term opioid use within regions only in persons diagnosed with colorectal or lung cancer to reduce the influence of breast and prostate cancer survivors on our results. We found strong declines among opioid naïve persons in the south but did not observe declines in other regions regardless of previous opioid use. One reason for the difference in the results between the main findings and the sensitivity analysis could be that colorectal and lung cancer survivors were more likely to be diagnosed with metastatic tumors that extended regionally or distantly and, therefore, experience more adverse consequences related to treatment and requiring more prescription opioid use in survivorship.

There are several possible explanations for the reduction in long-term opioid therapy rates observed in this study. Declines in the rate of long-term opioid therapy may be associated with the rescheduling of hydrocodone combination products (HCP) from schedule III to the more restrictive schedule II by the Drug Enforcement Administration in October 2014.[138,143-146] However, in an unadjusted analysis we noted that declines in the rate of long-term opioid therapy preceded the enforcement of hydrocodone reclassification. We also observed regional variation in the declines of long-term opioid use after HCP rescheduling, despite HCP rescheduling being a broad federal policy initiative. Statewide variation in the relative reductions of HCP prescribing and receipt of long-term opioid therapy after the enforcement of HCP rescheduling has been previously observed,[95,143] but regional differences in receipt of long-term opioid therapy could also be associated with state prescription drug monitoring programs policy and changes to hospital and insurance organizational guidelines restricting opioid prescribing.

During the study period, state legislatures, governors, and medical boards aimed to reduce opioid prescribing by implementing policies, rules, and guidelines that attempted to change prescriber behavior. Some commonly enacted state policies regulated pain clinics, limited the initial amount or days-supplied of opioids, and mandated providers to check the prescription drug monitoring program (PDMP) before prescribing opioids.[147-154] However regional and temporal differences in the implementation of legislation and regulations have been noted.[150-154] For example, southern states were early adopters that required providers to enroll into a PDMP and review patient's opioid prescriptions – at least in some circumstances – before prescribing an opioid. Moreover, many southern states instituted strict regulations on pain clinics that specified clinic ownership, registration with the state, and best clinical practices. Some Midwestern states limited the daily amount of opioids prescribed but did not, in general, require PDMP review. Many northeastern states adopted policies mandating PDMP enrollment and use, and imposed limitations on the days supplied of prescription opioids for initial prescriptions. Similarly, legislation requiring

PDMP enrollment and restricting the daily amount of opioids prescribed or dispensed were common in western states.

We did not observe that states with most of the person-time observed in our study were more likely to require providers use PDMP programs than states with smaller percentage of cancer survivors. Through 2015, only 10 states clustered in the northeast and Ohio River Valley and 3 states west of the Mississippi River had legislation mandating all providers to check the PDMP before an initial opioid prescription (Nevada, New Mexico, Oklahoma, Kentucky, Tennessee, West Virginia, Ohio, Pennsylvania, New Jersey, New York, Connecticut, Rhode Island, Massachusetts).[150] Further studies should be conducted to examine how state policies interact with federal policy to reduce opioid prescribing.

In 2016, the CDC and American Society of Clinical Oncology (ASCO) released guidelines on opioid prescribing for chronic pain and recommended the use of non-opioid analgesics and non-pharmacological treatment of chronic pain.[64,65] The dissemination of these guidelines, however, cannot explain declines in receipt of long-term opioid therapy that were observed to begin around 2014 in some regions but could explain some of the decline noted in 2016 in the northeast and Midwest. Our study did not have a long enough follow up time to isolate the effects of these guidelines on the rates of long-term opioid therapy. Furthermore, many insurers, hospital systems, and pharmacies implemented organizational guidelines to reduce opioid prescribing and dispensing. We are unable to examine how these organizational changes affected trends in long-term opioid therapy. Lastly, provider attitudes towards prescription opioids may have changed over time because of the reports on the increase in morbidity and mortality associated with prescription opioids use. Early reports suggested that physicians expressed relatively little concern about the addiction and dependence potential of prescription opioids, but recent surveys have shown greater concerns over opioid misuse.[155-157]

This study has several limitations. First, we used administrative claims data from Medicare from persons who were diagnosed with breast, colorectal, lung, or prostate cancer

in a SEER-region, lived at least 5 years post diagnosis, continuously enrolled in Part A, B, and D, and did not receive cancer treatment or hospice care. Our results are not generalizable to other cancer survivor populations, individuals who were enrolled in an HMO, or were not diagnosed in a SEER-region. Second, opioids that were not prescribed to a person in our cohort or opioids prescribed but not dispensed through Part D could not be counted towards total days of having an opioid prescription. Third, our analysis assumes the prescription for opioids was taken as directed. Fourth, our study using administrative claims data is not able to link prescription opioid utilization to patient reported pain severity or personal beliefs on prescription opioids. Fifth, our study did not have a large enough sample size of persons alive ≥ 5 years post-cancer diagnosis to conduct a state policy analysis. Sixth, we were unable to examine how current disease – 5 or more years after diagnosis – was associated with receipt of long-term opioid therapy. We attempted to address this limitation by excluding individuals if they were diagnosed with a second primary cancer and by requiring that persons be not receiving chemotherapy or radiation. Last, this study did not include information about opioid prescribers. The differences in receipt of long-term opioid therapy may be related to distribution of providers caring for cancer survivors or due to intra-specialty temporal trends in opioid prescribing. Future studies are needed to examine how opioid prescribing by providers changes over time and across regions.

This study has several strengths. This study utilizes information from multiple and geographically diverse regions or state-based registries with high capture rates for cases linked with part A, B, and D Medicare claims. This allows for detailed follow up using reliable information. Moreover, we could follow individuals if they moved to another state or region which allowed us to assess variation in long-term opioid therapy by a person's residence over time. Lastly, we were able to censor individuals at the time of death or receipt of hospice care or assess whether they received treatment for cancer in the year prior to follow up.

In conclusion, we found evidence that the rates of long-term opioid therapy varied by time, geographic region, and previous opioid use for older cancer survivors. Receipt of long-term opioid therapy was highest in the south and lowest in the northeast. Variation in a clinical practice suggests the need for more research and interventions to improve efficiency, process, cost and quality of care.[158] Research should explore what factors explain the geographical variation in prescribing, and what policy and public health interventions are needed to reduce high rates of long-term opioid therapy for the growing number of older long-term cancer survivors.

Appendix B

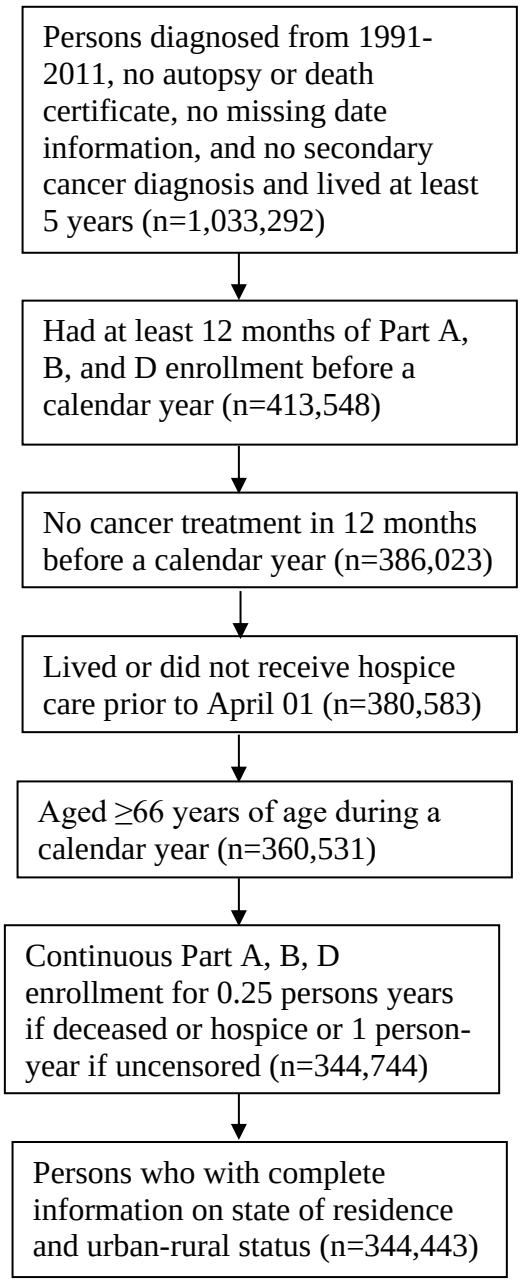

Figure 2.1. Sample Flowchart of Cancer Survivors Included in the Analysis for Specific Aim 1

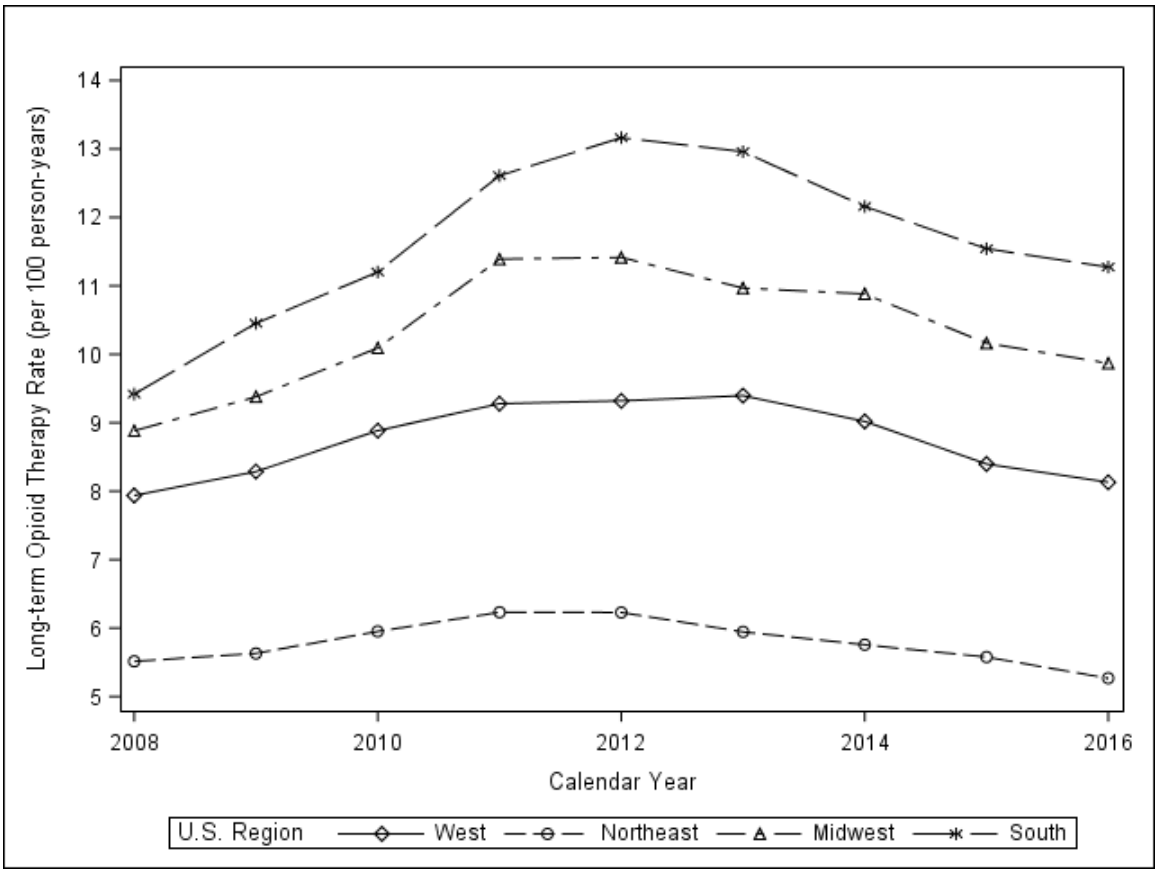

Figure 2.2. Prevalence Rate (per 100 Person-Years) of Long-Term Opioid Therapy Among Cancer Survivors Stratified by U.S. Census Region

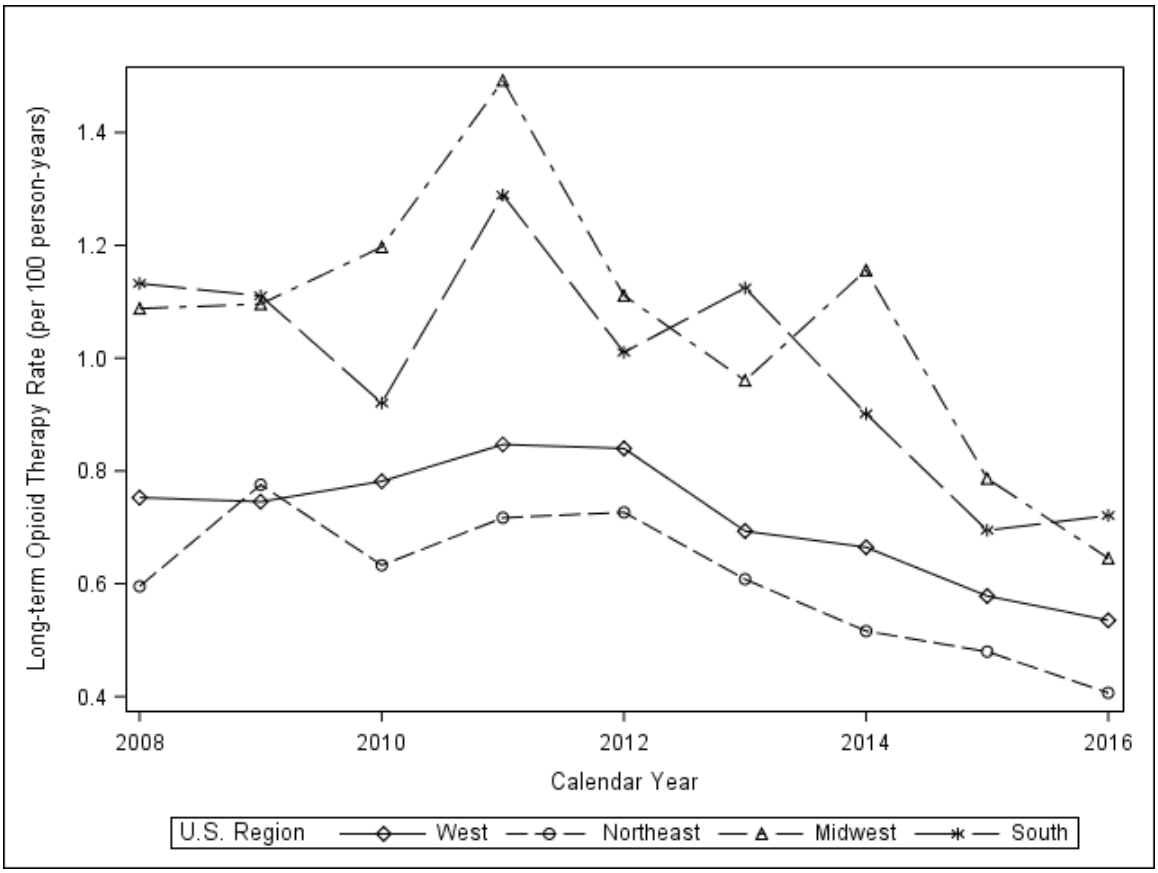

Figure 2.3. Prevalence Rate (per 100 Person-Years) of Long-Term Opioid Therapy Among Opioid Naïve Cancer Survivors Stratified by U.S. Census Region

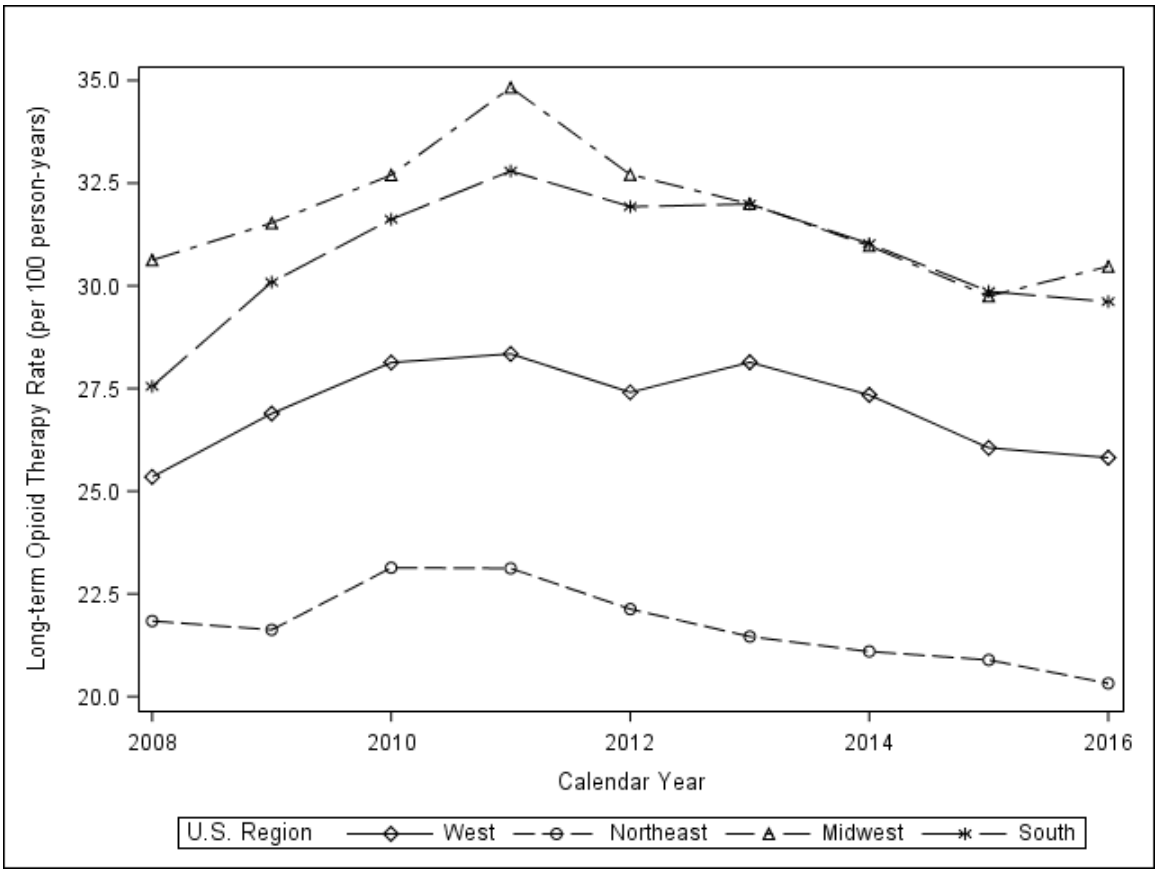

Figure 2.4. Prevalence Rate (per 100 Person-Years) of Long-Term Opioid Therapy Among Opioid Non-Naïve Cancer Survivors Stratified by U.S. Census Region

Table 2.1. ICD-9-CM and ICD-10-CM Codes for Chemotherapy or Radiation

	Chemotherapy	**Radiation**
ICD-9 Diagnosis Codes	V581, V662, V672	V580, V661, V671
ICD-10 Diagnosis Codes	Z5111, Z5112	Z510
ICD-9 Procedure Codes	9925	9221-9229
ICD-10 Procedure Codes**	3E03305, 3E04305, XW03351, XW04351	D0000ZZ, D0010ZZ, D0060ZZ, D0070ZZ, D7000ZZ… **(Exhaustive list is available upon request as there are several hundred available codes)**
Revenue Center Codes		0330, 0333
CPT/HCPCS Codes	964xx, 96400-96549, Q0083-Q0085, 51720, J9000-J9999	77401-77499, 77520, 77523, 77750-77799, G0265, G0261

Table 2.2. Descriptive Characteristics of Cancer Survivors Within Each Calendar Year

Variables	**2008 (n=74773)**	**2009 (n=86666)**	**2010 (n=97355)**	**2011 (n=111243)**	**2012 (n=128691)**	**2013 (n=152846)**	**2014 (n=190539)**	**2015 (n=209667)**	**2016 (n=226417)**
Age mean(std)	78.4 (7.5)	78.4 (7.5)	78.3 (7.6)	78.3 (7.6)	78.2 (7.5)	78.0 (7.5)	78.0 (7.5)	77.9 (7.5)	77.8 (7.4)
Age median(IQR)	78.0 (72.2, 83.8)	77.8 (72.1, 83.8)	77.8 (72.0, 83.8)	77.5 (72.0, 83.8)	77.4 (72.0, 83.6)	77.1 (71.9, 83.5)	77.0 (71.8, 83.4)	77.0 (71.9, 83.3)	76.9 (71.9, 83.1)
Age, Categorical									
66-74 years	24490 (32.9%)	28890 (33.5%)	32903 (34.0%)	38017 (34.4%)	44080 (34.6%)	53016 (35.1%)	67024 (35.6%)	74271 (35.8%)	83878 (36.1%)
75-84 years	28961 (38.9%)	32678 (37.9%)	36138 (37.4%)	40909 (37.1%)	47029 (36.9%)	55689 (36.9%)	69745 (37.0%)	76578 (37.0%)	85678 (36.9%)
≥85 years	24490 (32.9%)	28890 (33.5%)	32903 (34.0%)	38017 (34.4%)	36227 (28.4%)	42411 (28.1%)	51636 (27.4%)	56395 (27.2%)	62624 (27.0%)
Years Post Cancer Diagnosis									
Mean(std)	9.0 (3.3)	9.3 (3.4)	9.7 (3.6)	10.0 (3.7)	10.3 (3.9)	10.6 (4.1)	11.0 (4.3)	11.3 (4.4)	11.7 (4.6)
Median(IQR)	7.8 (6.3, 11.4)	8.3 (6.7, 11.6)	8.8 (6.8, 11.8)	9.2 (7.0, 11.9)	9.6 (7.2, 12.2)	9.9 (7.3, 12.7)	10.3 (7.5, 13.3)	10.7 (7.7, 13.9)	11.0 (7.9, 14.6)
Gender									
Female	40640 (54.5%)	46743 (54.2%)	52109 (53.9%)	59243 (53.7%)	67317 (52.9%)	78332 (51.8%)	95895 (50.9%)	105338 (50.8%)	117976 (50.8%)
Male	33868 (45.5%)	39465 (45.8%)	44578 (46.1%)	51127 (46.3%)	60019 (47.1%)	72784 (48.2%)	92510 (49.1%)	101906 (49.2%)	114204 (49.2%)
Race and Ethnicity									
Hispanic	4507 (6.0%)	5506 (6.4%)	6360 (6.6%)	7214 (6.5%)	8081 (6.3%)	9068 (6.0%)	10081 (5.4%)	10655 (5.1%)	12076 (5.2%)
Non-Hispanic Black	5084 (6.8%)	5954 (6.9%)	6422 (6.6%)	7326 (6.6%)	8412 (6.6%)	10175 (6.7%)	14159 (7.5%)	15011 (7.2%)	16249 (7.0%)

Variables	2008 (n=74773)	2009 (n=86666)	2010 (n=97355)	2011 (n=111243)	2012 (n=128691)	2013 (n=152846)	2014 (n=190539)	2015 (n=209667)	2016 (n=226417)
Non-Hispanic Other	5197 (7.0%)	5826 (6.8%)	6577 (6.8%)	7603 (6.9%)	8612 (6.8%)	9790 (6.5%)	11373 (6.0%)	12260 (5.9%)	14276 (6.1%)
Non-Hispanic White	59720 (80.2%)	68922 (79.9%)	77328 (80.0%)	88227 (79.9%)	102231 (80.3%)	122083 (80.8%)	152792 (81.1%)	169318 (81.7%)	189579 (81.7%)
Cancer Diagnosis									
Breast Cancer	29896 (40.1%)	34724 (40.3%)	39063 (40.4%)	44703 (40.5%)	51232 (40.2%)	60343 (39.9%)	75001 (39.8%)	83172 (40.1%)	94149 (40.6%)
Colorectal Cancer	14364 (19.3%)	16214 (18.8%)	17727 (18.3%)	19812 (18.0%)	22117 (17.4%)	25096 (16.6%)	29718 (15.8%)	31524 (15.2%)	34043 (14.7%)
Lung Cancer	2846 (3.8%)	3232 (3.7%)	3631 (3.8%)	4173 (3.8%)	4760 (3.7%)	5491 (3.6%)	6575 (3.5%)	7206 (3.5%)	8044 (3.5%)
Prostate Cancer	27402 (36.8%)	32038 (37.2%)	36266 (37.5%)	41682 (37.8%)	49227 (38.7%)	60186 (39.8%)	77111 (40.9%)	85342 (41.2%)	95944 (41.3%)
Diagnosis Cohort									
1991-1994	12199 (16.4%)	11774 (13.7%)	11241 (11.6%)	10810 (9.8%)	10728 (8.4%)	10822 (7.2%)	12120 (6.4%)	11683 (5.6%)	11555 (5.0%)
1995-1998	17436 (23.4%)	17059 (19.8%)	16492 (17.1%)	16227 (14.7%)	16412 (12.9%)	16786 (11.1%)	18850 (10.0%)	18530 (8.9%)	18683 (8.0%)
1999-2002	43678 (58.6%)	43512 (50.5%)	42351 (43.8%)	42734 (38.7%)	43637 (34.3%)	46277 (30.6%)	52060 (27.6%)	51709 (25.0%)	52431 (22.6%)
2003-2006	1195 (1.6%)	13863 (16.1%)	26603 (27.5%)	40599 (36.8%)	55130 (43.3%)	59208 (39.2%)	66531 (35.3%)	66680 (32.2%)	68367 (29.4%)
2007-2011					1429 (1.1%)	18023 (11.9%)	38844 (20.6%)	58642 (28.3%)	81144 (34.9%)
Census Region									
Midwest	13891 (18.6%)	14825 (17.2%)	16469 (17.0%)	18148 (16.4%)	19940 (15.7%)	21880 (14.5%)	29482 (15.6%)	30936 (14.9%)	32554 (14.0%)
Northeast	12476 (16.7%)	14735 (17.1%)	16863 (17.4%)	19212 (17.4%)	22445 (17.6%)	31152 (20.6%)	38225 (20.3%)	43088 (20.8%)	49424 (21.3%)

Variables	2008 (n=74773)	2009 (n=86666)	2010 (n=97355)	2011 (n=111243)	2012 (n=128691)	2013 (n=152846)	2014 (n=190539)	2015 (n=209667)	2016 (n=226417)
South	14160 (19.0%)	17596 (20.4%)	19457 (20.1%)	23556 (21.3%)	28192 (22.1%)	32831 (21.7%)	40821 (21.7%)	46052 (22.2%)	51814 (22.3%)
West	33981 (45.6%)	39052 (45.3%)	43898 (45.4%)	49454 (44.8%)	56759 (44.6%)	65253 (43.2%)	79877 (42.4%)	87168 (42.1%)	98388 (42.4%)
Urban-Rural Status									
Metropolis	60394 (81.1%)	70960 (82.3%)	79810 (82.5%)	91220 (82.6%)	105462 (82.8%)	126802 (83.9%)	159580 (84.7%)	175752 (84.8%)	197609 (85.1%)
Rural	1718 (2.3%)	1862 (2.2%)	2046 (2.1%)	2332 (2.1%)	2640 (2.1%)	2896 (1.9%)	3444 (1.8%)	3754 (1.8%)	4102 (1.8%)
Urban	12396 (16.6%)	13386 (15.5%)	14831 (15.3%)	16818 (15.2%)	19234 (15.1%)	21418 (14.2%)	25381 (13.5%)	27738 (13.4%)	30469 (13.1%)
Metropolis Status									
Rural or Urban	14114 (18.9%)	15248 (17.7%)	16877 (17.5%)	19150 (17.4%)	21874 (17.2%)	24314 (16.1%)	28825 (15.3%)	31492 (15.2%)	34571 (14.9%)
Metropolis	60394 (81.1%)	70960 (82.3%)	79810 (82.5%)	91220 (82.6%)	105462 (82.8%)	126802 (83.9%)	159580 (84.7%)	175752 (84.8%)	197609 (85.1%)
Original Reason for Enrollment									
Age	68499 (91.9%)	79149 (91.8%)	88556 (91.6%)	100954 (91.5%)	116360 (91.4%)	138358 (91.6%)	172700 (91.7%)	190127 (91.7%)	213030 (91.8%)
Disability and End Stage Renal Disease	26 (0.0%)	37 (0.0%)	41 (0.0%)	55 (0.0%)	62 (0.0%)	75 (0.0%)	102 (0.1%)	128 (0.1%)	141 (0.1%)
Disability	5954 (8.0%)	6989 (8.1%)	8052 (8.3%)	9310 (8.4%)	10842 (8.5%)	12591 (8.3%)	15485 (8.2%)	16854 (8.1%)	18859 (8.1%)
End Stage Renal Disease	29 (0.0%)	33 (0.0%)	38 (0.0%)	51 (0.0%)	72 (0.1%)	92 (0.1%)	118 (0.1%)	135 (0.1%)	150 (0.1%)
Age Related Medicare Enrollment									

Variables	2008 (n=74773)	2009 (n=86666)	2010 (n=97355)	2011 (n=111243)	2012 (n=128691)	2013 (n=152846)	2014 (n=190539)	2015 (n=209667)	2016 (n=226417)
Not Age Related	6009 (8.1%)	7059 (8.2%)	8131 (8.4%)	9416 (8.5%)	10976 (8.6%)	12758 (8.4%)	15705 (8.3%)	17117 (8.3%)	19150 (8.2%)
Age Related	68499 (91.9%)	79149 (91.8%)	88556 (91.6%)	100954 (91.5%)	116360 (91.4%)	138358 (91.6%)	172700 (91.7%)	190127 (91.7%)	213030 (91.8%)
Medicaid Eligible	16578 (22.2%)	18698 (21.7%)	20667 (21.4%)	23357 (21.2%)	25703 (20.2%)	27438 (18.2%)	27683 (14.7%)	27611 (13.3%)	30114 (13.0%)
Charlson ≥1	49138 (65.9%)	57581 (66.8%)	64830 (67.1%)	73821 (66.9%)	85012 (66.8%)	99868 (66.1%)	123725 (65.7%)	135520 (65.4%)	152987 (65.9%)
Depressive Disorder	7949 (10.7%)	9325 (10.8%)	10922 (11.3%)	12609 (11.4%)	15517 (12.2%)	18647 (12.3%)	23167 (12.3%)	26378 (12.7%)	31092 (13.4%)
Anxiety Disorder	4877 (6.5%)	6071 (7.0%)	7317 (7.6%)	8950 (8.1%)	11458 (9.0%)	14592 (9.7%)	19419 (10.3%)	22814 (11.0%)	28640 (12.3%)
Alcohol Use Disorder	718 (1.0%)	790 (0.9%)	932 (1.0%)	1106 (1.0%)	1416 (1.1%)	1859 (1.2%)	2699 (1.4%)	3281 (1.6%)	4174 (1.8%)
Drug Use Disorder	395 (0.5%)	459 (0.5%)	584 (0.6%)	719 (0.7%)	928 (0.7%)	1203 (0.8%)	1718 (0.9%)	2207 (1.1%)	3297 (1.4%)
Opioid Naïve	53491 (71.8%)	61674 (71.5%)	68422 (70.8%)	76461 (69.3%)	85718 (67.3%)	102645 (67.9%)	128567 (68.2%)	142374 (68.7%)	161347 (69.5%)

Table 2.3. Adjusted Odd Ratios (aOR) and 95% Confidence Intervals (CI) of Receipt of Long-Term Opioid Therapy Stratified by U.S. Region

	West	**Northeast**	**Midwest**	**South**
Calendar Year	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
2008	**0.89 (0.82, 0.98)**	1.04 (0.88, 1.24)	**0.86 (0.75, 0.98)**	**0.85 (0.77, 0.95)**
2009	**0.90 (0.84, 0.97)**	0.97 (0.84, 1.12)	**0.87 (0.78, 0.97)**	**0.88 (0.80, 0.96)**
2010	**0.94 (0.89, 1.00)**	0.97 (0.86, 1.09)	0.93 (0.85, 1.01)	**0.87 (0.80, 0.93)**
2011	0.98 (0.94, 1.03)	1.01 (0.92, 1.11)	1.06 (0.98, 1.13)	1.00 (0.94, 1.05)
2012	0.99 (0.96, 1.02)	0.98 (0.91, 1.04)	1.03 (0.98, 1.08)	0.99 (0.95, 1.03)
2013	REF	REF	REF	REF
2014	1.01 (0.98, 1.04)	0.98 (0.92, 1.04)	**1.05 (1.00, 1.10)**	0.97 (0.94, 1.01)
2015	0.96 (0.92, 1.00)	0.98 (0.91, 1.06)	0.99 (0.93, 1.06)	**0.93 (0.89, 0.98)**
2016	0.99 (0.93, 1.04)	1.02 (0.92, 1.12)	1.03 (0.95, 1.12)	0.97 (0.91, 1.03)
Years Post-Cancer Diagnosis	0.99 (0.97, 1.01)	0.99 (0.96, 1.02)	0.99 (0.96, 1.01)	0.99 (0.97, 1.01)
Age, years				
66-74	REF	REF	REF	REF
75-84	**1.06 (1.03, 1.10)**	**1.07 (1.01, 1.14)**	**1.12 (1.06, 1.18)**	1.06 (1.02, 1.10)
≥85	**1.07 (1.04, 1.11)**	**1.12 (1.06, 1.20)**	**1.25 (1.19, 1.31)**	1.07 (1.03, 1.11)
Cohort				
1991-1994	REF	REF	REF	REF
1995-1998	**0.88 (0.79, 0.97)**	0.87 (0.70, 1.09)	0.92 (0.81, 1.06)	0.92 (0.77, 1.09)
1999-2002	0.95 (0.82, 1.09)	0.89 (0.67, 1.18)	0.90 (0.73, 1.11)	1.05 (0.86, 1.28)
2003-2006	0.93 (0.77, 1.14)	0.90 (0.62, 1.31)	0.88 (0.66, 1.18)	1.12 (0.87, 1.44)
2007-2011	1.01 (0.78, 1.29)	0.97 (0.60, 1.55)	0.91 (0.62, 1.33)	1.18 (0.86, 1.63)
Gender				
Male	REF	REF	REF	REF
Female	**1.35 (1.25, 1.45)**	**1.51 (1.32, 1.72)**	1.34 (1.19, 1.51)	1.39 (1.28, 1.51)
Race-Ethnicity				
Non-Hispanic White	REF	REF	REF	REF
Non-Hispanic Black	**1.30 (1.21, 1.40)**	1.05 (0.94, 1.17)	**1.69 (1.57, 1.82)**	**0.84 (0.80, 0.90)**
Non-Hispanic Other	**0.38 (0.35, 0.41)**	**0.52 (0.39, 0.71)**	**0.52 (0.39, 0.70)**	**0.45 (0.33, 0.60)**

Hispanic	**0.77 (0.73, 0.82)**	**0.75 (0.65, 0.87)**	0.81 (0.61, 1.06)	**0.73 (0.61, 0.88)**
Cancer Diagnosis				
Prostate	REF	REF	REF	REF
Breast	**1.15 (1.05, 1.25)**	1.01 (0.87, 1.18)	1.13 (0.99, 1.29)	1.07 (0.97, 1.18)
Colorectal	**1.14 (1.06, 1.23)**	1.09 (0.96, 1.25)	1.06 (0.95, 1.19)	**1.10 (1.01, 1.19)**
Lung	**1.72 (1.56, 1.89)**	**1.48 (1.26, 1.74)**	**1.44 (1.24, 1.67)**	**1.58 (1.43, 1.74)**
Original Reason for Entitlement				
Age Related	REF	REF	REF	REF
Non-Age Related	**2.63 (2.51, 2.76)**	**2.45 (2.24, 2.67)**	**2.16 (2.00, 2.32)**	**2.48 (2.36, 2.62)**
Urban-Rural Status				
Metropolis	REF	REF	REF	REF
Urban-Rural	**1.26 (1.19, 1.32)**	1.12 (0.95, 1.31)	0.97 (0.91, 1.03)	**1.34 (1.28, 1.40)**
Medicaid-Eligible	**1.85 (1.78, 1.93)**	**1.80 (1.67, 1.93)**	**2.00 (1.89, 2.12)**	**1.79 (1.72, 1.88)**
Charlson≥1	**1.21 (1.18, 1.23)**	**1.33 (1.26, 1.40)**	**1.27 (1.22, 1.32)**	**1.22 (1.18, 1.25)**
Depressive Disorder	**1.20 (1.17, 1.24)**	**1.19 (1.12, 1.26)**	**1.19 (1.13, 1.24)**	**1.14 (1.10, 1.18)**
Anxiety Disorder	**1.11 (1.08, 1.15)**	**1.18 (1.12, 1.25)**	**1.12 (1.07, 1.17)**	**1.22 (1.18, 1.26)**
Alcohol Use Disorder	**1.11 (1.04, 1.19)**	0.94 (0.81, 1.10)	0.98 (0.86, 1.11)	0.97 (0.87, 1.07)
Drug Use Disorder	**1.49 (1.39, 1.59)**	**1.69 (1.47, 1.96)**	**1.38 (1.24, 1.54)**	**1.56 (1.43, 1.70)**
Opioid Naïve	**0.25 (0.25, 0.26)**	**0.17 (0.16, 0.18)**	**0.26 (0.25, 0.27)**	**0.30 (0.29, 0.31)**

Note: **Bolded** values indicate statistical significance at level of $p<0.05$.

Table 2.4. Adjusted Odd Ratios (aOR) and 95% Confidence Intervals (CI) of Receipt of Long-Term Opioid Therapy Stratified by U.S. Region and Prior Opioid Use

Opioid Naïve Subgroup				
	West	**Northeast**	**Midwest**	**South**
Calendar Year	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
2008	0.90 (0.69, 1.16)	0.80 (0.51, 1.25)	1.13 (0.80, 1.60)	1.18 (0.84, 1.66)
2009	0.93 (0.74, 1.16)	1.09 (0.76, 1.57)	1.13 (0.84, 1.54)	1.11 (0.83, 1.48)
2010	1.01 (0.83, 1.23)	0.92 (0.67, 1.27)	1.26 (0.96, 1.65)	0.88 (0.68, 1.15)
2011	1.12 (0.94, 1.34)	1.08 (0.82, 1.42)	**1.61 (1.27, 2.04)**	1.22 (0.98, 1.52)
2012	1.16 (0.98, 1.36)	1.13 (0.88, 1.45)	1.19 (0.93, 1.50)	0.94 (0.76, 1.15)
2013	REF	REF	REF	REF
2014	1.02 (0.88, 1.20)	0.88 (0.69, 1.12)	1.18 (0.95, 1.47)	**0.78 (0.64, 0.94)**
2015	0.92 (0.78, 1.09)	0.83 (0.64, 1.07)	0.80 (0.62, 1.02)	**0.58 (0.47, 0.71)**
2016	0.85 (0.71, 1.02)	**0.71 (0.53, 0.94)**	**0.63 (0.48, 0.82)**	**0.57 (0.46, 0.71)**
Opioid Non-Naïve Subgroup				
	West	**Northeast**	**Midwest**	**South**
Calendar Year	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
2008	**0.87 (0.79, 0.97)**	1.03 (0.86, 1.25)	0.90 (0.77, 1.06)	**0.86 (0.75, 0.98)**
2009	0.95 (0.87, 1.03)	0.99 (0.85, 1.16)	0.96 (0.84, 1.10)	0.95 (0.86, 1.06)
2010	1.00 (0.94, 1.07)	1.08 (0.95, 1.23)	1.02 (0.92, 1.14)	0.98 (0.90, 1.08)
2011	1.01 (0.96, 1.07)	1.06 (0.96, 1.17)	**1.12 (1.03, 1.22)**	1.04 (0.97, 1.11)
2012	0.96 (0.92, 1.00)	0.99 (0.92, 1.06)	1.03 (0.97, 1.10)	1.00 (0.95, 1.05)
2013	REF	REF	REF	REF
2014	0.98 (0.95, 1.02)	0.95 (0.89, 1.02)	0.97 (0.91, 1.03)	0.97 (0.92, 1.01)
2015	**0.91 (0.86, 0.95)**	0.94 (0.86, 1.02)	**0.92 (0.86, 1.00)**	**0.90 (0.85, 0.96)**
2016	**0.87 (0.82, 0.92)**	**0.87 (0.78, 0.97)**	0.94 (0.85, 1.03)	**0.88 (0.82, 0.95)**

Note: Models also adjusted for Years Post-Cancer Diagnosis, Age, Diagnosis Cohort, Gender, Race and Ethnicity, Cancer Diagnosis, Original Reason for Entitlement, Urban-Rural Status, Medicaid-Eligibility, Charlson Comorbidity ≥1, Depressive Disorder, Anxiety Disorder, Alcohol Use Disorder, Drug Use Disorder. Bolded values indicate statistical significance at level $p < 0.05$.

Table 2.5. Multivariable Sensitivity Analysis Estimating the Adjusted Odd Ratios (aOR) and 95% Confidence Intervals (CI) of Receipt of Long-Term Opioid Therapy Stratified by U.S. Region and Prior Opioid Use in Persons with a Full Year of Observation

Opioid Naïve Subgroup				
	West	**Northeast**	**Midwest**	**South**
Calendar Year	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
2008	0.89 (0.68, 1.16)	0.83 (0.53, 1.31)	1.05 (0.73, 1.51)	1.24 (0.87, 1.76)
2009	0.94 (0.74, 1.18)	1.09 (0.76, 1.59)	1.11 (0.81, 1.52)	1.16 (0.87, 1.56)
2010	1.00 (0.81, 1.22)	0.90 (0.65, 1.26)	1.25 (0.94, 1.65)	0.88 (0.67, 1.16)
2011	1.13 (0.94, 1.35)	1.08 (0.82, 1.43)	**1.57 (1.23, 2.01)**	1.26 (1.01, 1.58)
2012	1.16 (0.99, 1.38)	1.10 (0.85, 1.42)	1.20 (0.94, 1.54)	0.98 (0.79, 1.21)
2013	REF	REF	REF	REF
2014	1.03 (0.88, 1.21)	0.84 (0.66, 1.08)	1.19 (0.95, 1.50)	**0.77 (0.63, 0.93)**
2015	0.95 (0.80, 1.12)	0.77 (0.59, 1.00)	0.82 (0.63, 1.05)	**0.57 (0.46, 0.70)**
2016	0.86 (0.72, 1.04)	**0.65 (0.49, 0.87)**	**0.65 (0.49, 0.86)**	**0.56 (0.45, 0.70)**
Opioid Non-Naïve Subgroup				
	West	**Northeast**	**Midwest**	**South**
Calendar Year	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
2008	**0.86 (0.78, 0.96)**	1.04 (0.86, 1.26)	0.90 (0.76, 1.07)	**0.86 (0.75, 0.99)**
2009	0.95 (0.87, 1.04)	0.97 (0.83, 1.14)	0.97 (0.84, 1.11)	0.95 (0.85, 1.07)
2010	1.00 (0.93, 1.07)	1.08 (0.95, 1.23)	1.01 (0.90, 1.13)	0.98 (0.89, 1.07)
2011	1.01 (0.95, 1.07)	1.06 (0.96, 1.17)	**1.12 (1.02, 1.22)**	1.05 (0.98, 1.13)
2012	0.96 (0.93, 1.00)	1.00 (0.93, 1.08)	1.03 (0.97, 1.10)	1.00 (0.95, 1.05)
2013	REF	REF	REF	REF
2014	0.98 (0.95, 1.02)	0.96 (0.90, 1.03)	0.98 (0.92, 1.04)	0.96 (0.92, 1.01)
2015	**0.90 (0.86, 0.95)**	0.94 (0.86, 1.03)	0.94 (0.86, 1.01)	**0.90 (0.84, 0.95)**
2016	**0.87 (0.82, 0.93)**	**0.88 (0.79, 0.98)**	0.95 (0.86, 1.05)	**0.88 (0.81, 0.95)**

Note: Models also adjusted for Years Post-Cancer Diagnosis, Age, Diagnosis Cohort, Gender, Race and Ethnicity, Cancer Diagnosis, Original Reason for Entitlement, Urban-Rural Status, Medicaid-Eligibility, Charlson Comorbidity ≥1, Depressive Disorder, Anxiety Disorder, Alcohol Use Disorder, Drug Use Disorder. **Bolded** values indicate statistical significance at level $p < 0.05$.

Table 2.6. Adjusted Odd Ratios (aOR) and 95% Confidence Intervals (CI) of Receipt of Long-Term Opioid Therapy Stratified by U.S. Region and Prior Opioid Use in Colorectal and Lung Cancer Survivors

Opioid Naïve Subgroup				
	West	**Northeast**	**Midwest**	**South**
Calendar Year	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
2008	1.04 (0.60, 1.79)	0.95 (0.38, 2.37)	1.55 (0.78, 3.07)	0.93 (0.45, 1.92)
2009	1.14 (0.69, 1.87)	1.09 (0.49, 2.39)	1.23 (0.66, 2.29)	1.20 (0.67, 2.14)
2010	1.22 (0.79, 1.87)	0.82 (0.41, 1.66)	1.38 (0.79, 2.41)	0.87 (0.51, 1.49)
2011	1.13 (0.76, 1.68)	1.22 (0.69, 2.15)	1.45 (0.86, 2.43)	1.10 (0.70, 1.71)
2012	1.11 (0.76, 1.60)	1.25 (0.75, 2.08)	1.01 (0.60, 1.72)	0.88 (0.58, 1.34)
2013	REF	REF	REF	REF
2014	1.25 (0.88, 1.77)	0.60 (0.35, 1.03)	1.42 (0.90, 2.26)	**0.66 (0.45, 0.97)**
2015	0.91 (0.62, 1.35)	0.75 (0.44, 1.28)	0.86 (0.50, 1.47)	**0.41 (0.26, 0.64)**
2016	0.92 (0.61, 1.40)	0.56 (0.30, 1.03)	0.65 (0.36, 1.20)	**0.54 (0.35, 0.84)**
Opioid Non-Naïve Subgroup				
	West	**Northeast**	**Midwest**	**South**
Calendar Year	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
2008	**0.59 (0.47, 0.74)**	**0.55 (0.35, 0.87)**	**0.64 (0.46, 0.88)**	0.80 (0.62, 1.03)
2009	**0.67 (0.55, 0.80)**	**0.58 (0.40, 0.85)**	**0.67 (0.52, 0.88)**	**0.80 (0.65, 0.98)**
2010	**0.73 (0.63, 0.85)**	**0.67 (0.49, 0.91)**	0.81 (0.65, 1.00)	0.86 (0.73, 1.02)
2011	**0.82 (0.73, 0.92)**	0.82 (0.65, 1.04)	0.97 (0.82, 1.15)	0.99 (0.87, 1.12)
2012	**0.88 (0.81, 0.97)**	**0.82 (0.68, 0.98)**	1.03 (0.90, 1.18)	1.01 (0.92, 1.11)
2013	REF	REF	REF	REF
2014	**1.10 (1.01, 1.20)**	1.11 (0.94, 1.31)	1.03 (0.91, 1.17)	0.98 (0.90, 1.08)
2015	1.11 (1.00, 1.23)	1.14 (0.92, 1.41)	0.99 (0.85, 1.15)	0.92 (0.82, 1.03)
2016	1.09 (0.96, 1.24)	1.25 (0.94, 1.65)	0.99 (0.82, 1.20)	0.95 (0.82, 1.09)

Note: Models also adjusted for Years Post-Cancer Diagnosis, Age, Diagnosis Cohort, Race and Ethnicity Original Reason for Entitlement, Urban-Rural Status, Medicaid-Eligibility, Charlson Comorbidity ≥1, Depressive Disorder, Anxiety Disorder, Alcohol Use Disorder, Drug Use Disorder. Bolded values indicate statistical significance at level of $p<0.05$.

Table 2.7. Adjusted Odd Ratios (aOR) and 95% Confidence Intervals (CI) of Receipt of Long-Term Opioid Therapy Stratified by Cancer Diagnosis

	Breast Cancer Survivors	**Colorectal Cancer Survivors**	**Lung Cancer Survivors**	**Prostate Cancer Survivors**
Calendar Year	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
2008	**0.91 (0.84, 0.99)**	**0.81 (0.71, 0.93)**	1.00 (0.79, 1.27)	**0.85 (0.76, 0.94)**
2009	**0.91 (0.85, 0.98)**	**0.83 (0.74, 0.93)**	1.05 (0.86, 1.27)	**0.84 (0.77, 0.92)**
2010	**0.92 (0.87, 0.97)**	**0.89 (0.81, 0.98)**	1.06 (0.91, 1.24)	**0.89 (0.83, 0.95)**
2011	1.02 (0.98, 1.06)	0.97 (0.90, 1.04)	1.07 (0.95, 1.21)	0.96 (0.91, 1.01)
2012	0.99 (0.96, 1.02)	0.98 (0.93, 1.03)	0.97 (0.89, 1.07)	0.99 (0.95, 1.03)
2013	REF	REF	REF	REF
2014	0.99 (0.96, 1.02)	1.01 (0.96, 1.06)	1.04 (0.96, 1.13)	1.02 (0.98, 1.06)
2015	0.96 (0.92, 0.99)	0.97 (0.91, 1.04)	0.97 (0.87, 1.08)	0.97 (0.93, 1.02)
2016	0.95 (0.90, 1.00)	1.04 (0.96, 1.14)	0.98 (0.85, 1.12)	1.04 (0.98, 1.10)
Years Post-Cancer Diagnosis	1.00 (0.98, 1.01)	0.98 (0.95, 1.00)	0.98 (0.94, 1.02)	0.99 (0.97, 1.01)
Age, years				
66-74	REF	REF	REF	REF
75-84	**1.16 (1.12, 1.20)**	1.02 (0.97, 1.08)	**0.84 (0.77, 0.91)**	0.99 (0.96, 1.03)
≥85	**1.19 (1.16, 1.23)**	1.04 (0.98, 1.09)	**0.85 (0.78, 0.92)**	1.03 (0.99, 1.07)
Cohort				
1991-1994	REF	REF	REF	REF
1995-1998	0.93 (0.85, 1.03)	0.90 (0.76, 1.06)	0.97 (0.69, 1.36)	**0.85 (0.74, 0.96)**
1999-2002	1.03 (0.90, 1.18)	0.88 (0.70, 1.11)	0.88 (0.58, 1.34)	0.86 (0.72, 1.02)
2003-2006	1.02 (0.85, 1.23)	0.90 (0.66, 1.22)	0.99 (0.58, 1.69)	0.87 (0.69, 1.10)
2007-2011	1.13 (0.89, 1.44)	0.92 (0.62, 1.37)	1.10 (0.56, 2.14)	0.89 (0.67, 1.19)
Gender				
Male	REF	REF	REF	REF
Female	-	**1.41 (1.33, 1.50)**	**1.31 (1.19, 1.43)**	-
Race-Ethnicity				
Non-Hispanic White	REF	REF	REF	REF
Non-Hispanic Black	1.02 (0.96, 1.09)	1.05 (0.96, 1.15)	1.01 (0.86, 1.18)	**1.26 (1.18, 1.34)**
Non-Hispanic Other	**0.36 (0.32, 0.40)**	**0.31 (0.26, 0.37)**	**0.36 (0.26, 0.48)**	**0.50 (0.44, 0.56)**
Hispanic	**0.75 (0.69, 0.81)**	**0.74 (0.65, 0.83)**	0.82 (0.66, 1.03)	**0.79 (0.73, 0.86)**
Census Region				
West		REF	REF	
Northeast	**0.61 (0.58, 0.64)**	**0.63 (0.58, 0.69)**	**0.60 (0.53, 0.69)**	**0.62 (0.58, 0.67)**
Midwest	**1.11 (1.06, 1.16)**	1.07 (0.98, 1.16)	0.93 (0.81, 1.07)	**1.15 (1.09, 1.22)**
South	**1.06 (1.02, 1.11)**	1.05 (0.98, 1.12)	1.00 (0.90, 1.12)	1.05 (1.00, 1.11)
Original Reason for Entitlement				
Age Related	REF	REF	REF	REF
Non-Age Related	**2.57 (2.46, 2.69)**	**2.13 (1.98, 2.29)**	**2.12 (1.91, 2.35)**	**2.73 (2.59, 2.88)**

Urban-Rural Status				
Metropolis	REF	REF	REF	REF
Urban-Rural	**1.16 (1.11, 1.21)**	**1.16 (1.08, 1.24)**	**1.30 (1.17, 1.45)**	**1.26 (1.20, 1.33)**
Medicaid-Eligible	**1.72 (1.66, 1.78)**	**1.84 (1.74, 1.94)**	**1.91 (1.74, 2.09)**	**2.09 (1.99, 2.19)**
Charlson≥1	**1.22 (1.19, 1.24)**	**1.21 (1.16, 1.26)**	**1.24 (1.14, 1.35)**	**1.26 (1.22, 1.29)**
Depressive Disorder	**1.19 (1.16, 1.22)**	**1.11 (1.06, 1.16)**	1.06 (0.99, 1.14)	**1.20 (1.15, 1.25)**
Anxiety Disorder	**1.12 (1.10, 1.15)**	**1.13 (1.08, 1.19)**	**1.26 (1.17, 1.35)**	**1.21 (1.16, 1.27)**
Alcohol Use Disorder	0.98 (0.91, 1.06)	1.05 (0.93, 1.18)	1.01 (0.83, 1.22)	1.04 (0.96, 1.12)
Drug Use Disorder	**1.43 (1.34, 1.53)**	**1.60 (1.44, 1.78)**	**1.46 (1.26, 1.69)**	**1.54 (1.41, 1.68)**
Opioid Naïve	**0.29 (0.29, 0.30)**	**0.24 (0.23, 0.24)**	**0.20 (0.19, 0.21)**	**0.25 (0.24, 0.25)**

Chapter 3. Provider Specialty and Long-Term Opioid Therapy Among Older Breast, Colorectal, Lung and Prostate Cancer Survivors

ABSTRACT

Objective: Previous research findings in noncancer populations have shown that opioid prescribing differs across provider specialties, with significant relationship between characteristics of providers and the odds of long-term opioid prescribing (opioid prescription for ≥3 months). However, no research exists on the relationship between provider specialty, type of pain, prior opioid use, and the odds of long-term opioid therapy in long-term cancer survivors (≥5 years post-cancer diagnosis)

Methods: A retrospective cohort study was performed using SEER-Medicare linked datasets. We followed persons aged ≥66 years who lived ≥5 years after a breast, colorectal, lung, or prostate cancer diagnosis from 1/1/2012 to 12/31/2016. Pain conditions experienced from 2012-2016 were identified with ICD-9-CM and ICD-10-CM codes. Outpatient visits from 2012-2016 were identified with relevant evaluation and management codes. Provider specialty was assigned based on greatest number of claims in the Carrier claims file. Generalized estimating equations was used to examine the association between provider specialty visited as an outpatient and receipt of long-term opioid.

Results: Chronic pain was associated with higher odds of receiving long-term opioid therapy among opioid naïve persons (aOR = 3.22, 95%: 2.73, 3.79) and persons with prior opioid use (opioid non-naïve) (aOR = 3.42, 95% CI: 3.27, 3.58). Cancer pain among opioid non-naïve cancer survivors was associated with lower odds of long-term opioid therapy (aOR = 0.83, 95% CI: 0.80, 0.86). Outpatient visits with a primary care physician, advanced practice provider, physical medicine and rehabilitation provider, and pain management specialist were associated with higher odds of long-term opioid therapy, regardless of previous opioid use. Among persons who previously used prescription opioids, outpatient care provided by a urologist (aOR = 0.90, 95%

CI: 0.87, 0.93) or medical oncologist (aOR = 0.95, 95% CI: 0.92, 0.99) was associated with lower odds of long-term opioid therapy, but this association was not observed in opioid naïve persons. **Conclusion:** Noncancer pain conditions and care provided by noncancer providers was associated with increased likelihood of being prescribed long-term opioid therapy, but cancer pain and cancer specialists were not. Providers should adhere to opioid prescribing guidelines and use risk reduction strategies with patients on opioid therapy.

INTRODUCTION

From 1999 to 2016, over 350,000 persons in the United States have died from an opioid overdose.[24] Prescription opioid sales and opioid overdose deaths, both, increased four-fold during the first wave of the opioid epidemic, indicating that the opioid epidemic may be driven by the distribution of prescription opioids.[48] Even though the prescription opioid dispensing rate has declined, the mortality rate due to natural and semi-synthetic opioids in 2019 is 3.5 times higher than the mortality rate in 1999.[56,85]

Patient level characteristics have largely been the focus of high-risk patterns of opioid prescribing – such as high dose or long-term opioid therapy – despite the development of conceptual frameworks that hypothesize opioid prescribing patterns are likely influenced by interactions between patients, providers, and organizational environments.[100] Deepmala and colleagues (2012) conducted a systematic review examining which provider's characteristics are associated with analgesic prescribing and identified that a provider's demographics, years of experience, and designated specialty were influential.[101] Variation in opioid prescribing across different specialties has been well documented. Overall, primary care physicians (PCP) are the largest opioid prescribers with respect to total dispensed prescriptions, but pain management and physical medicine and rehabilitation specialists have the highest opioid prescribing rate per number of providers.[24,103-105,110,159-162] Hematologists and oncologists prescribe a similar morphine milligram equivalents of opioids per prescription[110] but have, on average, a lower prescribing rate

per provider than pain management and physical medicine and rehabilitation specialists.[111] In recent years, opioid prescribing by most physician specialties have declined but prescribing has increased among specialties that provide care for chronic pain.[104,105,111]

Long-term opioid therapy is common among persons who have lived ≥5 years after a cancer diagnosis.[99] Cancer related pain in long-term cancer survivors can arise from a previous cancer treatment regimen (surgery, radiation, chemotherapy, hormonal treatment, biologics, hematopoietic stem-cell transplantation).[135,176] Furthermore, cancer related pain can last for years after diagnosis and interact with noncancer pain conditions.[135,177] Identifying the etiology of pain in long-term cancer survivors is complicated because they can have cancer-related and noncancer related pain, and the presence of both categories of pain may impact cancer survivors quality of life. Currently, the prevalence of chronic pain that interferes with or limits personal or work activities in cancer survivors is estimated to be about 16%, which is twice as high as the prevalence in the general population 18 years and older.[61,163] Given that cancer survivors receive multidisciplinary care that changes over time,[106] understanding the association between provider specialty and receipt of long-term opioid therapy can inform guidelines on how to coordinate pain management for cancer survivors. In the present study we examine the potential relationship provider specialties by cancer survivors and the potential association between specialty and receipt of long-term opioid therapy.

METHODS

We performed a serial cross-sectional study using Surveillance, Epidemiology, and End Results (SEER) registry datasets linked with Medicare administrative claims data of persons diagnosed with breast, colorectal, lung, or prostate cancer. The University of Texas Medical Branch Institutional Review Board (IRB) approved this study.

Study Cohort

Descriptions of this cohort with inclusion and exclusion criteria have been previously described in Specific Aim 1. Annual cohorts (2012-2016) were created for each year and persons who lived 5 or more years after a cancer diagnosis were followed from January 1 to December 31 of a given year. We chose to focus on the years 2012 and later because this was the period in which there was a decreasing trend in opioid prescribing. The index date for each year of study was January 1, 201X. Persons were included in the study if they were ≥66 years of age on the index date and enrolled in Medicare Parts A, B, or D for 12 months before and after the index date for each calendar year (2012-2016). Persons who died or received hospice care during a given year were required to be alive on April 1 to meet the minimum number of days (90) for the ascertainment of the outcome (long-term opioid therapy). Persons were excluded from the analysis if they were: 1) had not been diagnosed for at least 5 years on the index date, 2) had noncontinuous Part A, B, and D enrollment or was enrolled in a Health Maintenance Organization (HMO) in the 12 months prior to the index date of a given year, or 3) had a claim for hospice care, were deceased, or had received cancer treatment (**Table 2.1**) in the 12 months prior to the index date of a given year.

Long-Term Opioid Therapy

Opioid prescriptions were identified from the Prescription Drug Event file with National Drug Codes provided by RedBook. We calculated the cumulative number of calendar days a person had been prescribed an opioid from January 1 to December 31 of a given year. The maximum number of days a person could have been prescribed an opioid in a year was 366 days, accounting for leap year. Persons who possessed an opioid prescription for ≥90 calendar days were classified as having received long-term opioid therapy.

Pain Conditions, Provider Specialty, and Covariates

Pain conditions experienced during each calendar year of the study (2012-2016) were identified from any diagnostic position in the Medicare Provider Analysis and Review (MEDPAR), Outpatient Standard Analytical File (OUTSAF), and Carrier claims files with ICD-9-CM and ICD-10-CM codes based on previous studies.[78,164] There were 12 classes of pain conditions included in this study: 1) chronic pain, 2) abdominal or chest pain, 3) cancer pain, 4) muscle pain, 5) fractures, 6) visceral pain, 7) wound, 8) headache, 9) joint pain, 10) back pain, 11) nerve pain, 12) other pain conditions.

We identified all providers in a calendar year who provided outpatient care to each cancer survivor from 2012 to 2016 via a provider's National Provider Identifier (NPI). NPI is a unique identification code for each healthcare provider that filed an administrative claim for reimbursement to Centers for Medicare and Medicaid Services. Outpatient visits were identified by using outpatient evaluation-and-management and billing codes (CPT codes 99201-99205, 99211-99215, and 99241-99245) from the OUTSAF and Carrier Claims Medicare Datasets. Attending physicians for each outpatient visit were identified by an NPI number.

Each provider was assigned at least 1 specialty code based on information in the Carrier Claims dataset. All specialty taxonomy codes for each NPI were identified from all Carrier Claims filed from 2012-2016.[165] For each NPI, the specialty taxonomy code with the greatest number of claims filed per year was assigned as the provider's specialty. NPI numbers that were associated with the same number of claims for 2 or more specialties had all specialties with an equal number of claims assigned to them.

We created 13 provider categories based on groupings provided by the literature.[104] These groups were as follows: 1) Primary Care Physicians (family practice, geriatric medicine, general practice, internal medicine), 2) Hematology-Oncology (hematology, hematology-oncology, medical oncology, gynecologist/oncologist, radiation oncology, surgical oncology), 3) Urologist, 4) Advanced Practice Provider (nurse practitioner, physician assistant), 5) Pain Management

(anesthesiology, interventional pain management, pain management), 6) General Surgery, 7) Neurology, 8) Orthopedic Surgery, 9) Physical Medicine and Rehabilitation (physical medicine and rehabilitation, sports medicine, chiropractor), 10) Rheumatology, 11) Emergency Medicine, 12) Other Surgical Specialties (cardiac surgery, colorectal surgery, hand surgery, maxillofacial surgery, neurosurgery, plastic and reconstructive surgery, thoracic surgery, vascular surgery), and 13) Other Non-Surgical Specialties (Allergy/immunology, Diagnostic radiology, Hospice and Palliative Care, Infectious disease, Interventional radiology, Nephrology, Nuclear medicine, Obstetrics/gynecology, Opthalmology, Osteopathic manipulative therapy, Otolaryngology, Pathology, Pediatric medicine, Peripheral vascular disease, Preventive medicine, Sleep medicine, Podiatry).

Patient gender, race-ethnicity, year of diagnosis, original reason for Medicare entitlement, and cancer diagnosis were non-time varying covariates. Time varying covariates were age, census-region, urban-rural location, Medicaid eligibility, comorbid conditions, and opioid naïve status. We classified comorbid conditions as Charlson comorbidity score ≥ 1, depressive disorder, anxiety disorder, alcohol use disorder, and drug use disorder.[132,136] Opioid naïve persons did not receive any prescription opioid in the previous 12 months prior to a given calendar year, while opioid non-naïve individuals possessed an opioid prescription for 1 or more days in the 12 months prior to a calendar year.

Statistical Analysis

Descriptive analysis was conducted by calculating the frequency and percentage of cancer survivors who were diagnosed with each of the 12 pain conditions and who had ≥1 outpatient visit to each of the 13 provider specialties from 2012-2016 stratified by previous opioid use. We also calculated the prevalence of receipt of long-term opioid therapy (per 100 person-years) among cancer survivors who had at least 1 visit to each provider specialty group from 2012-2016, stratified by previous opioid use.

Multivariable logistic regression modelling was conducted to examine the association between each pain condition diagnosed and the receipt of long-term opioid therapy in 2016, stratified by previous opioid use. A cross-sectional analysis using only information from 2016 was chosen because we found that the ICD-9-CM to ICD-10-CM change in October 2015 was associated with changes in the number of claims filed for some pain conditions. Next, we performed a longitudinal analysis using generalized estimating equations with a binomial distribution and logit link function to examine the relationship between providers specialties visited and receipt of long-term opioid therapy. We selected an autoregressive (AR1) and independent correlation structure to account for repeated measures in opioid naïve and non-naïve persons, respectively. We did not perform hierarchical modelling – nesting of patients in providers – because most providers in our study only saw 1 or 2 cancer survivors in each year (**Table 3.1**). A statistical interaction testing opioid naïve status and pain conditions and provider specialties was significant ($p<0.05$) for some pain conditions and specialties, therefore all descriptive analyses and multivariable analyses with pain conditions and provider specialties were stratified by history of previous opioid use. All statistical tests were two-sided with $\alpha = 0.05$. All data management steps and analyses were performed with SAS version 9.4 (SAS Inc, Cary, NC).

RESULTS

Sample characteristics have been previously described in Aim 1 (**Table 2.2**). In total, there were 305,560 unique individuals who contributed person-time to the study. Overall, the rate of long-term opioid therapy declined from 10.0 (2012) to 8.5 per 100 person-years (2016, data not shown, as reported in Specific Aim 1). The decline in the rate of long-term opioid therapy, however, differed by previous opioid use, such that the decrease in the rate of long-term opioid therapy was smaller among opioid naïve (0.9 to 0.6 per 100 person-years) than non-naïve (28.7 to 26.6 per 100 person-years) cancer survivors. There were several trends in the prevalence of pain conditions from 2012 to 2016 that were similar between opioid naïve and non-naïve cancer survivors (**figures not shown**). The percentage of individuals who were diagnosed with cancer or

back pain remained constant from 2012-2016. However, the percentage of individuals diagnosed with the following pain conditions declined sharply from 2015 to 2016: 1) joint (54.2% to 31.2%), 2) muscle (41.6% to 18.0%), 3) visceral (22.4% to 9.8%), and 4) nerve (16.0% to 10.8%). The percentage of cancer survivors, overall, who were diagnosed with chronic pain increased from 8.6% (2012) to 11.8% (2016) and those who were diagnosed with a fracture increased from 8.6% (2014) to 12.6% (2016). We observed the number of diagnoses declined substantially from September to October 2015 for joint, muscle, nerve, visceral, and wound pain conditions (**figures not shown**). Due to concerns about the effect of changes in administrative claims coding from ICD-9-CM to ICD-10-CM on the prevalence of pain conditions, we focused only on pain conditions experienced in 2016.

The percentage of cancer survivors diagnosed with each of the 12 pain conditions in opioid naïve and non-naïve persons in 2016 is shown in **Table 3.2**. Opioid non-naïve individuals had a higher prevalence of all 12 pain conditions than opioid naïve persons. However, the smallest absolute difference in the prevalence of a pain condition between opioid naïve and non-naïve cancer survivors was for cancer pain (0.7%).

In a cross-sectional analysis of pain conditions diagnosed in 2016 and receipt of long-term opioid therapy controlling for other person-level demographics, cancer diagnosis, year of cancer diagnosis, original reason for Medicare eligibility, Medicaid eligibility, geographical region, urban-rural status, and comorbidities, cancer survivors diagnosed with chronic, joint, back, or nerve pain had higher odds of receiving long-term opioid therapy than persons not diagnosed with each of these conditions (**Table 3.3**). The relationships between chronic, joint, back, or nerve pain and long-term opioid therapy were similar in the opioid naïve and non-naïve cohorts.

The relationships of some pain conditions with long-term opioid therapy varied based on history of opioid use. Among opioid naïve individuals, being diagnosed with cancer pain (aOR = 0.93, 95% CI: 0.81, 1.07) was not associated with receipt of long-term opioid therapy but cancer survivors who used prescription opioids in the previous year and were diagnosed with cancer pain were significantly less likely to receive long-term opioid therapy (aOR = 0.83, 95% CI: 0.80, 0.86).

Persons diagnosed with cancer pain were primarily comprised of persons who were diagnosed with prostate cancer or a locally staged tumor (**Tables 3.4 and 3.5**). Moreover, the direction of the relationship between some pain conditions and long-term opioid therapy were different between opioid naïve and non-naïve individuals. For example, the odds of receiving long-term opioid therapy were 60% higher among opioid naïve cancer survivors with a fracture compared to those without a fracture (aOR = 1.60, 95% CI: 1.36, 1.88) but the odds of long-term opioid therapy were 9% lower among non-naïve cancer survivors with a fracture (aOR = 0.91, 95% CI: 0.87, 0.96).

Tables 3.6 and 3.7 display the percentage of opioid naïve and non-naïve cancer survivors who had at least 1 outpatient visit each provider specialty within each calendar year. In general, a higher percentage of opioid non-naïve cancer survivors had a visit to all provider specialties than opioid naïve persons. Most cancer survivors, regardless of previous opioid use, visited a primary care physician (PCP) each year of the study. There was a small increase in the percentage of cancer survivors who visited a PCP from 2012 to 2016 in the opioid naïve (76.8% to 77.9%) and opioid non-naïve (80.9% to 82.2%) persons. However, a similar percentage of opioid naïve and non-naïve cancer survivors visited a hematologist-oncologist or urologist. In 2016, 19.0% of opioid naïve persons visited an oncologist compared to 20.2% of non-naïve persons. In 2016, 21.0% of opioid naïve cancer survivors 23.1% of non-naïve cancer survivors who visited a urologist. Other specialties that were visited each year similarly between opioid naïve and non-naïve persons included emergency medicine, general surgery, neurology, and rheumatology. Regardless of previous opioid use, cancer survivors increasingly received care from an advance practice provider. The increase in percentage of cancer survivors who received outpatient care from an advanced practice provider from 2012 to 2016 was larger in opioid non-naïve (13.4%) than naïve (10.8%) cancer survivors. There were some notable differences in provider specialties visited by opioid naïve and non-naïve cancer survivors. The percentage of opioid naïve cancer survivors who visited a pain management specialist increased slightly from 1.4% (2012) to 1.7% (2016) but non-naïve cancer survivors were increasingly likely to visit a pain management specialist with 6.5% of

individuals cared for by a pain specialist in 2012 and 8.1% in 2016. Orthopedic surgeons were visited more often by opioid non-naïve (26.5%) than naïve (14.7%) cancer survivors in 2016.

Tables 3.8 and 3.9 present the rate of long-term opioid therapy by provider specialties visited within a calendar year within opioid naïve and non-naïve persons, respectively. The lowest rates of long-term opioid therapy throughout the study for opioid naïve cancer survivors was observed in persons who had ≥1 outpatient visit with a PCP, urologist, hematologist-oncologist, and other non-surgical specialties. The rate of long-term opioid therapy was lowest among cancer survivors who used opioids in the previous year and had ≥1 outpatient visit with a urologist. Cancer survivors who visited pain management providers had the highest rates of long-term opioid therapy from 2012 to 2016, regardless of previous opioid use. The rate of long-term opioid therapy among cancer survivors who visited a pain management specialist in 2016 was 5.3 per 100 person-years among opioid naïve persons and was 59.5 per 100 persons years among persons who received prescription opioids in the previous year.

Table 3.10 presents the odds of long-term opioid therapy associated with each provider specialty after adjusting for patient level characteristics. Opioid naïve and non-naive persons who visited a PCP (Naïve: aOR = 1.16, 95% CI: 1.06, 1.28; Non-Naïve: aOR = 1.15, 95% CI: 1.11, 1.19), advance practice provider (Naïve: aOR = 1.13, 95% CI: 1.05, 1.22; Non-Naïve: aOR = 1.13, 95% CI: 1.10, 1.16), pain management specialist (Naïve: aOR = 6.60, 95% CI: 5.94, 7.34; Non-Naïve: aOR = 4.54, 95% CI: 4.36, 4.73), orthopedic surgeon (Naïve: aOR = 2.17, 95% CI: 2.01, 2.31; Non-Naïve: aOR = 1.09, 95% CI: 1.06, 1.11), other surgical specialty (Naïve: aOR = 1.43, 95% CI: 1.30, 1.57; Non-Naïve: aOR = 1.05, 95% CI: 1.02, 1.09), PMR/sports medicine/chiropractor (Naïve: aOR = 2.04, 95% CI: 1.83, 2.28; Non-Naïve: aOR = 1.72, 95% CI: 1.65, 1.80), and rheumatologist (Naïve: aOR = 1.93, 95% CI: 1.69, 2.20; Non-Naïve: aOR = 1.83, 95% CI: 1.74, 1.93) had significantly higher odds of receiving long-term opioid therapy than persons who did not visit these specialists. Opioid naïve cancer survivors who visited a hematologist-oncologist or a urologist were not significantly more likely to receive long-term opioid therapy. Cancer survivors who used opioids in the previous year and who were cared for

by either hematologist-oncologist or urologist were significantly less likely to receive long-term opioid therapy (Hematologist-Oncologist: aOR = 0.95, 95% CI: 0.92, 0.99; Urologist: aOR = 0.90, 95% CI: 0.87, 0.93).

DISCUSSION

We found that cancer survivors diagnosed with noncancer pain conditions – such as chronic pain, and joint or back pain – and who received care from noncancer provider specialties were more likely to receive long-term opioid therapy regardless of previous opioid use. Persons who were diagnosed with cancer pain or received care from hematologists-oncologists or urologists, however, were not significantly more likely to receive long-term opioid therapy.

Long-term cancer survivors have complex medical histories and are managed by a multidisciplinary group of providers.[106,109] Pollack et al. (2009) found that most persons who lived ≥5 years after a cancer diagnosis had received care from a primary care physician (75%) but some persons also received treatment from cancer (33%) or cancer-related specialists (50%).[106] We found that greater than 75% of cancer survivors from 2012-2016 were evaluated by a PCP at least once and about 20% of cancer survivors received care from a cancer specialist. We also identified that the cancer survivors increasingly received care from advanced practice providers which is consistent with trends in the general Medicare population have been increasingly cared for by nurse practitioners.[166-169] One explanation for the discrepancies in the percentage of cancer survivors who visited cancer specialists between the present study and a previous could be due to methodological differences in the assignment of a provider's specialty.[106,170] Pollack et al. (2009) assigned provider specialty using information from the American Medical Association Physician Masterfile and we used the available specialty codes in the Carrier claims file. In general, the American Medical Association Physician Masterfile and the specialty codes in the Carrier Claims are concordant across most provider specialty groups except internal medicine, as the American Medical Association Physician Masterfile provides more information about medical sub-specialties than the Carrier Claims dataset.[170]

Historically, PCPs have written approximately 50% of total dispensed opioid prescriptions.[104,105] Recently, there have been notable declines in opioid prescribing by internal medicine and family medicine providers suggesting policy and educational reforms may have altered prescriber behavior.[104] Romman et al. (2020) found evidence that PCPs may be shifting opioid prescribing to pain management and physical medicine and rehabilitation specialists.[104] We observed a small increase in opioid non-naïve cancer survivors receiving outpatient treatment from a pain management specialist but the reason for this increase is unclear. In 2017, advanced practice registered nurses and physician assistants were found to have written 11% and 7% of total opioid prescriptions dispensed to Part D enrollees.[105] Advanced practice providers are less likely to prescribe long-term opioid therapy compared to physicians, but their opioid prescribing rate is increasing, and, as a specialty, they are more likely to prescribe high-dose opioid therapy.[103-105,171,172]

Cancer survivors who were diagnosed with cancer pain or visited a cancer related specialist were not more likely to receive long-term opioid therapy. Approximately 50% of cancer survivors in our study were diagnosed with cancer pain each year of the study. Cancer pain frequently co-presents with noncancer chronic pain in cancer survivors that may result in frequent opioid use.[173] Therefore, it is notable that being diagnosed with cancer pain or visiting a cancer related specialist was not associated with long-term opioid prescribing. One reason is that the management of pain in long-term cancer survivors who are not receiving cancer treatment may be managed predominately by noncancer providers, specifically, PCPs and pain management specialists. We found that cancer survivors diagnosed with cancer pain were comprised mostly of persons diagnosed with prostate cancer, which have lower opioid utilization than other cancer survivors.[99] One systematic review found the prevalence of pain in prostate cancer survivors was lower than head and neck, breast, and lung cancer survivors.[134] However, the study pooled prevalence rates across survivorship – mixing actively treated and long-term cancer survivors – which prevented a direct comparison between long-term cancer survivors. Further studies comparing the prevalence

of cancer related pain across different cancer diagnosis among long-term cancer survivors are needed.

Chronic pain was found to be an influential factor on long-term opioid therapy among opioid naïve individuals. Initial duration and dose of an opioid prescription are important predictors of future long-term use.[69,72,93] Long-term opioid therapy has not been found to be efficacious for improving pain, function, or quality of life.[65] Due to safety concerns with prescribing opioids for chronic pain, opioids should be prescribed by a single provider and used sparingly after all nonpharmacological and nonopioid therapies have been exhausted. We recommend clinicians and organizations adopt risk mitigation strategies, including, prescription drug monitoring program review, screening for opioid misuse and use disorder, and avoiding concurrent benzodiazepine prescribing. Urine drug testing is recommended as a screening tool for patient adherence to prescribed long-term opioid therapy, but it is infrequently used among older adults.[65,174] Organizations and providers who use urine drug screening need to adopt procedures that do not result in drug testing being applied disproportionately to racial and ethnic minorities and adults earning low incomes.[175]

This study has several limitations. The results and conclusions of this study are not generalizable to persons diagnosed with cancers that were not included in our study, cancer survivors that were not diagnosed in a SEER capture area, or cancer survivors with incomplete Part A, B, and D enrollment. Opioid prescriptions included in this study were dispensed to Medicare beneficiaries through outpatient pharmacy services. Opioids that were administered inpatient or obtained through other sources were not included. The outcome, long-term opioid therapy, assumes that patients took the prescription opioid the number of days supplied. Most importantly, the present study did not examine opioid prescribers. Instead, we addressed the relationship between provider specialties seen outpatient by cancer survivors and the receipt of long-term opioid therapy. Specific information on opioid prescribers for persons diagnosed with cancer was not currently available for the SEER-Medicare Prescription Drug Event file. While our study included pain conditions that patients were diagnosed with, we do not have any patient

reported information about pain severity or quality of life. These measures may be informative because providers may continue opioid therapy for patients with improvement in pain and functioning.

In conclusion, we identified that noncancer pain conditions and receiving care from noncancer providers are associated with receipt of long-term opioid therapy among cancer survivors. Clinicians prescribing opioids to cancer survivors without a history of opioid use should strongly adhere to opioid prescribing guidelines for chronic pain and limit opioid prescribing for acute pain conditions to less than 7 days to prevent the development of long-term opioid use. Further research is needed to determine if cancer survivors who receive opioids from high-prescribing specialties are at an increased risk for experiencing opioid-related adverse events.

Appendix C.

Table 3.1. The Distribution of Number of Cancer Survivors Assigned to Each Provider During Each Calendar Year

Year	Minimum	Q1	Median	Q3	Max
2012	1	1	3	9	432
2013	1	1	2	8	427
2014	1	1	2	8	462
2015	1	1	2	7	422
2016	1	1	2	7	419

Table 3.2. The Number and Percentage of Cancer Survivors Diagnosed with Each Pain Condition in 2016 Stratified by Previous Opioid Use

Pain Conditions	Opioid Naïve N(%)	Opioid Non-Naïve N(%)
Chronic Pain	11525 (7.1)	15827 (22.3)
Abdominal or Chest Pain	38695 (24.0)	25387 (35.8)
Cancer Pain	81688 (50.6)	36347 (51.3)
Musculoskeletal Pain	24608 (15.2)	17302 (24.4)
Fracture	17075 (10.6)	12134 (17.1)
Visceral Pain	13520 (8.4)	9153 (12.9)
Wound pain	8907 (5.5)	5951 (8.4)
Headache	15346 (9.5)	10664 (15.0)
Joint Pain	41704 (25.8)	30837 (43.5)
Back Pain	43247 (26.8)	34610 (48.8)
Nerve Pain	13592 (8.4)	11521 (16.3)
Other pain	23761 (14.7)	14395 (20.3)

Table 3.3. The Adjusted Odds Ratios (aOR) and 95% Confidence Intervals (CI) of Long-Term Opioid Therapy by Pain Conditions and Patient-Level Characteristics in Cancer Survivors Stratified by Previous Opioid Use

Variable	Opioid Naïve Model	Opioid Non-Naïve Model
Specialties		
Chronic Pain	**3.22 (2.73, 3.79)**	**3.42 (3.27, 3.58)**
Abdominal or Chest Pain	**1.33 (1.15, 1.54)**	0.98 (0.94, 1.02)
Cancer Pain	0.93 (0.81, 1.07)	**0.83 (0.80, 0.86)**
Musculoskeletal Pain	**0.82 (0.70, 0.97)**	**0.70 (0.67, 0.73)**
Fracture	**1.60 (1.36, 1.88)**	**0.91 (0.87, 0.96)**
Visceral Pain	1.00 (0.82, 1.22)	**0.87 (0.82, 0.92)**
Wound pain	**1.28 (1.04, 1.58)**	0.98 (0.92, 1.05)
Headache	0.96 (0.80, 1.16)	**0.88 (0.84, 0.93)**
Joint Pain	**2.51 (2.17, 2.91)**	**1.74 (1.68, 1.81)**
Back Pain	**3.16 (2.70, 3.70)**	**1.97 (1.90, 2.06)**
Nerve Pain	**1.51 (1.28, 1.78)**	**1.21 (1.16, 1.28)**
Other pain	**1.37 (1.17, 1.60)**	**1.07 (1.02, 1.12)**
Age (ref = 65-74 years)		
75-84	0.95 (0.80, 1.13)	**1.07 (1.03, 1.12)**
85+	1.10 (0.92, 1.31)	**1.20 (1.14, 1.26)**
Female (ref = Male)	0.89 (0.66, 1.20)	1.06 (0.97, 1.16)
Race-Ethnicity (ref = NH-White)		
Hispanic	0.93 (0.68, 1.25)	**0.82 (0.75, 0.90)**
Non-Hispanic Black	0.91 (0.69, 1.19)	1.04 (0.97, 1.11)
Non-Hispanic Other	**0.64 (0.46, 0.88)**	**0.54 (0.48, 0.60)**
Cohort (ref = 1991-1994)		
1995-1998	1.11 (0.77, 1.60)	1.02 (0.91, 1.13)
1999-2002	0.95 (0.68, 1.31)	1.08 (0.98, 1.18)
2003-2006	1.04 (0.76, 1.43)	1.09 (1.00, 1.20)
2007-2011	1.06 (0.77, 1.46)	**1.13 (1.04, 1.24)**
Census-Region (ref = West)		
Northeast	**0.76 (0.63, 0.93)**	**0.77 (0.73, 0.81)**
Midwest	1.12 (0.91, 1.37)	**1.26 (1.19, 1.34)**
South	**1.40 (1.18, 1.67)**	**1.16 (1.10, 1.21)**
Non-Age Original reason for Medicare	**1.34 (1.08, 1.67)**	**1.94 (1.84, 2.05)**
Medicaid Enrollment (ref = No)	**1.69 (1.41, 2.02)**	**1.86 (1.77, 1.96)**
Rural Residence (ref = Urban)	1.20 (0.76, 1.90)	**1.20 (1.06, 1.36)**
Noncancer Charlson > 1	**1.50 (1.26, 1.78)**	**1.15 (1.09, 1.20)**
Depressive Disorder	**1.41 (1.18, 1.69)**	**1.20 (1.14, 1.25)**

Anxiety Disorder	1.00 (0.82, 1.22)	**1.19 (1.14, 1.25)**
Substance Use Disorder	**1.78 (1.06, 2.97)**	**3.02 (2.74, 3.33)**
Alcohol Use Disorder	0.95 (0.59, 1.53)	**0.83 (0.73, 0.94)**
Cancer Diagnosis (ref = Prostate)		
Breast	0.99 (0.71, 1.37)	**1.12 (1.02, 1.24)**
Colorectal	1.11 (0.85, 1.45)	**1.17 (1.08, 1.26)**
Lung	1.16 (0.78, 1.72)	**1.38 (1.24, 1.54)**

Table 3.4. Number and Percentage of Cancer Survivors Diagnosed with an Unknown Stage, Cancer In-Situ, or Local, Regional, and Distant Stage Tumor Stratified by Cancer Pain Diagnosis Status from 2012 to 2016

Calendar Year	Cancer Stage	N(%) with Cancer Pain	N(%) without Cancer Pain
2012	Unknown	8770 (14.1)	15428 (23.7)
	In-Situ	2728 (4.4)	6940 (10.7)
	Local	38367 (61.5)	33789 (51.9)
	Regional	11832 (19.0)	8587 (13.2)
	Distant	667 (1.1)	354 (0.5)
2013	Unknown	8966 (12.0)	15853 (20.7)
	In-Situ	3354 (4.5)	8633 (11.3)
	Local	47304 (63.5)	41325 (53.9)
	Regional	14141 (19.0)	10486 (13.7)
	Distant	756 (1.0)	430 (0.6)
2014	Unknown	9992 (10.8)	17960 (18.7)
	In-Situ	4253 (4.6)	11261 (11.7)
	Local	59865 (64.6)	53035 (55.3)
	Regional	17584 (19.0)	13158 (13.7)
	Distant	928 (1.0)	526 (0.5)
2015	Unknown	10307 (9.9)	17260 (16.7)
	In-Situ	4870 (4.7)	12720 (12.3)
	Local	68214 (65.5)	58301 (56.4)
	Regional	19639 (18.9)	14463 (14.0)
	Distant	1078 (1.0)	567 (0.5)
2016	Unknown	10867 (9.2)	17031 (14.9)
	In-Situ	5512 (4.7)	14709 (12.9)
	Local	78203 (66.3)	65419 (57.2)
	Regional	22246 (18.8)	16518 (14.4)
	Distant	1207 (1.0)	650 (0.6)

Table 3.5. Number and Percentage of Cancer Survivors Diagnosed with Cancer of the Breast, Colorectum, Lung, or Prostate Stratified by Cancer Pain Diagnosis Status from 2012 to 2016

Calendar Year	Cancer Diagnosis	Persons Diagnosed with Cancer Pain N(%)	Persons not Diagnosed with Cancer Pain N(%)
2012	Breast	23367 (37.5)	27900 (42.9)
	Colorectal	7029 (11.3)	15108 (23.2)
	Lung	2603 (4.2)	2160 (3.3)
	Prostate	29365 (47.1)	19930 (30.6)
2013	Breast	27420 (36.8)	32971 (43.0)
	Colorectal	8091 (10.9)	17025 (22.2)
	Lung	3024 (4.1)	2470 (3.2)
	Prostate	35986 (48.3)	24261 (31.6)
2014	Breast	33730 (36.4)	41324 (43.1)
	Colorectal	9417 (10.2)	20328 (21.2)
	Lung	3623 (3.9)	2955 (3.1)
	Prostate	45852 (49.5)	31333 (32.7)
2015	Breast	37297 (35.8)	45934 (44.5)
	Colorectal	10678 (10.3)	20875 (20.2)
	Lung	4093 (3.9)	3117 (3.0)
	Prostate	52040 (50.0)	33385 (32.3)
2016	Breast	41459 (35.1)	52755 (46.1)
	Colorectal	12134 (10.3)	21932 (19.2)
	Lung	4712 (4.0)	3336 (2.9)
	Prostate	59730 (50.6)	36304 (31.8)

Table 3.6. The Number and Percentage of Opioid Naïve Cancer Survivors Who Had At Least 1 Outpatient Visit to Each Provider Specialty from 2012 to 2016

Specialty	2012	2013	2014	2015	2016
Emergency Medicine	2379 (2.8)	3066 (3.0)	3899 (3.0)	4747 (3.3)	5597 (3.5)
General Surgery	7688 (9.0)	8975 (8.7)	10854 (8.4)	11781 (8.3)	12950 (8.0)
Neurology	6744 (7.9)	8526 (8.3)	10559 (8.2)	12183 (8.6)	13922 (8.6)
Advanced Practice Provider	14244 (16.6)	19121 (18.6)	26593 (20.7)	34179 (24.0)	44144 (27.4)
Hematology-Oncology	16527 (19.3)	19977 (19.5)	24301 (18.9)	26987 (19.0)	30701 (19.0)
Orthopedic Surgery	11665 (13.6)	14141 (13.8)	17633 (13.7)	20355 (14.3)	23784 (14.7)
Other Non-Surgical Specialty	33164 (38.7)	40242 (39.2)	49606 (38.6)	55854 (39.2)	62949 (39.0)
Other Surgery Specialty	6281 (7.3)	7717 (7.5)	9573 (7.4)	10956 (7.7)	12906 (8.0)
Pain Management	1224 (1.4)	1550 (1.5)	1994 (1.6)	2218 (1.6)	2685 (1.7)
Primary Care	65833 (76.8)	79288 (77.2)	99156 (77.1)	110099 (77.3)	125744 (77.9)
Physical Medicine and Rehabilitation	3136 (3.7)	4154 (4.0)	5421 (4.2)	6581 (4.6)	7845 (4.9)
Rheumatology	2405 (2.8)	3013 (2.9)	3691 (2.9)	4124 (2.9)	4764 (3.0)
Urology	17892 (20.9)	21927 (21.4)	27199 (21.2)	30247 (21.2)	33904 (21.0)

Table 3.7. The Number and Percentage of Opioid Non-Naïve Cancer Survivors Who Had At Least 1 Outpatient Visit to Each Provider Specialty from 2012 to 2016

Specialty	2012	2013	2014	2015	2016
Emergency Medicine	1587 (3.8)	1989 (4.1)	2368 (4.0)	2800 (4.3)	3237 (4.6)
General Surgery	4684 (11.3)	5516 (11.4)	6325 (10.6)	6856 (10.6)	7402 (10.4)
Neurology	4457 (10.7)	5312 (11.0)	6555 (11.0)	7351 (11.3)	8260 (11.7)
Advanced Practice Provider	9462 (22.7)	12341 (25.5)	16534 (27.6)	20646 (31.8)	25566 (36.1)
Hematology-Oncology	8586 (20.6)	10047 (20.7)	12161 (20.3)	12916 (19.9)	14295 (20.2)
Orthopedic Surgery	10417 (25.0)	12382 (25.5)	15314 (25.6)	16791 (25.9)	18780 (26.5)
Other Non-Surgical Specialty	18278 (43.9)	21540 (44.4)	26430 (44.2)	28845 (44.5)	31679 (44.7)
Other Surgery Specialty	4999 (12.0)	5891 (12.2)	7249 (12.1)	8028 (12.4)	9137 (12.9)
Pain Management	2661 (6.4)	3228 (6.7)	4185 (7.0)	4774 (7.4)	5689 (8.0)
Primary Care	33678 (80.9)	39236 (80.9)	48636 (81.3)	52627 (81.1)	58191 (82.2)
Physical Medicine and Rehabilitation	2810 (6.8)	3352 (6.9)	4431 (7.4)	5235 (8.1)	6083 (8.6)
Rheumatology	2318 (5.6)	2780 (5.7)	3387 (5.7)	3751 (5.8)	4099 (5.8)
Urology	9116 (21.9)	10899 (22.5)	13683 (22.9)	14863 (22.9)	16385 (23.1)

Table 3.8. Rate of Long-Term Opioid Therapy (per 100 Person-Years) Among Opioid Naïve Cancer Survivors Who Visited Each Provider Specialty in the Outpatient Setting from 2012 to 2016

Specialty	**2012**	**2013**	**2014**	**2015**	**2016**
Emergency Medicine	1.4	1.1	0.5	0.8	0.7
General Surgery	1.2	1.0	1.0	0.7	0.6
Neurology	1.2	1.2	1.1	0.9	0.9
Advanced Practice Provider	1.2	1.0	1.0	0.9	0.8
Hematology-Oncology	0.9	0.9	0.7	0.7	0.7
Orthopedic Surgery	2.0	1.8	1.5	1.5	1.2
Other Non-Surgical Specialty	1.0	0.8	0.7	0.7	0.6
Other Surgery Specialty	1.7	1.1	1.3	1.3	1.2
Pain Management	7.1	5.3	6.0	7.3	5.3
Primary Care	0.9	0.8	0.8	0.6	0.6
Physical Medicine and Rehabilitation	2.2	2.1	2.0	1.8	1.3
Rheumatology	2.6	2.1	1.9	1.6	1.2
Urology	0.9	0.8	0.8	0.6	0.6

Table 3.9. Rate of Long-Term Opioid Therapy (per 100 Person-Years) Among Opioid Non-Naïve Cancer Survivors Who Visited Each Provider Specialty in the Outpatient Setting from 2012 to 2016

Specialty	**2012**	**2013**	**2014**	**2015**	**2016**
Emergency Medicine	28.6	28.4	26.3	26.5	25.8
General Surgery	29.4	29.2	28.6	28.7	26.5
Neurology	28.6	29.1	27.3	26.5	25.8
Advanced Practice Provider	30.3	30.4	29.6	28.7	28.1
Hematology-Oncology	27.7	27.3	27.3	26.3	26.0
Orthopedic Surgery	29.3	29.0	28.0	27.0	26.2
Other Non-Surgical Specialty	27.1	26.7	26.3	25.3	25.1
Other Surgery Specialty	30.1	30.1	28.7	27.4	26.6
Pain Management	57.7	59.2	58.8	59.7	59.5
Primary Care	28.3	28.0	27.4	26.5	26.3
Physical Medicine and Rehabilitation	36.0	35.3	35.1	36.1	36.1
Rheumatology	38.6	38.3	37.7	37.8	37.8
Urology	23.5	23.2	22.6	21.6	21.9

Table 3.10. The Adjusted Odds Ratios (aOR) and 95% Confidence Intervals (CI) of Long-Term Opioid Therapy by Outpatient Provider Specialty, Number of Providers, and Patient-Level Characteristics in Cancer Survivors Stratified by Previous Opioid Use

Variable	Opioid Naïve Model	Opioid Non-Naïve Model
Number of Providers	**1.03 (1.01, 1.05)**	**0.95 (0.95, 0.96)**
Year (continuous 2012-2016)	**0.87 (0.85, 0.89)**	**0.96 (0.96, 0.97)**
Provider Specialty		
Primary Care	**1.16 (1.06, 1.28)**	**1.15 (1.11, 1.19)**
Hematology-Oncology	0.98 (0.90, 1.07)	**0.95 (0.92, 0.99)**
Urology	0.98 (0.90, 1.07)	**0.90 (0.87, 0.93)**
Advanced Practice Provider	**1.13 (1.05, 1.22)**	**1.13 (1.10, 1.16)**
Pain Management	**6.60 (5.94, 7.34)**	**4.54 (4.36, 4.73)**
General Surgery	1.09 (0.98, 1.22)	**1.04 (1.00, 1.08)**
Other Surgery Specialty	**1.43 (1.30, 1.57)**	**1.05 (1.02, 1.09)**
Neurology	1.07 (0.97, 1.19)	**0.95 (0.92, 0.99)**
Orthopedic Surgery	**2.17 (2.01, 2.35)**	**1.09 (1.06, 1.11)**
Physical Medicine and Rehabilitation	**2.04 (1.83, 2.28)**	**1.72 (1.65, 1.80)**
Rheumatologist	**1.93 (1.69, 2.20)**	**1.83 (1.74, 1.93)**
Emergency Medicine	1.01 (0.86, 1.19)	1.03 (0.97, 1.08)
Other Specialties	**0.90 (0.84, 0.97)**	**0.93 (0.91, 0.95)**
Age (ref = 65-74 years)		
75-84	**1.16 (1.08, 1.26)**	**1.13 (1.09, 1.16)**
85+	**1.51 (1.39, 1.64)**	**1.25 (1.20, 1.29)**
Female (ref = Male)	1.14 (0.98, 1.31)	**1.17 (1.10, 1.25)**
Race-Ethnicity (ref = NH-White)		
Hispanic	1.03 (0.89, 1.18)	**0.76 (0.72, 0.81)**
Non-Hispanic Black	**1.26 (1.11, 1.42)**	**1.10 (1.05, 1.16)**
Non-Hispanic Other	**0.66 (0.56, 0.76)**	**0.47 (0.43, 0.51)**
Cohort (ref = 1991-1994)		
1995-1998	1.13 (0.97, 1.33)	0.98 (0.91, 1.06)
1999-2002	1.06 (0.92, 1.22)	**1.08 (1.01, 1.15)**
2003-2006	1.10 (0.95, 1.26)	**1.08 (1.02, 1.15)**
2007-2011	**1.18 (1.02, 1.37)**	**1.11 (1.04, 1.18)**
Non-Age Original reason for Medicare	**1.53 (1.37, 1.71)**	**2.13 (2.05, 2.22)**
Medicaid Enrollment (ref = No)	**2.34 (2.14, 2.56)**	**2.04 (1.96, 2.11)**
Rural Residence (ref = Urban)	**1.28 (1.04, 1.57)**	**1.21 (1.10, 1.33)**
Noncancer Charlson > 1	**1.54 (1.42, 1.66)**	**1.35 (1.31, 1.39)**
Depressive Disorder	**1.42 (1.29, 1.56)**	**1.32 (1.28, 1.36)**

Anxiety Disorder	**1.32 (1.20, 1.46)**	**1.34 (1.30, 1.38)**
Substance Use Disorder	**1.72 (1.25, 2.38)**	**3.23 (3.04, 3.44)**
Alcohol Use Disorder	**1.33 (1.05, 1.69)**	0.96 (0.89, 1.04)
Cancer Diagnosis (ref = Prostate)		
Breast	0.97 (0.83, 1.14)	**1.13 (1.06, 1.22)**
Colorectal	1.04 (0.91, 1.18)	**1.16 (1.10, 1.23)**
Lung	1.13 (0.93, 1.37)	**1.41 (1.30, 1.52)**
Census-Region (ref = West)		
Northeast	**0.67 (0.61, 0.74)**	**0.65 (0.63, 0.68)**
Midwest	**1.40 (1.27, 1.53)**	**1.16 (1.11, 1.21)**
South	**1.23 (1.13, 1.35)**	1.02 (0.99, 1.06)

Chapter 4. Risk of an Opioid-Related Emergency Department Visit or Hospitalization Among Older Breast, Colorectal, Lung, and Prostate Cancer Survivors

ABSTRACT

Background: Cancer survivors have a similar or higher opioid use compared to matched noncancer controls. Research also suggests a higher likelihood of a nonfatal opioid overdose among cancer survivors in the one-to-two years after cancer diagnosis and treatment. It is not known, however, if long-term cancer survivors (≥5 years post-diagnosis) are at an increased risk of experiencing an opioid-related emergency department (ED) visit or hospitalization than persons without cancer.

Methods: A 1:1 matched retrospective cohort study was performed using SEER-Medicare linked datasets. Persons who lived ≥5 years after a breast, colorectal, lung, or prostate cancer diagnosis were matched to noncancer controls based on age, gender, race, pain conditions, and previous opioid use. Fine-Gray regression models were used to assess the relationship between cancer survivorship status and opioid-related ED visit or hospitalization.

Results: Overall, the risk of an opioid-related ED visit was 6 times higher in opioid non-naïve than naïve cancer survivors. No significant association was observed between survivorship and opioid-related adverse event among opioid naive (HR = 0.79, 95% CI: 0.61, 1.02) and non-naïve (HR = 1.26, 95% CI: 0.84, 1.89) cohorts.

Conclusions: Cancer survivors and noncancer controls had a similar risk of an ED visit or inpatient admission. Cancer survivors who previously used opioids had a higher rate of ED visits and admissions than opioid naïve cancer survivors. Guidelines and policies should promote non-opioid pain management approaches, especially to opioid non-naive older adults – a population at high risk for an opioid-related ED visit or hospitalization.

INTRODUCTION

Overall, 66% of older adults 65 to 74 years old diagnosed with cancer are expected to live for ≥5 years after diagnosis.[133] Unfortunately, chronic pain – possibly related to cancer treatment – is a common experience among cancer survivors.[61,63,134] Prescription opioids are important for the management of acute cancer related pain but given the lack of evidence of long-term effectiveness with known safety concerns, the role of opioid analgesics outside of cancer treatment is uncertain; thus, guidelines have recommended opioids be used conservatively.[64,67]

From 2010 to 2015, the incidence of opioid-related emergency department (ED) visits and hospitalizations in the United States (US) among persons ≥65 years increased 74% and 34%, respectively, and were highest in the western US.[29] The incidence of opioid-related ED visits,[115] the mortality rate of opioid overdose,[178] and the number of opioid-related hospitalizations[116] among cancer survivors have risen since the mid-2000s. Two studies have found that mood disorders, substance use disorders, and a greater number of comorbid conditions are associated with an opioid-related ED visit or hospitalization among cancer survivors within the first 2 years of cancer survivorship.[115,179]

It is unclear if these associations seen in cancer survivors are mirroring opioid-related ED visit and hospitalization trends in the general population. Therefore, there is a need for population-based studies comparing use and outcomes of prescription opioids in long-term cancer survivors[128] (≥5-years post diagnosis) with matched noncancer controls. Cancer survivors have been observed to have similar or higher utilization of prescription opioids than persons without cancer; they were also more likely to experience opioid use disorder or an overdose but these relationships vary by cancer diagnosis and years after diagnosis.[99,117,118,180,181] Given that the population of older long-term cancer survivors is growing[59] and the prevalence of chronic pain is high,[61] more studies are needed to address the gap in knowledge on the potential harms of opioid-based pain management approaches in this population and how these harms compare between persons with and without a

history of a cancer diagnosis. Therefore, our study sought to assess if long-term cancer survivors were at an increased risk of experiencing an opioid-related adverse event than noncancer controls.

METHODS

Data Source, Study Design, and Cohort Selection

A 1:1 matched retrospective cohort study was performed using linked Surveillance, Epidemiology, and End Results (SEER)-Medicare linked datasets of persons diagnosed with breast, colorectal, lung, or prostate cancer. A matched design was selected to increase the comparability between the cancer and noncancer groups on demographic and clinical characteristics associated with opioid prescribing and opioid-related ED visits or inpatient admissions.[182-184] The University of Texas Medical Branch Institutional Review Board (IRB) approved this study.

Two cohorts of cancer survivors, opioid naïve and non-naïve, were created based on opioid use before the index date (**Figure 4.1**). Opioid naïve cancer survivors did not receive an opioid prescription in the 12 months before their index date. Persons were eligible for inclusion if they were diagnosed with breast, colorectal, lung, or prostate cancer from 2003 to 2011 and survived for at least 5 years after the date of cancer diagnosis. Cancer survivors were assigned an index date corresponding to 5 years after the date of cancer diagnosis. Persons were excluded from the cancer survivor cohort if they were 1) diagnosed with a second primary cancer at any time, 2) younger than 66 years of age on the index date, 3) had noncontinuous Part A, B, and D enrollment or enrollment in a Health Maintenance Organization (HMO) in the 12 months prior to the index date, 4) had a claim for hospice care or cancer treatment in the 12 months prior to the index date, or 5) experienced an opioid-related emergency department (ED) visit or hospitalization in the 12 months prior to the index date.

Matching Strategy

Persons in both cohorts were matched to a single person without a known history of a cancer diagnosis at any time from the 5% Noncancer dataset without replacement. Noncancer controls (n=1,001,305) were assigned the same index date as cancer survivors and were excluded if they met exclusion criteria 2-5, as discussed above. Matching criteria included 1) age ± 1 year, 2) gender (male, female), 3) race-ethnicity (Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Other, Hispanic), 4) previous opioid use (± 5 days) and 5) noncancer pain conditions (chronic pain, back, joint, muscle, nerve, headache, abdominal/chest, visceral, fractures, wounds, other)[78,164] in the 12 months before follow up. Cancer survivors who were opioid naïve or received long-term opioid therapy (≥90 days of in a year) could only be matched to controls with the same pattern of opioid use.

Opioid-Related Emergency Department Visit and Hospitalization

The outcome in this study was opioid-related ED visit or hospitalization. ED visits from the Outpatient Standard Analytical File were identified with revenue center codes (0450-0459, 0981). Hospitalizations were identified from the Medicare Provider Analysis and Review (MEDPAR) file. ICD-9-CM and ICD-10-CM codes were used to identify persons with an ED visit or hospitalization for an opioid-related poisoning, or an opioid specific adverse event codes and an associated overdose diagnostic code on the same date (**Table 4.1**).[185]

Independent Variable and Covariates

Cancer survivorship (cancer survivor, noncancer control) was the primary independent variable. Time independent covariates were the age on the index date, gender, race and Hispanic ethnicity, the year that follow up began (2008-2016), and the original reason for receipt of Medicare benefits (age, disability). Time dependent covariates were the U.S. census region (assigned each calendar year; West, Northeast, Midwest, South), the urban-rural status (assigned

each calendar year; urban, rural), Medicaid enrollment (assigned each follow-up month), and comorbidities (assigned on the date of diagnosis).

For noncancer Charlson comorbidities[132] and depressive, anxiety, alcohol use, and drug use disorders[136], the first date of diagnosis for each condition was identified from 12 months prior to the index date until the date of the outcome, death, or censor. At each study day, the cumulative number of noncancer Charlson comorbidities each person was diagnosed with since the 12 months prior to follow up were summed. For depressive disorder, anxiety disorder, alcohol use disorder, or drug use disorder, instead of a cumulative sum, there was a single indicator variable indicating if the person had been diagnosed with each disorder before a specific study day (0 = no, 1 = yes).[26] Once a person had been diagnosed with a comorbidity, they were considered to have remained diagnosed with that condition throughout the study.

Statistical Analysis

The incidence of opioid-related emergency department visit or hospitalization among matched and unmatched cancer survivors with corresponding 95% confidence intervals[186] was calculated assuming a Poisson distribution. Means (standard deviations), and frequencies (percentages) were calculated to examine the distribution of person-level characteristics across cancer survivors and controls. The Kaplan-Meier method was applied to generate estimates of unadjusted, cumulative incidence rates. The dependent variable was the time until an opioid-related ED visit or hospitalization. Persons were censored for unenrollment in Medicare Parts A, B, or D or enrollment in an HMO, death, had claim for hospice care or cancer treatment, or were censored on December 31, 2016, the last date of data availability. The Log-rank test was used to assess for differences in the probability of experiencing an opioid-related outcome between cancer survivors and matched controls.

Multivariable analysis was performed using the Fine and Gray model because of differential mortality between cancer survivors and controls, which violates the assumption of random censoring.[187] Random censoring implies that individuals who are censored are

representative of all others with similar covariate values. Persons who die, however, may use more opioid prescriptions and be at a higher risk for an opioid-related outcome. Cox proportional hazard model overestimates the probability of the outcome because persons who experienced a competing risk cannot experience the outcome of interest but are treated (censored) as if they have the same rate of the outcome as persons who are not censored.[188] The Fine-Gray model accounts for this overestimation by using the subdistribution hazard and incorporating different weighting schemes for individuals who experienced the competing outcome in the partial likelihood function.

Fine and Gray models stratified by previous opioid use and cancer diagnosis were conducted to assess the relationship between survivorship status and opioid-related ED visit or hospitalization. A sensitivity analysis which ended the study on September 30, 2015 to account for the change from ICD-9-CM to ICD-10-CM codes was performed. The proportional hazard assumption was assessed by examining the correlation between Schoenfeld residuals and the log(time). No violations were observed. Patterns of opioid use were examined by calculating the average days-supplied per opioid prescription, and morphine milligram equivalents (MME) prescribed per day. MME per day was calculated by dividing the total MME of a prescription by the days supplied using the 2018 MME conversion factors provided by the CDC.[189] All data management and analyses were performed with the use of SAS software (version 9.4) (SAS Institute).

RESULTS

Cancer survivors with prior opioid use had approximately 5 times higher rate of opioid-related ED visits or hospitalizations than opioid naïve individuals (208.4 vs 42.3 per 100000 person-years; **Table 4.2**). Lung cancer survivors were observed to have the highest incidence in opioid naïve (53.5 per 100000 person-years) and non-naïve (354.5) cohorts which were 1.5 and 2.3 times higher than the incidence for naïve and non-naive prostate cancer survivors.

The matched opioid naïve cancer survivor cohort was comprised of 32701, 15034, 4548, and 38232 individuals diagnosed with breast, colorectal, lung, and prostate cancer, respectively.

The matched opioid non-naïve cohort was comprised of 5862, 2073, 831, and 5008 breast, colorectal, lung, and prostate cancer survivors, respectively. We matched 90515 opioid naïve (match efficiency: 89.4%) and 13744 opioid non-naïve (match efficiency: 29.2%) cancer survivors to noncancer controls. Overall, there were small differences in demographic characteristics between opioid naïve and non-naïve cancer survivors and controls (**Table 4.3**). Opioid naïve cancer survivors were more likely to reside in the west and northeast and qualified for Medicare for age-related reasons. Opioid non-naïve cancer survivors were more likely to live in the northeast and Midwest than controls, but matched controls were more likely to be a Medicare beneficiary due to disability. At baseline, opioid naïve and non-naïve controls had a similar distribution of all comorbidities as their matched cancer survivors (**Table 4.4**) but, as the study progressed, controls were more likely to be diagnosed with all comorbidities (**Table 4.5**).

Figure 4.2 presents the percentage of matched cancer survivors and noncancer controls who experienced an opioid-related ED visit or hospitalization in the opioid naïve (**Figure 4.2A)** and non-naïve (**Figure 4.2B**) cohorts. Opioid naïve cancer survivors were significantly less likely than noncancer controls to experience an opioid-related ED visit or hospitalization ($p<0.01$), but opioid non-naïve cancer survivors and controls did not have significantly different rates ($p=0.82$). We observed that a higher percentage of noncancer controls died during follow up than cancer survivors regardless of prior opioid use.

Table 4.6 presents the fully adjusted time dependent covariate Fine and Gray models assessing the relationship between cancer survivorship status and opioid-related ED visit or hospitalization within each opioid naivety cohort. After adjusting for baseline person-level demographics, year of the index date, and time dependent census region, urban-rural status, Medicaid enrollment, and comorbid conditions, opioid naive (HR = 0.79, 95% CI: 0.61, 1.02) and non-naïve (HR = 1.26, 95% CI: 0.84, 1.89) cancer survivors were not significantly more likely to experience an opioid-related ED visit or hospitalization compared to controls.

An additional analysis comparing cancer survivors and their matched controls stratified by each cancer diagnosis was conducted (**Table 4.7**). Colorectal cancer survivors were significantly

less likely to experience an opioid-related ED visit or hospitalization compared to matched noncancer controls (HR = 0.55, 95% CI: 0.33, 0.91). From September 2015 to October 2015 we observed a 2-fold increase in the monthly count of opioid-related ED visits or hospitalizations. A sensitivity analysis in which the study was ended on September 30, 2015 was consistent with the main findings (**data not shown**).

A higher percentage of opioid naïve controls than survivors initiated opioid therapy at years 1.0 (23% vs 19%), 3.0 (49% vs 43%), and 5.0 (63% vs 58% p<0.0001, **data not shown**). **Table 4.8** compares average follow up time and various measures of utilization of opioids between cancer survivors and controls. Noncancer controls were more likely than cancer survivors to receive an opioid prescription, and they received a greater days-supplied but slightly less MME per day. Differences in the utilization of prescription opioids were mostly between survivors and controls who entered the study in earlier years (e.g. 2008). Compared to breast (32.5 MME/day), colorectal (32.4), and lung (33.6), prostate cancer survivors received more MME per day (35.7) but had fewer days-supplied (**data not shown**). Regardless of previous opioid use, cancer survivors received fewer opioid prescriptions than matched noncancer controls within each cancer diagnosis (**data not shown)**.

DISCUSSION

Cancer survivors had a similar risk of experiencing an opioid-related ED visit or hospitalization as persons without cancer, regardless of previous opioid use. Cancer survivors who used opioids before survivorship were 5 times more likely to have an opioid-related ED visit or inpatient admission than opioid naïve cancer survivors. One notable finding is noncancer controls had more comorbidities later in the study and were more likely to die than cancer survivors, suggesting that cancer survivors are a selected population, who, after surviving a serious diagnosis might be more motivated than noncancer controls to adopt healthier lifestyle changes that reduce the odds of developing diabetes, hypertension, and other comorbidities.[190,191] This possibility is an area for future study.

We found that colorectal cancer survivors were significantly less likely to experience an opioid adverse event than their matched controls despite a similar pattern of opioid utilization across by all cancer survivors. This is in contrast with Roberts et al. (2020), which demonstrated that age, gender, and region matched colorectal cancer survivors had a 233% higher rate of opioid overdose 1-year post cancer diagnosis compared to matched noncancer control.[181] Our study cohort – long-term cancer survivors – differed from Roberts et al. (2020), who, investigated opioid-related harms within 1 year of a person's cancer diagnosis.

Our results suggest lung cancer survivors are at an increased but non-significant risk of an opioid-related outcome compared to noncancer controls. Previous studies have shown that lung cancer survivors have a higher utilization of prescription opioids than the noncancer population.[117,118] Salz et al (2019) followed age, gender, race, Charlson comorbidity score, and region matched opioid naïve individuals with and without cancer and found that only lung cancer survivors were more likely to receive long-term and high-dose opioid therapy 4-5 years after cancer diagnosis.[117] Moreover, Sutradhar, Lokku, and Barbera (2017) identified that lung cancer survivors who lived 5 or more years after a diagnosis received opioid prescriptions at a higher relative rate than matched noncancer controls.[118] Such high risk opioid use might reflect the known association between long-term opioids use and any history of tobacco use disorder—which is most common in survivors of lung cancer, a prototype of smoking-related cancer.[192,193] One major difference between our study and prior survivorship studies is that the present study matched persons based on noncancer pain conditions.

Our findings of older age as a predictor of opioid-related ED visit or hospitalization among opioid-naïve cancer survivors are consistent with trends in opioid-related hospitalizations in the general population. Among older adults 65 years and older, the incidence of opioid-related inpatient stays was highest among persons 85 years and older in 2010 and 2015.[29] However, the rates of opioid-related ED visits was highest among adults aged 65-74 years and lowest among those ≥85 years.[29] Prescription opioid adverse drug events are responsible for most opioid-related ED visits among older adults in the United States.[114] Chronic use of prescription opioids can affect

multiple organ systems including the gastrointestinal, central nervous, cardiovascular, and pulmonary systems resulting in poorer health outcomes like constipation, syncope, falls and fractures, cardiorespiratory failure and delirium—syndromes and conditions that are common in older adults.[81,114,194] The risk of opioid-related harms may be increased in older adults due to age related changes in drug absorption, metabolism, and elimination and the presence of kidney and liver diseases that further affect drug pharmacokinetics.[5,6]

This study has several limitations. First, our conclusions about the association between survivorship and opioid-related ED visits or hospitalizations are not generalizable to persons who were younger than 66 years old, had incomplete enrollment in Medicare parts A, B, and D or enrolled in an HMO, received cancer treatment or hospice care or to persons diagnosed with cancers other than breast, colorectal, lung, or prostate cancer survivors. Second, noncancer controls may have been diagnosed with cancer if they were diagnosed outside of a SEER region. Third, the United States changed from ICD-9 to ICD-10 coding for administrative billing on October 1, 2015 but our sensitivity analysis ending the study earlier was consistent with our main findings. Last, the matching rate for opioid non-naïve persons was poor (~30%) and those that matched differed from persons that were unmatched based on demographics and previous opioid use. Non-naïve cancer survivors that matched to a noncancer control had possessed an opioid prescription, on average, for fewer days prior to follow up than unmatched cancer survivors.

This study has several strengths. SEER is a geographically diverse collection of state and regional cancer registries. SEER-Medicare also provides rich information about the utilization of healthcare services by persons with cancer and allows for comparisons to the noncancer population. Our analytical plan allowed us to model geographical covariates, Medicaid eligibility, and comorbid conditions by time and account for the competing risk of death. This was important because of imbalances in comorbidities and mortality that developed during the study.

Our study builds upon previous survivorship literature by demonstrating that long-term cancer survivors are as likely as persons without cancer to experience an opioid-related ED visit or hospitalization. Care is needed when prescribing opioids to older adults because prescription

opioids can lead to adverse events, even if taken as directed. Policies (e.g. less restrictive insurance coverage) and clinical guidelines that promote and incentivize increased adoption of evidence-informed non-opioid and non-drug approaches (e.g. physical therapy, transcutaneous electrical nerve stimulation, acupuncture) by clinicians for pain management in older adults with or without history of cancer diagnoses have potential to lessen high risk opioid use and its attendant opioid-related morbidity and mortality.

Appendix D

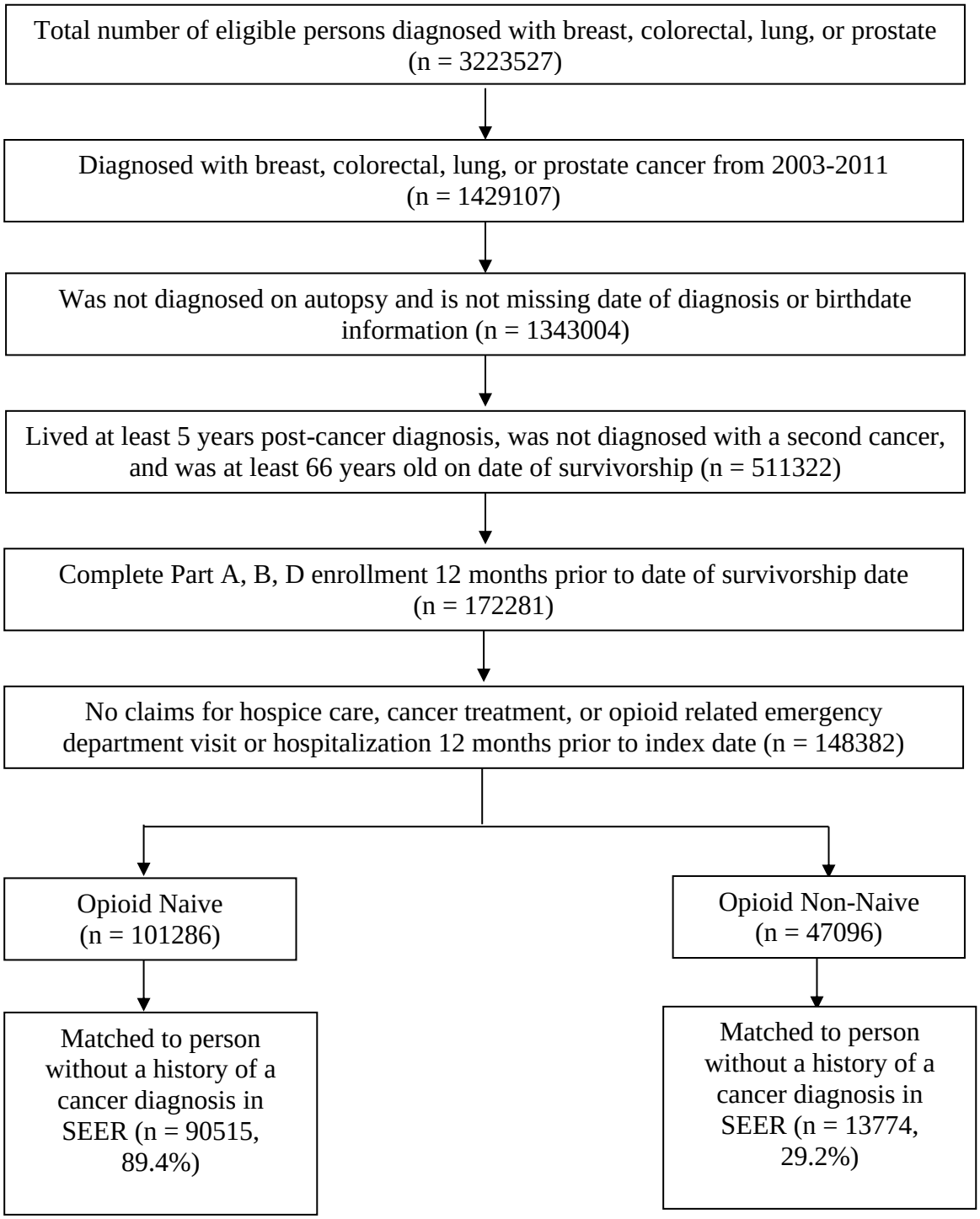

Figure 4.1. Sample Flow Chart for Cancer Survivors Included in the Analysis for Specific Aim 3

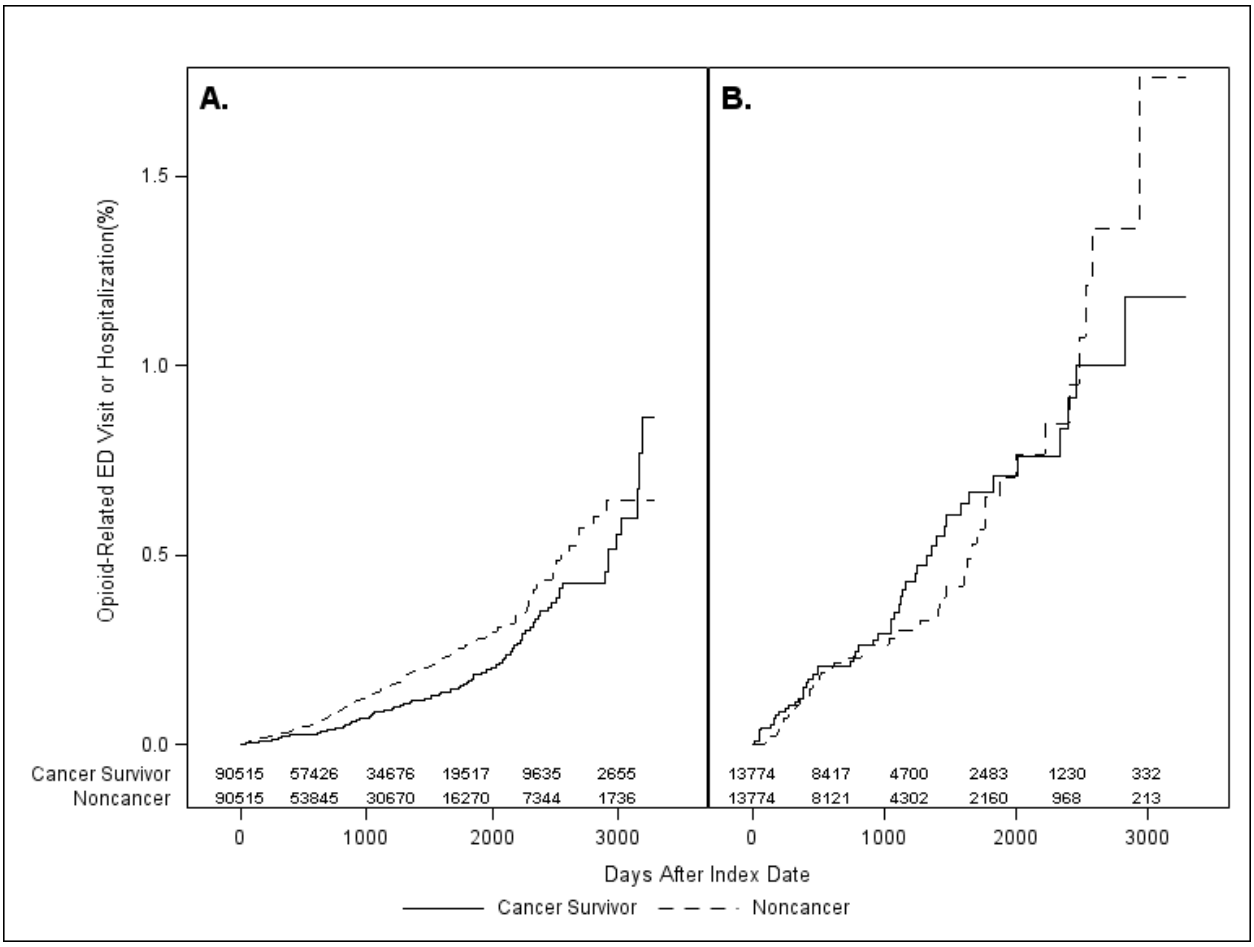

Figure 4.2. Time to Opioid-Related Emergency Department Visit or Hospitalization Among Opioid Naïve and Non-Naïve Cancer Survivors. Time to opioid related ED visit or hospitalization in days after the index date stratified by the opioid naïve (A) and non-naïve (B) cohorts. In the opioid naïve cohort, there was a significant difference between cancer survivors and matched noncancer controls (Log rank test, $X2=6.8$, 1 degree of freedom, $p<0.01$). However, no significant difference between opioid non-naïve cancer survivors and matched noncancer controls (Log rank test, $X2=0.05$, 1 degree of freedom, $p=0.82$). During follow up, a higher percentage of noncancer controls than cancer survivors died in the opioid naïve (9.0% vs 6.8%) and non-naïve (7.5% vs 5.7%) cohorts (data not shown).

Table 4.1. ICD-9 and 10-CM Codes for Opioid Related Emergency Department Visit or Hospitalization

Criteria	ICD-9-CM and ICD-10-CM Codes
Opioid Related Poisoning	9650, E8501, E9500, E9800, T400, T402, T403, T404, X42, X62, Y12
Opioid Specific Adverse Event	E9350, E9351, E9352, Y450 and one of the following overdose diagnostic codes on the same date: 2764, 2921, 2928, 486, 496, 51881, 51882, 7800, 78097, 78603, 78605, 78609, 78652, 7990, E950-E959

Table 4.2. The Incidence and 95% Confidence Interval (CI) of Opioid Related Emergency Department Visits or Hospitalizations (per 100,000 Person-Years) Stratified by Previous Opioid Use and Cancer Diagnosis Regardless of Matched Status

	N	Cases	Incidence (per 100000 Person-Years)
Opioid Naive			42.3 (35.3, 50.3)
Breast	36076	54	49.5 (37.1, 64.5)
Colorectal	17013	21	39.5 (24.5, 60.4)
Lung	5163	NS	53.5 (21.5, 110.2)
Prostate	43034	46	36.1 (26.5, 48.2)
Opioid Non-Naive			208.4 (184.2, 234.8)
Breast	18056	132	256.7 (214.8, 304.4)
Colorectal	7850	37	165.9 (116.8, 228.7)
Lung	3491	28	354.5 (235.5, 512.3)
Prostate	17249	72	151.7 (118.7, 191.0)

Note: Incidence was calculated with opioid naïve and non-naïve cancer survivors who were matched and unmatched (n = 148382). 95% confidence interval was calculated assuming a Poisson distribution. NS means Not Shown. Cells with values less than 11 were not reported to prevent this information from being used to identify persons.

Table 4.3. Distribution of Person-Level Characteristics of Cancer Survivors and Matched Noncancer Controls Stratified by Previous Opioid Use at Baseline

Variables	Naïve Cancer Survivors (n=90515)	Naïve Noncancer (n=90515)	Non-Naïve Cancer Survivors (n=13774)	Non-Naïve Noncancer (n=13774)
Age, Years Mean (STD)	76.3 (6.9)	76.2 (7.0)	74.7 (6.3)	74.6 (6.4)
Female	43922 (48.5%)	43922 (48.5%)	7785 (56.5%)	7785 (56.5%)
Race-Ethnicity				
Non-Hispanic White	76377 (84.4%)	76379 (84.4%)	12832 (93.2%)	12832 (93.2%)
Non-Hispanic Black	5991 (6.6%)	5991 (6.6%)	527 (3.8%)	527 (3.8%)
Non-Hispanic Other	1384 (1.5%)	1383 (1.5%)	53 (0.4%)	53 (0.4%)
Hispanic	6763 (7.5%)	6762 (7.5%)	362 (2.6%)	362 (2.6%)
Original Reason for Medicare Benefits				
Age	84603 (93.5%)	83152 (91.9%)	12388 (89.9%)	12175 (88.4%)
Disability	5829 (6.4%)	7254 (8.0%)	1368 (9.9%)	1577 (11.4%)
Census Region				
West	37910 (41.9%)	36824 (40.7%)	5515 (40.0%)	5657 (41.1%)
Northeast	20738 (22.9%)	19666 (21.7%)	2585 (18.8%)	2216 (16.1%)
Midwest or Unknown**	10898 (12.0%)	11049 (12.1%)	1694 (12.2%)	1604 (11.6%)
South	20969 (23.2%)	22976 (25.4%)	3980 (28.9%)	4297 (31.2%)
Urban-Rural Status				
Urban	88590 (97.9)	88425 (97.7)	13442 (97.6)	13392 (97.2%)
Rural	1819 (2.0%)	1945 (2.1%)	318 (2.3%)	368 (2.7%)
Unknown	106 (0.1%)	145 (0.2%)	14 (0.1%)	14 (0.1%)
Medicaid Enrollment at Baseline	14527 (16.0%)	18827 (20.8%)	2225 (16.2%)	2714 (19.7%)
Index Year				
2008	8357 (9.2%)	8357 (9.2%)	1021 (7.4%)	1021 (7.4%)
2009	8450 (9.3%)	8450 (9.3%)	1041 (7.6%)	1041 (7.6%)
2010	8467 (9.4%)	8467 (9.4%)	1072 (7.8%)	1072 (7.8%)
2011	8710 (9.6%)	8710 (9.6%)	1183 (8.6%)	1183 (8.6%)
2012	9326 (10.3%)	9326 (10.3%)	1370 (9.9%)	1370 (9.9%)
2013	10187 (11.3%)	10187 (11.3%)	1604 (11.6%)	1604 (11.6%)
2014	11637 (12.9%)	11637 (12.9%)	2091 (15.2%)	2091 (15.2%)
2015	11988 (13.2%)	11988 (13.2%)	2053 (14.9%)	2053 (14.9%)
2016	13393 (14.8%)	13393 (14.8%)	2339 (17.0%)	2339 (17.0%)

Table 4.4. Distribution of Comorbidities and Pain Conditions at Baseline of Cancer Survivors and Matched Noncancer Controls Stratified by Previous Opioid Use

Variables	**Naïve Cancer Survivors (n=90515)**	**Naïve Noncancer (n=90515)**	**Non-Naïve Cancer Survivors (n=13774)**	**Non-Naïve Noncancer (n=13774)**
Comorbid Conditions				
Number of Noncancer Charlson Comorbidities Mean (STD)	1.2 (1.4)	1.3 (1.5)	1.4 (1.5)	1.5 (1.6)
Depressive Disorder	7383 (8.2%)	8372 (9.2%)	1821 (13.2%)	1920 (13.9%)
Anxiety Disorder	6261 (6.9%)	6827 (7.5%)	1607 (11.7%)	1609 (11.7%)
Substance Use Disorder	309 (0.3%)	365 (0.4%)	150 (1.1%)	186 (1.4%)
Alcohol Use Disorder	944 (1.0%)	989 (1.1%)	200 (1.5%)	214 (1.6%)
Pain Conditions				
Chronic Pain	2619 (2.9%)	2619 (2.9%)	748 (5.4%)	748 (5.4%)
Abdominal or Chest Pain	20006 (22.1%)	20006 (22.1%)	3889 (28.2%)	3889 (28.2%)
Cancer Pain	63176 (69.8%)	3325 (3.7%)	10004 (72.6%)	637 (4.6%)
Musculoskeletal Pain	26411 (29.2%)	26411 (29.2%)	6717 (48.8%)	6717 (48.8%)
Fractures	2477 (2.7%)	2477 (2.7%)	733 (5.3%)	733 (5.3%)
Visceral Pain	12405 (13.7%)	12405 (13.7%)	2645 (19.2%)	2645 (19.2%)
Wound Pain	2655 (2.9%)	2655 (2.9%)	262 (1.9%)	262 (1.9%)
Headache Pain	6609 (7.3%)	6609 (7.3%)	905 (6.6%)	905 (6.6%)
Joint Pain	38206 (42.2%)	38206 (42.2%)	8780 (63.7%)	8780 (63.7%)
Back Pain	18605 (20.6%)	18605 (20.6%)	5091 (37.0%)	5091 (37.0%)
Nerve Pain	6945 (7.7%)	6945 (7.7%)	1542 (11.2%)	1542 (11.2%)
Other Pain	11435 (12.6%)	11435 (12.6%)	1431 (10.4%)	1431 (10.4%)

Table 4.5. Average Number of Charlson Comorbidities and Percentage of Persons Diagnosed with Depressive, Anxiety, Substance Use, or Alcohol Use Disorders Every 300 Days After the Index Date

		Days After the Index Date										
	Group	**0-300**	**301-600**	**601-900**	**901-1200**	**1201-1500**	**1501-1800**	**1801-2100**	**2101-2400**	**2401-2700**	**2701-3000**	**3001-3300**
		Mean (STD) Number of Noncancer Charlson Comorbidities										
Non-Naive	Cancer Survivor	1.4 (1.5)	1.8 (1.7)	2.1 (1.9)	2.4 (2.0)	2.7 (2.1)	2.9 (2.2)	3.0 (2.2)	3.2 (2.3)	3.5 (2.4)	3.7 (2.4)	3.8 (2.5)
	Noncancer	1.5 (1.6)	1.9 (1.8)	2.3 (2.0)	2.6 (2.1)	2.9 (2.2)	3.1 (2.3)	3.3 (2.4)	3.5 (2.4)	3.7 (2.4)	3.9 (2.5)	4.0 (2.4)
Naive	Cancer Survivor	1.2 (1.4)	1.6 (1.6)	1.9 (1.8)	2.2 (1.9)	2.4 (2.0)	2.6 (2.1)	2.8 (2.2)	3.0 (2.2)	3.2 (2.3)	3.3 (2.3)	3.5 (2.4)
	Noncancer	1.3 (1.5)	1.7 (1.8)	2.1 (1.9)	2.3 (2.1)	2.6 (2.1)	2.8 (2.2)	3.1 (2.3)	3.3 (2.3)	3.5 (2.4)	3.7 (2.4)	3.9 (2.4)
		Depressive Disorder (%)										
Non-Naive	Cancer Survivor	13.2%	17.7%	21.3%	23.9%	26.1%	27.7%	29.1%	29.7%	33.4%	34.3%	32.0%
	Noncancer	14.0%	19.3%	22.6%	25.6%	27.9%	29.9%	32.2%	33.7%	36.3%	40.9%	39.2%
Naive	Cancer Survivor	8.2%	11.3%	13.8%	15.6%	17.2%	18.5%	19.9%	21.3%	22.3%	23.2%	24.2%
	Noncancer	9.3%	12.9%	15.7%	18.0%	20.2%	22.2%	24.1%	25.5%	27.0%	28.1%	30.4%
		Anxiety Disorder (%)										
Non-Naive	Cancer Survivor	11.7%	16.7%	20.2%	23.1%	25.4%	27.2%	29.1%	29.7%	33.5%	37.6%	34.4%
	Noncancer	11.7%	17.5%	21.7%	25.1%	27.7%	30.3%	32.1%	34.2%	37.0%	38.4%	40.1%
Naive	Cancer Survivor	6.9%	10.3%	13.0%	15.4%	17.7%	19.5%	21.6%	23.7%	25.5%	26.7%	28.2%
	Noncancer	7.5%	11.4%	14.5%	17.4%	19.7%	22.3%	24.9%	27.6%	29.9%	32.2%	33.9%
		Substance Use Disorder (%)										
Non-Naive	Cancer Survivor	1.1%	1.5%	1.8%	2.4%	2.8%	3.0%	3.1%	3.4%	3.3%	2.7%	3.9%
	Noncancer	1.4%	2.3%	2.9%	3.6%	4.0%	5.0%	5.4%	5.6%	5.8%	5.8%	9.9%
Naive	Cancer Survivor	0.3%	0.6%	0.8%	1.0%	1.1%	1.3%	1.5%	1.7%	1.8%	2.0%	2.3%
	Noncancer	0.4%	0.7%	1.1%	1.4%	1.7%	1.9%	2.2%	2.5%	3.2%	3.5%	4.2%
		Alcohol Use Disorder (%)										

Non-Naive	Cancer Survivor	1.5%	2.2%	2.5%	3.1%	3.5%	3.8%	4.5%	4.4%	5.1%	6.7%	6.6%
	Noncancer	1.5%	2.4%	2.9%	3.1%	3.6%	4.0%	4.1%	4.7%	4.6%	5.4%	7.5%
Naive	Cancer Survivor	1.0%	1.6%	2.2%	2.6%	3.0%	3.2%	3.5%	3.8%	4.1%	4.4%	4.7%
	Noncancer	1.1%	1.8%	2.5%	3.0%	3.3%	3.8%	4.2%	4.4%	4.6%	5.0%	5.1%

Table 4.6. Fine and Gray Regression Sub-Distribution Hazard Ratios (HR) and 95% Wald Confidence Intervals (CI) for Experiencing an Opioid Related ED Visit or Hospitalization Adjusting for Person-Level Characteristics and Time Dependent Covariates

Parameter	Opioid Naïve Cohort HR (95% Wald CI)	Opioid Non-Naïve Cohort HR (95% Wald CI)
Group		
Noncancer	REF	REF
Cancer Survivor	0.79 (0.61, 1.02)	1.26 (0.84, 1.89)
Age, in years	**1.04 (1.02, 1.06)**	1.01 (0.97, 1.04)
Index Year (2008-2016)	**1.29 (1.17, 1.41)**	**1.14 (1.01, 1.29)**
Gender		
Male	REF	REF
Female	1.31 (0.99, 1.73)	**1.57 (1.00, 2.47)**
Race and Ethnicity		
Non-Hispanic White	REF	REF
Non-Hispanic Black	1.12 (0.65, 1.93)	0.22 (0.03, 1.60)
Non-Hispanic Other	0.84 (0.26, 2.69)	2.07 (0.26, 16.40)
Hispanic	**0.29 (0.12, 0.73)**	0.45 (0.06, 3.45)
Original Reason for Medicare Benefits		
Age	REF	REF
Disability	1.07 (0.66, 1.73)	1.57 (0.91, 2.73)
Census-Region		
West	REF	REF
Northeast	0.81 (0.59, 1.12)	**0.47 (0.24, 0.91)**
Midwest	0.74 (0.48, 1.13)	0.88 (0.47, 1.62)
South	**0.56 (0.39, 0.82)**	**0.60 (0.36, 0.99)**
Urban-Rural Status		
Metropolis/Urban	REF	REF
Rural	0.96 (0.35, 2.64)	1.67 (0.60, 4.68)
Medicaid Enrollment	0.77 (0.54, 1.08)	1.10 (0.65, 1.85)
Number of Noncancer Charlson conditions, continuous	**1.24 (1.18, 1.31)**	**1.29 (1.18, 1.41)**
Depressive Disorder	**1.58 (1.15, 2.16)**	1.48 (0.89, 2.43)
Anxiety Disorder	**1.57 (1.16, 2.12)**	**1.94 (1.17, 3.20)**
Substance Use Disorder	**3.26 (2.02, 5.26)**	**3.52 (1.97, 6.30)**
Alcohol Use Disorder	**2.13 (1.39, 3.27)**	1.42 (0.61, 3.26)

Table 4.7. Fine and Gray Regression Parameter Estimates of Hazard Ratios (HR) and 95% Wald Confidence Intervals for Experiencing an Opioid Related ED Visit or Hospitalization Stratified by Cancer Diagnosis

Parameter	Breast	Colorectal	Lung	Prostate
Group				
Noncancer	REF	REF	REF	REF
Cancer Survivor	0.97 (0.70, 1.34)	**0.55 (0.33, 0.91)**	1.76 (0.72, 4.33)	0.99 (0.67, 1.47)
Previous Opioid Use				
Naïve	REF	REF	REF	REF
Non-Naive	**2.41 (1.71, 3.38)**	1.64 (0.87, 3.08)	**3.88 (1.60, 9.43)**	**1.90 (1.18, 3.07)**

Note: Cancer specific stratified Fine and Gray regression models were adjusted for age on the index date, index date year, gender, original reason for receipt of Medicare benefits, baseline census-region, baseline urban-rural status, baseline Medicaid enrollment, and time varying number of noncancer Charlson comorbid conditions, depressive disorder, anxiety disorder, substance use disorder, and alcohol use disorder. Gender was removed from the breast and prostate cancer models. The reference for each cancer diagnosis group were the matched noncancer controls. Total sample sizes for each group: Breast cancer (n = 76960), Colorectal cancer (n = 34147), Lung cancer (n = 10738), Prostate cancer (n = 86223).

Table 4.8. Utilization of Prescription Opioids Among Older Cancer Survivors and Matched Noncancer Controls Who Received At Least 1 Opioid Prescription Stratified by Cancer Survivorship and Previous Opioid Use

		Year of the Index Date									
Opioid Naivety	**Group**	**Overall**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
		Mean (Std) Person-Years of Follow Up Time Per Person									
Non-Naive	**Noncancer**	2.6 (2.1)	4.1 (3.1)	4.4 (2.9)	4.4 (2.4)	3.8 (2.0)	3.4 (1.6)	3.0 (1.1)	2.2 (0.7)	1.4 (0.4)	0.5 (0.3)
	Cancer Survivor	2.8 (2.2)	5.3 (3.2)	4.8 (2.9)	4.6 (2.3)	4.0 (1.9)	3.5 (1.5)	2.9 (1.1)	2.2 (0.7)	1.4 (0.4)	0.5 (0.3)
Naive	**Noncancer**	2.7 (2.2)	4.1 (3.2)	4.2 (2.9)	4.2 (2.4)	3.8 (2.0)	3.4 (1.6)	2.9 (1.1)	2.2 (0.8)	1.4 (0.4)	0.5 (0.3)
	Cancer Survivor	3.0 (2.3)	5.2 (3.2)	4.9 (2.8)	4.6 (2.3)	4.1 (1.9)	3.5 (1.5)	2.9 (1.1)	2.2 (0.7)	1.4 (0.4)	0.5 (0.3)
		Percent Individuals Who Received ≥1 Prescription									
Non-Naive	**Noncancer**	59.9%	70.8%	71.4%	72.3%	72.7%	68.9%	67.4%	61.5%	52.2%	32.7%
	Cancer Survivor	59.3%	74.3%	75.7%	72.7%	71.8%	68.6%	66.5%	59.0%	50.4%	30.7%
Naive	**Noncancer**	39.5%	51.7%	52.9%	55.1%	51.5%	47.1%	42.7%	37.2%	26.8%	11.5%
	Cancer Survivor	37.4%	53.2%	52.9%	51.9%	49.5%	45.1%	39.7%	33.4%	23.3%	10.0%
		Mean (Std) Number of Prescriptions Written Per Person Who Received >1 Prescription									
Non-Naive	**Noncancer**	11.6 (20.5)	20.6 (33.4)	19.6 (28.0)	16.3 (24.7)	14.5 (22.8)	12.3 (18.1)	10.3 (18.1)	8.0 (12.1)	5.2 (7.2)	3.5 (3.8)
	Cancer Survivor	10.0 (18.4)	15.9 (27.4)	13.6 (21.9)	13.7 (24.9)	12.2 (21.9)	11.0 (18.1)	9.2 (14.9)	7.5 (12.5)	5.4 (7.8)	3.5 (4.1)
Naive	**Noncancer**	5.5 (11.2)	9.3 (17.2)	8.4 (15.2)	7.6 (13.9)	5.8 (11.1)	4.4 (7.2)	3.5 (5.6)	2.9 (4.3)	2.2 (2.5)	1.5 (1.2)
	Cancer Survivor	4.1 (8.0)	6.1 (11.9)	5.6 (10.5)	5.4 (10.1)	4.2 (7.4)	3.6 (5.8)	3.0 (4.4)	2.5 (3.1)	2.0 (2.1)	1.5 (1.2)
		Mean Days-Supplied Written Per Opioid Prescription Per Person Who Received >1 Prescription									
Non-Naive	**Noncancer**	14.5 (11.8)	14.6 (9.6)	14.5 (11.0)	13.6 (9.4)	13.6 (10.2)	14.4 (11.7)	14.1 (12.7)	14.2 (11.6)	14.0 (12.8)	17.6 (14.9)
	Cancer Survivor	13.6 (11.5)	13.2 (10.5)	12.9 (10.6)	13.1 (10.7)	13.4 (11.1)	13.2 (11.0)	13.1 (10.8)	13.4 (11.6)	13.8 (12.8)	17.4 (13.6)
Naive	**Noncancer**	10.3 (9.1)	11.3 (9.2)	11.3 (9.2)	11.3 (9.6)	10.6 (9.0)	10.1 (9.0)	9.7 (8.5)	9.4 (8.7)	8.9 (8.6)	8.8 (9.0)

	Cancer Survivor	9.3 (8.2)	9.8 (8.1)	9.8 (8.1)	9.8 (8.4)	9.3 (8.0)	9.1 (8.1)	8.9 (8.2)	9.0 (8.4)	8.5 (8.0)	8.4 (8.0)
		Mean Morphine Milligram Equivalents Prescribed Per Day									
Non-Naive	**Noncancer**	34.1 (25.4)	33.5 (32.7)	31.7 (17.2)	32.8 (21.2)	33.5 (26.0)	32.9 (21.4)	34.8 (24.2)	33.2 (20.2)	36.7 (28.2)	37.2 (34.6)
	Cancer Survivor	35.2 (30.5)	34.7 (23.7)	34.5 (23.5)	36.0 (47.3)	35.0 (33.8)	36.6 (36.8)	34.8 (27.8)	35.6 (25.1)	35.4 (25.9)	33.6 (24.4)
Naive	**Noncancer**	32.6 (24.6)	31.9 (23.5)	32.5 (29.7)	32.0 (24.8)	32.5 (24.4)	32.8 (22.6)	32.9 (24.8)	33.0 (23.1)	33.6 (21.7)	33.4 (26.6)
	Cancer Survivor	33.5 (22.5)	33.6 (25.9)	33.3 (23.5)	33.4 (23.1)	33.6 (24.5)	33.1 (19.4)	33.5 (20.3)	33.2 (21.2)	34.0 (20.2)	33.9 (22.4)

Chapter 5. Conclusion

The purpose of this dissertation was to extend our understanding of long-term opioid use and associated opioid-related harms in adults aged ≥66 years and who lived ≥5 years after breast, colorectal, lung, or prostate cancer diagnosis. The datasets used for this report were SEER registry data linked with Medicare administrative claims data. The SEER registry collects information on persons who are diagnosed with cancer from diverse geographical settings in the United States, encompassing about 35% of the U.S. population.[200] Medicare information provides details about healthcare services and prescription drugs received. Together, SEER-Medicare datasets are the largest source of information for healthcare services utilized by older adults diagnosed with cancer.

Older adults who lived 5 or more years after a cancer diagnosis may be a more selected or healthy population than older adults who have not been diagnosed with cancer. Previous research has demonstrated that persons who are diagnosed with cancer who adopt healthy behaviors, such as, eating a healthier diet, engage in more physical activity, and do not smoke have improved survival.[242-246] Therefore, long-term cancer survivors may reflect a population who adopted and maintained these health behaviors. To have more comparable groups and reduce the bias of comparing a healthy population to a less selected population—particularly for Specific Aim 3—we matched on factors that could influence opioid prescribing and the risk of an opioid-related emergency department and hospitalization. We matched on age, gender, race-ethnicity, previous opioid use, and pain conditions. One cancer survivorship study[117] matched broadly on the number of Charlson comorbidities (0, 1, ≥2) a person had been diagnosed with. We did not match on the number of comorbidities in our present study. Instead, we matched on pain conditions as these might be more influential on opioid prescribing and the risk of an opioid-related adverse event. Our matching criteria produced adequate balance between groups on the average

number of comorbidities that were diagnosed per individual at baseline. Past opioid use has been associated with the development of opioid and substance use disorders and serious opioid-related adverse events, particularly, when individuals have been prescribed concurrent psychoactive medications.[122,247-249] Therefore, by matching on opioid use prior to follow up, we may have controlled for one of the strongest risk factors for opioid-related emergency department visits and hospitalizations.

One concern in matched designs is overmatching. Overmatching is the result of when there is matching on mediators and characteristics that are not risk factors between exposed and unexposed groups or cases and controls.[285] Overmatching results in loss of statistical efficiency and may lead to erroneous conclusions. One method for identifying overmatch is to explore the relationship of an exposure (e.g. opioid prescription) with a positive (e.g. opioid-related overdose) and negative (e.g. cataract) control outcome variable in both unmatched and matched cohorts to assess if the relationship is moderated by matching. This would suggest that overmatching may be present.

One concern with respect to Specific Aim 3 is that we may have overmatched the cohorts of persons with and without a history of a cancer diagnosis by matching on noncancer pain conditions experienced before baseline. In Specific Aim 2, we identified that noncancer pain conditions may strongly be associated with a potential mediator—long-term opioid therapy—of the relationship between cancer survivorship status and experiencing an opioid-related emergency department visit or hospitalization. For example, we identified among both opioid naïve and non-naïve cancer survivors who experienced chronic, back, or joint pain were significantly more likely to have long-term opioid therapy. Cancer survivors have been found to have a higher prevalence of chronic pain that limits functioning than noncancer populations.[61] Among Medicare beneficiaries, long-term opioid therapy has been shown to be associated with a higher likelihood of experiencing an opioid-related emergency department visit or hospitalization.[82] Conversely, in Specific Aim 3, we did not match on cancer-related pain because we

hypothesized that cancer-related pain may be one pathway that cancer survivors are more likely to receive opioid therapy and this diagnosis would be infrequent among noncancer controls.[204] In Specific Aim 2, however, we identified that cancer survivors who were diagnosed with cancer-related pain were less likely to receive long-term opioid therapy, as many of these individuals were found to have low-stage prostate cancers. Therefore, by matching on noncancer pain conditions at baseline we may have inadvertently adjusted for patterns of higher opioid use, a potential mediator between cancer survivorship status and opioid-related adverse events resulting in a biased estimate of the relative hazards of opioid-related emergency department visits or hospitalizations between cancer survivors and noncancer controls.

The first aim of this study examined the temporal and geographical variation in the rates of long-term opioid therapy among cancer survivors. Our findings indicate that the rate of long-term opioid therapy changed significantly over time and across geographical regions of the U.S. We found the rates of long-term opioid therapy increased from 2008 to 2012 and declined until 2016, when our study ended. We also found cancer survivors residing in the southern region of the U.S. had the highest rates of long-term opioid therapy from 2008-2016 while individuals who lived in the northeast had the lowest rates. We also observed that the long-term opioid therapy temporal trends differed across U.S. regions and previous opioid use. For example, we noted sharp declines in the South among opioid naïve and non-naïve cohorts, but we only observed consistent declines in the Western U.S. among a cohort of individuals who previously used opioids.

Our Specific Aim 1 findings are consistent with observed temporal and geographical variation in opioid therapy in the general population. Studies that examined opioid prescribing rates by state,[84,91,96] county,[88,90,94] and congressional district[87] have consistently demonstrated that opioid prescribing has been high in the Southeastern region of the U.S. These studies have also demonstrated that Western geographical areas, particularly rural counties, of the U.S. also had high rates of opioid prescribing. We,

however, found that long-term cancer survivors who resided in the Midwest had the second highest rates of chronic opioid therapy, with rates approximately 1-2 percentage points higher than cancer survivors in the Western U.S. region. These differences may be due to differences in the inclusion of states in the SEER-registry. For example, Hawaii has the lowest rates of long-term opioid therapy in the United States.[82,95] Since Hawaii is included as a SEER state – but higher opioid prescribing states like Oregon are not – the prevalence of long-term opioid therapy in the U.S. western region may be underestimated. Our findings are also consistent with Kuo et al. (2016), who observed that long-term opioid therapy rates of Schedule II and Schedule III prescription opioids peaked in 2011 among Medicare beneficiaries.[82] One previous report demonstrated that after the federal rescheduling of hydrocodone in 2014 there was a 7% decline in the prevalence of long-term opioid therapy among Medicare beneficiaries.[95] We, however, identified that rates of long-term opioid therapy declined before the enforcement of the federal rescheduling of hydrocodone. This suggests opioid prescribing behavior change occurred before federal action. This may be related to publication of high opioid prescribing and opioid-related morbidity and mortality occurring in the United States in 2012. Moreover, behavior change may have resulted from anticipatory effects of federal action, as the Drug Enforcement Administration held public hearings and released public statements related to federal action on opioid prescribing before the date of enforcement (October 6th, 2014).[143]

Large geographic variation in a medical care service (e.g. prescription medicine, surgery) suggests the lack of a consensus on the appropriate use. Other examples of medical services that have been found to have substantial geographic variation with higher rates of use in the South include testosterone use[250] and the prescribing of antibiotics.[251] Overall, the evidence suggests that the large variation in opioid prescribing is most likely not due to the population-level distributions of painful or chronic conditions. Instead, this variation may be explained by contextual factors, such as, area-level education and income.[91,252] Opioid prescribing has previously been associated with county level indicators of

sociodemographic factors. For example, opioid prescribing at a county level has been associated with a higher percentage of individuals without a high school education, higher rates of unemployment, and a higher percentage of white residents.[90,91] Goodwin, Kuo, Brown, Juurlink, and Raji (2018) found that counties who had higher rates of long-term opioid therapy among older adults had a lower median household income, and higher rates of unemployment, higher percentage of adults whose original Medicare entitlement was for disability, and were more likely to have a higher percentage of non-Hispanic whites, higher percentage of males.[94] One of the strongest correlates of area-level opioid prescribing, however, is the density of physicians suggesting local supply of potential opioid prescribers may be important in driving opioid prescribing.[88,90]

Overall, the total variation explained in opioid prescribing by contextual and supply factors is around 33%, which suggests that other important factors have not been identified. One important factor could be the local culture of providers and the use of health services. In 2009, Dr. Atul Gawande wrote about his explorations into why health care costs varied across the United States by comparing McAllen, Texas – a high healthcare cost city – to El Paso, Texas and other low-cost medical systems throughout the United States.[253] Dr. Gawande found that there was a local culture of high utilization of many different types of medical services by medical providers in McAllen.[253] Therefore, high variation in health services may identify areas where the local medical systems promote the overuse of services to increase revenue—especially medical services in which there are not clear guidelines regarding appropriate use. Areas with medical systems that overutilize services may be more likely to have high rates of opioid prescribing and this could be one reason why we observe a geographic patterning in opioid prescribing and long-term opioid use. One area of future research would be for a large qualitative study examining providers' and patients' beliefs on opioids and different pain management techniques to explore the potential relationship between local patient and provider cultures and over utilization of prescription opioids.

The purpose of the second dissertation aim was to assess the potential relationship between provider specialties visited as an outpatient by cancer survivors and patient level pain conditions with the receipt of long-term opioid therapy. Theoretical work and empirical evidence have indicated that the providers have a great influence on a patient's pattern of opioid use.[100,101] We found that cancer survivors who were diagnosed with chronic pain as compared to not being diagnosed with chronic pain or persons who received treatment from noncancer providers were more likely to receive long-term opioid therapy, regardless of previous opioid use. Persons who had cancer related pain or received outpatient treatment from cancer related specialists—oncologists and urologists—were not more likely to receive long-term opioid therapy.

One systematic review determined the prevalence of pain conditions after curative treatment was 39%.[134] Another study observed that 16% of cancer survivors have chronic pain that interferes with their daily life, which is about twice as great as the prevalence of chronic pain in noncancer populations.[61] Scholars have suggested the opioid epidemic was initiated by aggressive marketing for the use of prescription opioids to manage chronic pain.[36] In 2000, 16% of ambulatory office visits for chronic pain had an opioid prescribed compared to only 8% of visits in 1980.[201] The rate of opioid prescribing for chronic pain outpatient visits increased 79% from 2001 to 2010, such that, almost 1 in 4 office visits for chronic pain had an opioid prescribed.[202] These findings correspond with a rapid increase in opioid prescribing seen in the United States in the 2000s without evidence of an increase in pain related conditions.[48]

Chronic pain is typically managed by primary care providers and pain management specialists. Primary care physicians – predominately internal medicine and family medicine – have written most of the opioid prescriptions and pain management and physical medicine and rehabilitation physicians have the highest opioid prescribing rate in the U.S.[84,104] Oncologists and urologists, however, have lower than average opioid prescribing rates which may be because they do not typically manage chronic pain,

particularly in long-term cancer survivors.[84] The pattern of care for long-term cancer survivors also changes over time, such that, as an individual progresses through survivorship they will be less likely to see their cancer related specialist.[106] Therefore, our findings may be explained by the management of long-term cancer survivors with and without chronic pain. Long-term cancer survivors with chronic noncancer or musculoskeletal pain conditions may be followed more closely by noncancer providers and, therefore, more likely to receive long-term opioid therapy. Cancer pain, however, in previous studies has been associated with impairments in functioning and higher opioid use.[203,204] Among persons who lived 5 or more years after a cancer diagnosis, the prevalence of opioid use was greater among cancer survivors who were diagnosed with chemotherapy-induced neuropathic pain than persons who were not.[204] Our study sample with cancer related pain was predominately comprised of persons diagnosed with prostate cancer. Prostate cancer survivors have been found to have lower rates of opioid use than other cancer survivors which could also explain why we did not see a relationship between cancer pain and higher likelihood of long-term opioid therapy.

The purpose of third aim was to assess if cancer survivors were more likely to experience an opioid-related ED visit or hospitalization than persons without a clinical history of cancer. We were unable to examine opioid-related mortality as an outcome in this study because SEER-Medicare linked datasets only provide ICD-10 cause of death information for cancer survivors and not persons in the noncancer dataset. We found that opioid non-naïve cancer survivors had approximately 5 times higher incidence of opioid-related ED visits or hospitalizations compared to opioid naïve cancer survivors. Overall, the incidence of opioid-related adverse events was highest among lung cancer survivors and lowest among prostate cancer survivors. Lastly, we found cancer survivors and noncancer controls were similarly likely to experience an opioid-related ED visit or hospitalization, despite lower opioid use by cancer survivors.

In addition to identifying that the incidence of opioid-related emergency department visits and hospitalizations was highest among lung cancer survivors, we found that lung cancer survivors were more likely to experience these opioid-related adverse events than noncancer controls; however, this difference was not significant. Lung cancer survivors were observed to have higher opioid use than other cancer survivors and persons without cancer. Shah et al. (2019) observed the prevalence of long-term opioid therapy was higher among lung cancer survivors than breast, colorectal, or prostate cancer survivors, regardless of the number of years after diagnosis.[99] In Specific Aim 1, we found that lung cancer survivors were significantly more likely to receive long-term opioid therapy than prostate cancer survivors. Lung cancer survivors may be more likely to receive long-term opioid therapy resulting from chronic pain that follows serious surgical procedures and chemotherapeutic treatments.

A medical history of or current tobacco use, a risk factor for lung cancer, has also been associated with receipt of long-term opioid therapy, particularly among cancer survivors.[97,254,255] Patterns of high-risk opioid use – like long-term opioid therapy – may mediate the relationship between different cancer diagnoses and the incidence of opioid-related emergency department visits and hospitalizations that was observed in our study. Long-term opioid therapy has been found to predict higher odds of an opioid-related ED visit or hospitalization.[82] Lung cancer survivors may be more likely to experience opioid-related adverse events due to long-term reductions in lung functioning following surgical procedures that involve the removal of lung tissue.[256,257] Prescription opioids depress respiratory function by inhibiting neurons in the brain that are responsible for driving respiratory rhythm and prescription opioids blunt the physiologic response to increased carbon dioxide. Therefore, the use of prescription opioids in long-term lung cancer survivors may increase the risk for opioid-related respiratory depression and overdose. Further research is needed to assess if surgical procedures that remove more lung tissue

following a cancer diagnosis predispose lung cancer survivors to a higher risk of serious opioid-related adverse events.

Our results from Specific Aim 3 results should inform guidelines about the risks of opioid-related adverse events observed in long-term cancer survivors. The CDC guidelines for opioid prescribing for chronic pain clarified that they only exempted actively treated cancer patients from its purview, but the guidelines apply to long-term cancer survivors not undergoing treatment.[65,66] Paice et al. (2016), the authors of the American Society of Clinical Oncology guidelines for chronic pain management in cancer survivors, recommended that nonopioid analgesics be used to manage chronic pain and function before moving onto opioid therapy in selected individuals.[64] Future guidelines should incorporate our findings as evidence of the potential harms that can results from opioid therapy. Future quality improvement projects should explore how the implementation of opioid prescribing guidelines and standardized practices is associated with reductions in opioid-related morbidity. Continuous research should be conducted examining how opioid therapy is being used in cancer survivor and examine its relationship with opioid-related morbidity and mortality to further refine guidelines. Ultimately, the goal of this research should be to demonstrate little geographical variation in opioid prescribing and low levels of prescription opioid-related morbidity and mortality in all populations. This would suggest that the prescribing of opioids is consistent with the notion of effective care.[158]

Cancer survivors have been found to have comparable or higher opioid use than persons without cancer. For example, Salz et al. (2019) observed colorectal and lung cancer survivors were more likely to receive long-term opioid therapy than matched noncancer controls.[117] Furthermore, Barbera et al. (2017) observed that long-term cancer survivors had a prevalence of opioid use that was higher than the noncancer population but lower than cancer survivors whose diagnosis was less than 5 years before.[118] In Norway, cancer survivors who lived ≥10 years after a cancer diagnosis were more likely to receive an opioid prescription than persons without cancer.[119] Our study demonstrated that long-term

cancer survivors and persons without cancer were similarly likely to experience an opioid-related ED visit or hospitalization.

We observed that colorectal cancer survivors were 45% less likely to experience an opioid-related emergency department visit or hospitalization than persons without a medical history of cancer. Roberts et al. (2020) observed that colorectal cancer survivors—but not breast or lung cancer survivors—aged ≥66 years old and within their first year of being diagnosed were more likely to experience an opioid overdose or be diagnosed with opioid use disorder than matched persons without cancer.[122] However, there were two differences between our study and the study conducted by Roberts et al. (2020). First, our study matched on diagnosed pain conditions between cancer survivors and noncancer controls, in addition to age, gender, race, and previous opioid use while Roberts et al. (2020) matched on demographic characteristics and geographical region. Second, our study examined the relationship between cancer survivorship and opioid adverse events in persons who had lived 5 or more years after diagnosis. Roberts et al. (2020) studied a similar relationship in persons newly diagnosed with cancer and conducted a secondary analysis exploring this relationship throughout survivorship until 6 years after a cancer diagnosis.

One possible reason for the lower risk of an opioid-related emergency department visit or hospitalization among colorectal cancer survivors is that they may have adopted healthier habits that promote better gastrointestinal health. Colorectal cancer survivors who increased fiber intake have been found to have better survival.[242] Fiber is an important dietary component that can help lower serum glucose and cholesterol and keep the gastrointestinal tract regular and increases stool bulk. Therefore, increased fiber in colorectal cancer survivors could play a role in preventing gastrointestinal complications of opioid therapy, such as, opioid induced constipation. Another possibility is that healthcare providers prescribe or recommend prophylactic laxatives for opioid induced constipation more in colorectal cancer survivors. It may also be likely colorectal cancer

survivors are using laxatives more often given long-term colorectal cancer survivors experience constipation at rates higher than persons without a history of a cancer diagnosis.[258] Constipation and gastrointestinal concerns are the most common reasons older adults have an opioid-related emergency department visit.[114] Therefore, prophylaxis for opioid-induced constipation after initiating opioid therapy may reduce the risk of serious opioid-related adverse events related to therapeutic use of opioids. The use of laxatives to prevent opioid-induced constipation is rare among persons diagnosed with lung cancer.[259] However, the rates of prophylactic laxative use among long-term cancer survivors, including colorectal cancer survivors, is not known. Future research should explore if medical practitioners are more likely to prescribe prophylaxis to colorectal cancer survivors than other cancer survivors and persons without a history of cancer.

We observed that colorectal cancer survivors had a lower incidence of opioid-related ED visit and hospitalizations than lung and breast cancer survivors. The prevalence of long-term opioid therapy has been found to be comparable between breast and colorectal cancer survivors ≥5 years after a cancer diagnosis. Colorectal cancer survivors have also been observed to be more likely than matched controls to receive long-term opioid therapy. Further research studying differences in opioid use and associated health outcomes among cancer survivors need to be conducted. For example, more information is needed if greater chronic pain severity or psychiatric diagnoses can explain the differences in opioid use and associated outcomes among long-term cancer survivors.

In this report, we document widespread variation in long-term opioid therapy, the influence of provider specialty on long-term opioid therapy, and associated opioid prescribing harms among cancer survivors. Recent declines in the prevalence of long-term opioid therapy within the South and Midwest indicate that variation in opioid prescribing is decreasing. Decreasing variation across the United States may indicate that state and federal policies and dissemination of opioid prescribing guidelines may have been effective in reducing opioid prescribing.[143,147,205,206] However, the effect of policy and guidelines on

utilization of health services (e.g. opioid-related hospitalizations) and opioid mortality are unclear.[207] More research is needed investigating opioid-related policy and the effect on opioid-related outcomes.

It is concerning that national trends indicate opioid prescribing has decreased the least among older adults, given that this cohort of individuals may be at the greatest risk for opioid-related adverse events related to therapeutic use.[114] Opioid misuse—using a prescription opioid in a way that was not directed by a healthcare provider or using a non-prescribed opioid—is not as common among adults who are ≥65 years and older, compared to younger individuals.[208-210] Most older adults who reported opioid misuse stated they received the prescription from their healthcare provider, instead of a diverted prescription from friends, family or other individuals.[210] Older adults with chronic pain may have more severe pain that requires prescription opioids to manage pain and improve function than younger age groups and providers may also feel that untreated pain in older adults is of greater concern than addiction.[163,213] Even though cancer survivors may be more likely to receive an opioid prescription, they report a lower prevalence of opioid misuse than persons without a history of cancer diagnosis.[211] Therefore, opioid misuse among older adults with a history of cancer may not be a major concern, but healthcare providers should be concerned about the sequela of therapeutic use of prescription opioids in this population.

Reducing the high rates of long-term opioid therapy in cancer survivors could be enhanced by improvements to delivery of care for cancer survivors. Cancer survivorship clinics are important centralized settings or interpersonal relationships for establishing routine medical care and surveillance of cancer recurrence for cancer survivors outside of active cancer treatment. They are necessary for the identification and management of healthcare needs that result from the physical, psychological, and sociological aspects of cancer and treatment. There are several different types of cancer survivorship clinic models, which range from shared cared models which require coordination between a primary care physician and oncologist, to a single consult visit to the oncologist to identify

potential health needs related to the cancer or the cancer treatment.[260-263] Some centers have attempted to staff adult survivorship clinics with multidisciplinary teams based on the model for pediatric survivorship clinic, however, these have shown to be resource intensive for some institutions. In the United States, there is a disagreement about the optimal model of survivorship care between primary care physicians and oncologists.[264] However, there is a strong agreement between cancer and noncancer related providers that primary care physicians play an important role throughout the care of a person with cancer – from active cancer treatment to long-term survivorship.[265]

Shared care for cancer survivorship clinics may be a more optimal delivery of care than models that rely on oncologists to provider sole survivorship care. Cancer-related specialties currently do not have enough practitioners to provide care for cancer patients and long-term cancer survivors. Further, multispecialty teams that share the management of more cancer survivors have been found to reduce hospitalizations and may increase use of preventive services.[212] Patients who are receiving shared care report higher satisfaction and the shared care model is also as effective in delivery of care as oncology centered care models, suggesting that this may be a more appropriate delivery of survivorship care.[273] There are two important characteristics that are needed for shared care models to work efficiently: 1) high coordination of care and 2) all providers understand their roles and responsibilities.[266-270,278] Poor coordination of care and lack of understanding roles may result in gaps in medical care or duplication of services, such as, cancer recurrence surveillance. In one Canadian study, communication between family medicine providers and cancer-related specialties was the most cited barrier for coordination of care.[274]

Given that developing clinics staffed with multidisciplinary teams is logistically challenging, one method for improving coordination and facilitate an understanding of provider responsibilities may be to continue implementing survivorship care plans into medical systems. Survivorship care plans are important pieces of communication between oncologists and other medical providers and may help to identify the relevant roles for each

provider in a cancer survivor's care.[271] Primary care physicians who received survivorship care plans reported higher coordination of care. Approximately 5% to 20% of oncologists in the United States use survivorship care plans for their patient and other providers.[268,272] This rate of uptake may be low because oncologists frequently report insufficient institutional resources have impeded its use.[263,275] These system level barriers include no training on how to develop survivorship care planes, inadequate compensation for writing and discussing the plans with the patient, and insufficient time to write the plans.

Automatic generation of survivorship care plans from the electronic health record have helped, but there are concerns about how much information is being shared with patients.[276] Additionally, electronic medical records have helped improve coordination of care, but there are difficulties with communicating to providers who are in different networks.[277] Therefore, adequate reimbursement for the time necessary to develop and discuss survivorship care plans with patients and other providers may help improve uptake. Work force shortages may be addressed by hiring advanced practice providers for survivorship clinics. We also recommend institutional support to automatically generate survivorship care plans based on information in the electronic health records and consider development of medical record sharing system for out-of-network providers. Lastly, it is necessary to incorporate training with respect to the development of survivorship care plans into hematology and oncology fellowship programs. Further training concerning survivorship care guidelines and planning should be pursued for physicians in primary care by implementing continuing medical education programs covering survivorship care plans.

While a shared care model for survivorship care may be beneficial in increasing coordination of care, this model can also be beneficial in reducing opioid prescribing. In Specific Aim 1 and 2, we demonstrated substantial variation in long-term opioid therapy across regions and noncancer specialties, indicating the prescribing of opioids in this population is inefficient. By improving care coordination and assigning responsibilities to each provider in the care of a long-term cancer survivor through the development and

dissemination of cancer survivorship plans, opioid prescribing may become more efficient as duplication of opioid prescriptions is eliminated. We recommend that all providers who care for cancer survivors communicate frequently with other providers through survivorship care plans. This means not relying on only oncologists to submit care plans, but for open communication from all providers.

Another method for reducing the high variation in opioid prescribing is through mandatory and comprehensive pain management education for all students entering the medical system and providers who prescribe opioids. Most states already have continuing medical education requirements for pain management, prescribing of controlled substances, opioid misuse and abuse, and diversion of medications for physicians and physician assistants.[280] Most medical schools have reported education requirements for pain and substance use disorder assessment and management, but there appears to be a substantial variation in how medical schools teach these concepts.[283] A survey by the Association of American Medical Colleges identified that there needs to be more active learning experiences for the proper management of pain and substance use disorders and, opioid prescribing practices.[283] Future physicians may be inadequately prepared to navigate the nuance of pain management, despite pain being a common reason for persons to seek medical care.[281] This finding underscores it is necessary for accreditation bodies to create regulations requiring the need for all students to receive comprehensive pain management requirements through lecturers and clinical experiences, and engage with faculty about proper opioid prescribing behavior. Education should focus on adequate history taking and assessment of pain with incorporating findings concerning the psychosocial impact of pain and detailed review of all nonpharmacological and pharmacological pain management techniques.[282] Pain management education should also be required for all residents and attending physicians. Instruction should mandate detailed review of the CDC guidelines for opioid prescribing along with state laws governing opioid prescribing. Further education on proper tapering of prescription opioid therapy and on

identifying, diagnosing, and the management of opioid use disorder with appropriate pharmacological therapy and supplementary psychiatric and group therapy sessions. Our recommendations should not only be limited to medical students, but instead, to any individual who is entering medical education and training programs and who will have the potential to prescribe opioids. In Specific Aim 2, we observed that nurse practitioners and physicians assistants were increasingly providing outpatient management to long-term cancer survivors. Opioid prescribing by nurse practitioners and physician assistants is also increasing.[104] Therefore, it is important that medical students and providers who have the potential to prescribe opioids also receive comprehensive pain management training.

There are several general limitations that are present in all three studies. First, this study is only generalizable to individuals who were aged ≥66 years, lived 5 or more years after a breast, colorectal, lung, or prostate cancer, were diagnosed within a SEER capture area, and had 12 months of enrollment in Medicare Parts A, B, and D. Our results are not generalizable to other cancer survivor populations, individuals who were enrolled in an HMO, Part C, Medicare. Moreover, our sample is not representative of long-term cancer survivors who are still receiving active cancer treatment as we excluded long-term cancer survivors if they received chemotherapy or radiation treatment in the 12 months before follow-up. Lastly, for Specific Aim 3, by matching based on person level demographics and clinical histories, we improved the internal validity of the study by creating more comparable cancer and noncancer groups but we reduced the external validity, or generalizability, of the study. Individuals who were matched and included in the analysis tended to be younger, have less pain conditions, and had lower opioid utilization. These differences between the two groups suggest that our findings for Specific Aim 3 are only generalizable to younger, more healthy individuals who have lower levels of opioid utilization. Therefore, we did not analytically include persons who were unmatched who had higher opioid use which could lead to us underestimating the risk of an opioid-related emergency department visit or hospitalization in cancer survivors. The effect of matching

on the generalizability of the study can be examined by comparing how the Kaplan-Meier curves examining time to an opioid-related hospitalization or emergency department visit changed from before to after the match.

Our study also was limited in its ability to capture prescription opioids in which Medicare Part D was used for coverage. Prescription opioids that were paid for by cash, covered under another insurance plan, given to an individual by a friend or family member, or obtained through other means were not included in our study. Our studies that investigated patterns of long-term opioid therapy—Specific Aims 1 and 2—assumed prescription opioids were taken as directed. Our analyses encompassed a period of 9 years of data in the United States – January 1, 2008 to December 31, 2016. During this time, there were organizational and state policies that were enacted to reduce opioid prescribing. Due to small sample sizes in some states, we were unable to examine how more localized policy affected our results. Moreover, on October 1, 2015, Centers for Medicare and Medicaid Services required ICD-10-CM codes for administrative billing. We did find evidence that the change from using ICD-9-CM to ICD-10-CM in administrative billing resulted in changes in the prevalence of pain conditions and the number of opioid-related ED visits and hospitalizations. Lastly, our study only included patient characteristics and health services that were recorded on a medical record or billed to Medicare. We lacked patient-reported information. Information on activities of daily living, pain severity and characteristics of the pain, and quality of life are important surrogates for individual well-being.

One last serious limitation for our study concerns the possibility of differential misclassification. This is an example of an information bias since the quality of information on an exposure or outcome may differ between groups. One possibility is that we misclassified dichotomous opioid-related exposures and outcomes in the three present studies included in this dissertation. Understanding the implications of misclassification on our findings requires a thought experiment. First, if we assume that persons without cancer

obtained prescription opioids from unregulated settings or diverted prescription opioids with the same frequency of long-term cancer survivors, we will have nondifferential misclassification. Nondifferential misclassification of either a dichotomous exposure or outcome generally biases the estimates of relative hazard of an outcome towards the null. However, if we assume that noncancer controls obtain opioids from unregulated settings or we undercounted opioid prescriptions in this population more often than long-term cancer survivors, we will have differential misclassification. As a result of differential misclassification, we do not know which direction our estimates of relative hazards for our outcome would be biased. Differential misclassification with respect to the exposure can be identified by assessing the relationship between an opioid-related exposure (e.g. opioid use) and positive and negative control (e.g. cataracts) outcomes within cancer survivors and noncancer controls, and examine if the relationship differs within each group. If the association differs between the groups in each outcome of interest, we could claim that there may be differential misclassification that is biasing our results. If we do not see a moderation of the relationship between exposure and outcome between cancer and noncancer groups, then we have evidence that any misclassification is likely to be nondifferential.

This brief discussion over the implications of misclassification in opioid-related exposures and outcomes also relates to the possibility we may have also misclassified cancer survivorship status. SEER registry sites have excellent case capture rates (>95%) for persons diagnosed with cancer in a specific area. Therefore, we do not have much concern for misclassifying cancer survivors as noncancer controls. However, it is likely that a small percentage of individuals we classified as noncancer controls were diagnosed with cancer in a non-SEER area and were not included. This is an example of differential misclassification on exposure status because the quality of information on survivorship status differs between the exposed and unexposed groups. In Specific Aim 3, we observed a small number of noncancer controls were censored due to receiving cancer treatment.

Moreover, a small percentage of noncancer controls were diagnosed with cancer-related pain at baseline and throughout the study. This indicates that misclassification could have occurred based on cancer survivorship status as noncancer controls may have been diagnosed with cancer outside of the capture area for a SEER region and they did not have their cancer diagnosis recorded in SEER. Noncancer controls who were newly diagnosed with cancer and underwent treatment would be expected to have higher opioid use than both persons without cancer and long-term cancer survivors which may place these individuals at higher risk of serious opioid-related adverse events.[122] Noncancer controls who were diagnosed with cancer pain could be more similar to cancer survivors. One study found that long-term cancer survivors who had cancer pain were more likely to use opioids than long-term cancer survivors without cancer pain.[204] Therefore, we also would expect that misclassified noncancer controls with cancer pain would be at a higher risk of serious opioid-related adverse events.

We managed the possibility of differential misclassification in several ways. First, we applied the same inclusion and exclusion criteria to cancer survivors and noncancer controls. This included not including individuals who had a claim for chemotherapy or radiation in the 12 months before an assigned index date, which was the 5 years after the date of cancer diagnosis for the potential cancer survivor match. We also censored individuals in both noncancer and cancer survivor groups if they had a diagnostic code in any position for receipt of cancer treatment during the study. Noncancer controls without evidence of receiving cancer treatment but having been diagnosed with cancer related pain may be more similar to cancer survivors. As a result of this misclassification, we would expect that the rate of opioid-related outcomes for noncancer controls would be biased in the direction of cancer survivors. Since our outcome in Specific Aim 3 was the relative hazard of an opioid-related adverse event, we expect we would bias the estimate toward 1.0.

This report is innovative and significant because it uses SEER-Medicare administrative datasets—the largest available dataset for health service utilization among individuals diagnosed with cancer—to address current cancer survivorship research gaps pertaining to how opioids are being utilized and the comparative risk of opioid associated harms. We built upon previous studies that examined opioid use and harms among cancer survivors by exploring national patterns of opioid use and focusing on harms in individuals who lived ≥5 years after a breast, colorectal, lung, or prostate cancer. Previous studies were limited geographically or assessed opioid-related harms in actively treated cancer survivors. In Specific Aim 3 when we matched cancer survivors and persons without a history of a cancer diagnosis, we matched on noncancer pain conditions, which helped us adjust for differential reasons in opioid prescribing between cancer survivors and noncancer controls that could have influenced our outcome, opioid-related ED visit or hospitalization.

There are several necessary avenues for future research. First, extensive variation of a clinical practice across contextual factors (e.g. time, region) suggest that further research on guidelines and policy should be conducted to increase efficiency and quality of care. Further research should be conducted to assess how the Centers for Disease Control and Prevention opioid prescribing guidelines for chronic pain influenced opioid prescribing practices among older adults with a history of a cancer diagnosis. Our study ended at the end of 2016 and did not have enough time points to examine changes in high-risk opioid prescribing practices, like, long-term opioid therapy. Specific Aim 2 was limited because it could not identify which provider prescribed the opioids to the cancer survivor. Therefore, further research is needed to explore which provider specialties are prescribing opioids to cancer survivors and if cancer survivors are at a higher risk of an opioid-related adverse event if they receive opioids from a particular specialty.

Our study findings imply receipt of long-term opioid therapy is common among cancer survivors and that the risk of experiencing an opioid-related ED visit and

hospitalization is comparable between cancer survivors and matched noncancer controls. Furthermore, our findings also indicate cancer survivors who have a history of opioid use are at a much greater risk for poorer outcomes related to prescription opioids. Therefore, it is important policies and guidelines continue to encourage and incentivize the use of nonpharmacological and nonopioid therapies to manage pain among older adults.

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Curriculum Vita

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PRESENT POSITION AND ADDRESS: M.D.-Ph.D Student and Graduate Research Assistant (08/2017)

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University of Texas Medical Branch at Galveston,
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BIOGRAPHICAL:

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EDUCATION:

05/2015 B.S. University of Texas at Austin, Austin, TX (Biochemistry)

PROFESSIONAL WORK HISTORY AND TEACHING EXPERIENCE:

08/2017 - Present Graduate Research Assistant, Department of Preventive Medicine and Population Health, University of Texas Medical Branch, Galveston, TX

RESEARCH ACTIVITIES:

Area of Research
Health services research
Policy evaluations
Opioid prescribing to persons diagnosed with cancer
Environmental determinants of health

Grant Support
Current
1. 1F30CA254479-01A1 National Cancer Institute
Opioid Prescribing and Health Outcomes Among Cancer Survivors
(PI: Gibson, Derrick, 100% effort, 09/2020 to Present)

Past
1. T32 HS02613301 Agency for Healthcare Research and Quality
(PI: Kuo, Yong-Fang, 04/2019 to 09/2020)
Role: Trainee

2. T32 AG051131 National Institute on Aging
(PI: Markides, Kyriakos, 08/2017 to 04/2019)
Role: Trainee

COMMITTEE RESPONSIBILITIES:

International

National

State/Regional

UTMB

School

Departmental

Delta Omega – Delta Nu Chapter. Student Liaison. 2020

Other

Committee Responsibility other than UTMB

(optional)

Scientific Sessions Organized

Scientific Sessions Chaired/ Discussion Leader

TEACHING RESPONSIBILITIES

A. TEACHING RESPONSIBILITIES AT UTMB:

a. Teaching:

Graduate School (GSBS):
Introduction to Epidemiology. Teaching Assistant (Fall 2019)
Biostatistics. Teaching Assistant. (Fall 2018)

HONORS:

1. Don W. Micks Scholarship in Preventive Medicine and Community Health. 2020.
2. Patricia Parker Scholarship Endowment in the Graduate School of Biomedical Sciences. 2020.
3. The Patricia Parker Scholarship Endowment in the Graduate School of Biomedical Sciences. 2019.
4. Arthur V. Simmang Scholarship Fund – Graduate School of Biomedical Sciences. 2019.
5. Induction into Delta Omega – Delta Nu Chapter. 2019.
6. Scholarship from Carl J. Herzog Foundation. 2013-2015.
7. University Honors from University of Texas at Austin. 2013-2015.
8. Dean's List from University of Texas at San Antonio. 2011-2012.

PUBLISHED:

A. ARTICLES IN PEER-REVIEWED JOURNALS:

1. **Gibson DC**, Prochaska JD, Yu X, Kaul S. An examination between census tract unhealthy food availability and colorectal cancer incidence. Cancer Epidemiology. 2020;67:101761. doi:10.1016/j.canep.2020.101761
2. Goodman ML, Seidel SE, **Gibson D**, et al. Intimate Partnerships, Suicidal Ideation and Suicide-Related Hospitalization Among Young Kenyan Men. Community Mental Health Journal. February 2020. doi:10.1007/s10597-020-00572-0
3. Goodman ML, **Gibson DC**, Baker L, Seidel SE. Family-level factors to reintegrate street-involved children in low- and middle-income countries: A scoping review. Children and Youth Services Review. 2020;109:104664. doi:10.1016/j.childyouth.2019.104664
4. **Gibson DC**, Chou L-N, Raji MA, Baillargeon JG, Kuo Y-F. Opioid Prescribing Trends in Women Following Mastectomy or Breast-Conserving Surgery Before and After the 2014 Federal Reclassification of Hydrocodone. Oncologist. December 2019. doi:10.1634/theoncologist.2019-0758
5. Goodman ML, **Gibson D**, Vo T, Wang A, Gitari S, Raimer B. Early childhood attachment and suicidal ideation among young Kenyan men. Advances in Life Course Research. 2018;35:126-134. doi:10.1016/j.alcr.2018.02.001
6. Goodman ML, **Gibson DC**, Keiser PH, Gitari S, Raimer-Goodman L. Family, Belonging and Meaning in Life Among Semi-rural Kenyans. Journal of Happiness Studies. August 2018. doi:10.1007/s10902-018-0017-9

B. OTHER:

Thesis/Dissertation

Proceedings and Symposia

Reviews

Book Chapters

Varia (online modules, CDs)

C. ABSTRACTS:

1. Johnson J, **Gibson DC**, Snih SA, Chen N-W, Macpherson V, Wong AWK. Frailty as a Predictor of Life-Space Mobility among Community Dwelling Older Mexican Americans. Archives of Physical Medicine and Rehabilitation. 2018;99(10):e17. doi:10.1016/j.apmr.2018.07.055

PUBLICATIONS - IN PRESS:

1. **Gibson DC**, Raji MA, Baillargeon JG, Kuo Y-F. Regional and Temporal Variation in Receipt of Long-term Opioid Therapy Among Older Breast, Colorectal, Lung, and Prostate Cancer Survivors in the United States. Cancer Medicine. January 2021.

PUBLICATIONS - SUBMITTED:

1. **Gibson DC**, Raji MA, Baillargeon JG, Kuo Y-F. Risk of an Opioid-Related Emergency Department Visit or Hospitalization Among Older Breast, Colorectal, Lung, and

Prostate Cancer Survivors. Mayo Clinic Proceedings. January 04, 2021.

PAPERS AND CONTINUING EDUCATION PROGRAMS PRESENTED:

1. **Gibson, DC**, Baillargeon, J, Raji, M, Kuo, YF. Examination of Regional Variation in and Effect of Federal Policy on Long-Term Opioid Therapy in Older Cancer Survivors. 26th Annual AHRQ National Research Service Award Program. (**Abstracted accepted for presentation, conference was cancelled due to COVID-19**).
2. **Gibson, DC**, Chou, LN, Baillargeon, J, Raji, M, Kuo, YF. Opioid Prescribing Trends in Women Following Mastectomy or Breast Conserving Surgery Before and After the 2014 Federal Reclassification of Hydrocodone. Academy Health Annual Research Meeting 2019 (**Podium Presentation**). Washington D.C. June 2019
3. **Gibson, DC**, Chou, LN, Baillargeon, J, Raji, M, Kuo, YF. Opioid Prescribing Trends in Women Following Mastectomy or Breast Conserving Surgery Before and After the 2014 Federal Reclassification of Hydrocodone (**Poster Presentation**). 25th Annual AHRQ National Research Service Award Program. Washington D.C. June 2019
4. **Gibson, DC**, Chou, LN, Baillargeon, J, Raji, M, Kuo, YF. Opioid Prescribing Trends in Women Following Mastectomy or Breast Conserving Surgery Before and After the 2014 Federal Reclassification of Hydrocodone (**Poster Presentation**). Houston Medication Safety Symposium. Houston, Texas. April 2019
5. **Gibson, DC**, Chou, LN, Baillargeon, J, Raji, M, Kuo, YF. Opioid Prescribing Trends in Women Following Mastectomy or Breast Conserving Surgery Before and After the 2014 Federal Reclassification of Hydrocodone (**Poster Presentation**). Public Health Symposium. Galveston, Texas. March 2019
6. Johnson, J, **Gibson, DC**, Chen, NW, Markides, K, Ottenbacher, K. Frailty as a Predictor of Life-Space Mobility Among Community Dwelling Older Mexican Americans (**Poster Presentation**). Public Health Symposium. Galveston, Texas. March 2019.
7. Downer, P., **Gibson, D.C.**, Prochaska, J. Evaluating Public Health Best Practice Recommendations Using a Social-Ecological Framework: Preliminary Findings (**Poster Presentation**). Public Health Symposium. Galveston, Texas. March 2019.
8. **Gibson, DC**, Prochaska, J, Kaul, S. Unhealthy Food Density, Poverty, and Colorectal Cancer Incidence 2005 to 2015 (**Poster Presentation**). Public Health Symposium. Galveston, Texas. March 2019
9. Johnson, J, **Gibson, DC**, Chen, NW, Markides, K, Ottenbacher, K. Frailty as a Predictor of Life-Space Mobility Among Community Dwelling Older Mexican Americans (**Poster Presentation**). 22nd Forum on Aging. Galveston, Texas. October 2018
10. **Gibson, DC**, Prochaska, J., Sapna, K. Exploring the Associations of Unhealthy Food Availability, Neighborhood Poverty, Race and Ethnicity and Stage at Diagnosis in Individuals Diagnosed with Colorectal Cancer in Texas (**Poster Presentation**). 22nd Forum on Aging, Galveston, TX. October 2018
11. **Gibson, DC**, Vo, T, Wang, A, Goodman, M. Exploring Common Terrain Between Attachment Theory and Interpersonal Theory of Suicide Among Young Kenyan Men (**Poster Presentation**). Society for Research in Child Development, Austin, TX. April 2017.

12. **Gibson, DC**, Patel, J, Lin, G, Vo, T, O'Leary K, Wang A. An Investigation into Suicide Attempts in Meru County, Kenya – Marital Conflict Predicts Higher Levels of Suicide Ideation Among Males 18-35 in Maua, Kenya (**Poster Presentation**). Global Health Symposium, University of Texas Medical Branch, Galveston, TX. October 2016.

I have read and take responsibility for the information in this document

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Signature Date

(Signature required for SOM APT purposes only)

APPROVED COD: May 2018