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I, Amarsinh M Desai, hereby submit this original work as part of the requirements for the degree of Doctor of Philosophy in Pharmaceutical Sciences/Biopharmaceutics.

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Pain Medication Utilization Among Cancer Survivors: Findings From Medical Expenditure Panel Survey

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Pain Medication Utilization Among Cancer Survivors: Findings From Medical Expenditure Panel Survey

A dissertation submitted to the
University of Cincinnati Graduate School
in partial fulfillment of the
requirements for the degree of

DOCTOR OF PHILOSOPHY

in the Department of Health Outcomes
of James L. Winkle College of Pharmacy
by

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ABSTRACT

Background: Cancer pain, either tumor-related or treatment-related, is common among cancer survivors. The objectives of this study were to 1) report recent trends in the pharmaceutical treatment of pain and HRQoL among cancer survivors; 2) to understand better the reasons for and the effects of pharmaceutical treatment of pain and 3) to assess relationship between pain medication use and workers' productivity.

Methods: This was a retrospective observational study using a nationally representative survey database. Cancer survivors, excluding survivors of non-melanoma skin cancer, were identified using survey questions and clinical classification codes. Utilization, cost and payer cost shares were obtained for following class of drugs such as non-opioids, opioids, narcotic analgesic combinations and adjuvants annually from 2008 to 2013. The demographic, geographical, clinical and economic predictor variables were regressed to assess their association with the total number of pain/opioid prescriptions. Productivity measures obtained from SF-12 and CSAQ were assessed for their association with pain/opioid medications use. Descriptive statistics were computed employing appropriate statistical procedures for the MEPS with its unique sampling design. Estimates were reported using zero-inflated Poisson regression.

Results: Out of 23.4 million cancer survivors in 2008, 40.8% took pain medications; in 2013, 43.9% of 24.8 million survivors took pain medications; these percentages exceed those for patients without a history of cancer. The total number of prescriptions for pain medications increased from 60.3 million in 2008 to 74.3 million in 2013. The utilization of opioids and adjuvant analgesics was significantly ($p \leq 0.05$) higher among the cancer survivors compared to individuals without cancer history. The cost (not adjusted for inflation) of pain medications increased from $3.5 billion in 2008 to $5.6 billion in 2013. Overall, the patient cost share decreased from 23.3% in 2008 to 17.0% in 2013. Stratified by opioid exposure the worst PCS and MCS scores were reported by opioid users. The odds of not receiving opioid medications was significantly ($p \leq 0.05$) higher among elderly [age 65-74, OR= 2.73 (1.32 - 5.64)],

minorities belonging to other race group [OR= 2.14 (1.03 - 4.43)], adjustment disorder [OR=3.41 (1.35 - 8.57)], more than one mental condition [OR=3.64 (1.51 - 8.76)]; from the count model significant ($p \leq 0.05$) association was obtained for variables, experiencing high/severe pain [3.49 (2.09 - 5.84)], arthritis [1.93 (1.33 - 2.80)], more than one painful comorbidities [1.69 (1.12 - 2.55)], higher income [1.52 (1.09 - 2.11)], insurance status change over time [2.12 (1.41 - 3.16)]. Nearly, 54.0%-62.0% experienced little/no work limitation reported through SF-12 productivity measures. Among those who experienced no work limitation, significantly ($p \leq 0.05$) higher proportion (73.0%) of respondents were non-users of pain medications. A higher proportion (75.0%) of post-treatment cancer survivors feels productive at work.

Conclusion: This study reported substantial changes in treatment of cancer pain over-time. The economic impact of cancer survivorship is increasing with growing cancer population. The spending in terms of patient share decreased. Poor HRQoL scores were obtained stratified by opioid exposure. Many post-treatment cancer survivors were employed and remained productive.

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LIST OF GLOSSARY AND ACRONYMS

ACS: American Cancer Society

AHRQ: Agency for Healthcare Research and Quality

AIC: Akaike's Information Criteria

ASCO: American Society for Clinical Oncology

BIC: Bayesian Information Criteria

BMI: Body Mass Index

BPI: Brief Pain Inventory

CAPI: Computer Assisted Personal Interview

CCC: Clinical Classification Code

CDC: Centers for Disease Control and Prevention

CIPN: Chemotherapy-Induced Peripheral Neuropathy

CSAQ: Cancer Self-Administered Questionnaire

GOF: Goodness-of-fit

HMO: Health Maintenance Organization

HRQoL: Health-Related Quality-of-Life

IASP: International Association for the Study of Pain

ICD-9-CM: International Classification Disease, Ninth Revision, Clinical Modification

IOM: Institute of Medicine

IRB: Institutional Review Board

MCS: Mental Component Summary

MEPS: Medical Expenditure Panel Survey

MEPS-HC: Medical Expenditure Panel Survey-Household Component

MSA: Metropolitan Statistical Area

NCCS: National Coalition for Cancer Survivorship

NCI: National Cancer Institute

NCHS: National Center for Health Statistics

NHIS: National Health Interview Survey

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

OTC: Over the Counter

PCS: Physical Component Summary

PSU: Primary Sampling Unit

QoL: Quality of Life

SNRI: Serotonin Norepinephrine Reuptake Inhibitor

SSRI: Selective Serotonin Reuptake Inhibitor

SSU: Secondary Sampling Unit

VIF: Variance Inflation Factor

WHO: World Health Organization

ZIP: Zero-Inflated Poisson

CHAPTER ONE:- INTRODUCTION

1.1 Overview

According to International Association for the Study of Pain (IASP), *"Pain is an unpleasant sensory or emotional experience associated with actual or potential tissue damage or an experience described in terms of such damage".*[1] Cancer pain, either tumor-related or treatment-related, is common among cancer survivors.

Virtually all patients with malignant form of cancer experience acute or chronic pain. The presence of long-term effects and emerging health problems secondary to the condition and treatment, are experienced by a number of cancer survivors for years following primary cancer treatment. Psychosocial and physical problems among cancer survivors are frequent and may include pain, fear of recurrence, feeling of isolation, anxiety and depression, problems with social relationships and economic hardships related to the cost of care, job loss, employment and insurance discrimination. There exist several patients-, clinicians- and system-related barriers which negatively impacts quality of life. Cancer pain may be acute or chronic. According to World Health Organization (WHO), if pain occurs prompt oral administration of drugs should begin with non-opioid analgesics such as NSAIDs and Salicylates followed by narcotic analgesic combinations and Opioids.[2] Adjuvant analgesics are routinely used in combinations with opioids and non-opioids in management of pain control. However, there exists tremendous gap in literature when it comes to real-world utilization data among cancer survivors. Therefore, the objective of this study was to quantify, explain and report recent trends in the pharmaceutical treatment of pain among cancer survivors in the United States capturing important study measures such as utilization, cost, payer cost share, Health-Related Quality-of-Life (HRQoL) and work-related productivity.

The study is significant because it will provide meaningful insight on pain medication utilization among cancer survivors. The study is innovative because it is the first study that summarizes pain medication utilization among cancer survivors using US civilian non-institutionalized population database.

1.2 Literature Review

The term "cancer survivor" is used variably and widely in the literature. Traditionally it relates to any person having no disease after completion of treatment. However, the National Coalition for Cancer Survivorship (NCCS) defines cancer survivorship as the collective process of living with, through and beyond a cancer diagnosis. Therefore, by definition, survivorship begins at the time of diagnosis and an individual is considered to be cancer survivor from time of diagnosis until end of the life. Presently this definition is accepted by authorities such as Institute of Medicine (IOM), Centers for Disease Control and Prevention (CDC), American Society for Clinical Oncology (ASCO), National Cancer Institute (NCI). The number of cancer survivors continuous to grow in United States and increased from approximately 3 million in the 1970s to nearly 14.5 million in 2014[3] and the number is expected to increase 18 million by 2022[4]. The increase survival rates may be due to advancement in cancer screening[5], aging and growth of the population[6] and increase in life expectancy as a result of definitive treatment care[4]. Among male cancer survivors, the most common cancers includes prostate cancer (43%), colorectal cancer (9%), melanoma (8%), urinary bladder (7%), non-Hodgkin lymphoma.[4] Among female cancer survivors, breast cancer (41%), uterine corpus (8%), colorectal (8%), melanoma (7%), thyroid (6%) were most commonly reported.[4] Cancer survivors may experience short- and long- term morbidity secondary to cancer and effects of treatment such as pain, fatigue, incontinence, cardiotoxicity, lymphedema, psychological distress, sexual dysfunction and cognitive decline.

Pain among cancer survivors is common and complex symptom that affects many aspects of person's life. Cancer pain may be acute or chronic. Cancer pain may be tumor-related, treatment-related or from non-cancer health conditions. Tumor-related pain can be categorized into 1) somatic pain caused by tumor

involvement of bone, joints, connective tissue or muscle 2) visceral pain caused by obstruction of any hollow viscus or injury to visceral structure such as hepatic capsule, visceral pleura, or peritoneum[7] and 3) neuropathic pain is caused by tumor invasion may involve the peripheral nerves, nerve roots, plexuses and spinal cord.[8] Approximately 50% to 75% of cancer patients who experiences chronic pain have tumor-related pain.[9,10] Occurrence rates of cancer pain range from 14% to 100%.[8] Symptom such as severe pain is often experienced by 30-50% of cancer patients undergoing active antineoplastic therapy and 75-90% of individuals with advance disease.[11-13] Post-treatment cancer survivors face challenges regarding late- and long-term effects from illness and treatm

ent. In certain subgroups, such as breast cancer survivors, more than 30% reported above average pain 10 years after treatment.[14] Among post-treatment cancer survivors pain is caused by treatment modalities such as surgery, radiation and chemotherapy. Each may be associated with acute or chronic form of pain. Surgery often may cause persistent post-surgical pain syndromes such as postmastectomy[15] and phantom pain. Different class of chemotherapeutic agents includes taxanes (paclitaxel, docetaxel), platinum compounds (cisplatin, carboplatin), vinca alkaloids (vincristine, vinblastine), proteasome inhibitors (bortezomib) and other (thalidomide, lenalidomide, lxabepilone). These agents are known to cause chemotherapy-induced pain neuropathy (CIPN).[16-19] Radiation therapy are known to produce persistent pain mostly plexopathies and osteoradionecrosis.[20] Similar other problems may not appear until for several months or even years. Regardless of when they appear, the long-term cancer symptoms and late-effects of cancer treatment can negatively impact patients' quality of life.

World Health Organization (WHO) has developed a pain ladder according to which for pain prompt oral administration of drugs should begin with non-opioid analgesics followed by weak opioids to strong opioids.[2] The adjuvant analgesics are routinely used in combinations with opioids and non-opioids analgesics to manage cancer pain. However, even with the well-established pain medications profile cancer survivor often encounters several barriers for effective cancer pain treatment. Current challenges in adequate treatment include patient-, clinician-, and system-related barriers.[21-24] Patients may underreport

pain because of poor understanding, communication problem, stoicism or concerns about chemotherapy or radiation therapy. In addition, fear of addiction, development of side effects, high costs of opioids, underinsured are often associated with poor adherence when opioid therapy is initiated. Clinicians may have inadequate knowledge and skills in context to pain identification, or attitudes towards ethnic minorities that minimize the importance of pain management. They may be reluctant to prescribe opioids due to concern about abuse, addiction and side-effects. System-related barriers to optimal analgesic therapy may include monetary concerns (lack of health insurance coverage, expensive drugs), a limited number of specialists in pain management or palliative care. In the US, opioids are designated as "controlled substances" under federal law known as Controlled Substance Act (CSA). Drugs with the potential for abuse and addiction are regulated with federal restrictions on whether and how they can be prescribed.[25] While opioids are the first-line approach for moderate or severe cancer pain they are potentially abusable drugs. The consequences of opioid abuse have been well documented among general US population; drive the imperative that its physician's responsibility for risk management when these drugs are prescribed for legitimate medical purposes. Uncontrolled pain and inadequate pain management results in prolong suffering, interference with daily activities, decreased ability to cope with illness, and even increased hospital readmission.

1.2.1 Types of Cancer Pain

Cancer pain types have been used widely and variably in literature. The different terms used to describe patients experience with cancer pain are:

(a) Breakthrough:

It is referred to as "periodic flares of pain that breaks through current analgesic regimen". Cancer patients often experiences moderate to severe episodes of pain. The elevated pain is triggered among patients who are already on pain medication to control background pain. Typical pain episodes can last around 30 minutes; however, breakthrough pain can persist for hours.

(b) Episodic:

Previous literature has used term episodic and breakthrough pain interchangeably. The term "episodic" has been used to refer any pain that varies with time; therefore, the pain intensity varies. It is characterized by rapid onset, usually severe with typical average pain duration of 30 min. The episodic pain subtypes including incident (caused by movement), idiopathic (of unknown origin) and end-of-dose pain (pain usually experienced between subsequent dose) have been described by Zeppetella *et al.*[26] The patient may experience more than one episodic pain which is subjective and vary among patients within same day or from day-to-day.

(c) Incident:

The pain of incident nature voluntary (by physical activities) or otherwise (idiopathic in nature) usually arises as a result of activities such as walking, standing, arthritic joint movement, wound stretching, dressing changes, coughing, leading to quantitative increase in pain intensity. Incident pain measured in clinical practice is one of those few indicators that can reliably predict patient poor response to conventional pharmacologic therapy.

(d) Analgesic gap:

It is also known as "End-of-dose pain"; sometimes classified as subtype of breakthrough pain. It occurs prior to the next scheduled dose of analgesic due to inadequate pain medication dose, declining analgesic level at end of treatment or the interval between administrations of subsequent dose is too long. It is usually characterized by gradual onset of intensity, longer duration and can be treated by adjusting pain medication dose.

(e) Acute:

Pain that persists for shorter duration of time is referred to as acute type. Some literature applies acute pain that lasts less than 30 days. It is commonly associated following course of treatment, surgery or with disease condition.

(f) Chronic:

Pain that persists for longer duration of time is referred to as chronic type. Unlike acute pain it may be associated with treatment, surgery or with disease condition however it lasts for 3 months or more. The chronic pain is mostly controlled by pain medication and if not treated disrupts patient's life negatively.

(g) Nociceptive:

Inflammatory pain caused by stimulation of peripheral nerve fibers and is predominantly sustained by ongoing tissue injury. It may be somatic or visceral.

If somatic involves injury to somatic structures like joints, bones, muscles can be localized by patients and often described pain as "throbbing", "stabbing", "aching" in quality.

If visceral involves injury to visceral structures such as myocardium, pleura, organ capsules usually more difficult for patients to localize and often described pain as "crampy" or "gnawing".

(h) Neuropathic:

Pain may be treatment- or tumor-related causing damage or injury to any part of nervous system. It is often described by patient as "sharp", "burning", "electric shock-like" associated with numbness or tingling sensation of site affected.

(i) Referred pain:

Referred type of pain is perceived at location other than site of origin. For example hepatic metastases patient referring shoulders pain.

(j) Phantom pain:

A phantom type of pain is experienced from part of the body that has been removed. A classic example related to this is chronic post-surgical pain felt by breast cancer patients following mastectomy.

1.2.2 Causes of Cancer Pain

Cancer pain is caused by tumor itself or by treatment received. Cancer-related pain may be due to growing of cancer cells and destroying the tissues at the site where cancer is located. Also, when tumor is spread to other parts of body (metastases) causes cancer-related chronic pain. As the cancer continues to grow and spread it may put pressures on bones, organs and nerves causing pain. Cancer treatments are also documented to cause many potentially painful syndromes. Among cancer patients there is substantial difference in perceiving, reporting and experiencing this pain. A group of clinically meaningful pain-related signs and symptoms is termed as cancer pain syndrome. Based on onset and duration the cancer pain syndromes are broadly categorized into acute or chronic.[27]

Acute pain syndromes are usually caused by diagnostic or therapeutic interventions; however, some are directly related to tumor itself. Chronic pain syndromes are directly related to tumor itself or due to antineoplastic treatment (including chemotherapy, radiation, surgery or hormonal).

Tumor-related cancer pain syndromes include somatic nociceptive (neoplasm associated with bone, muscle or connective tissue, joints causing persistent somatic pain), visceral nociceptive (caused by neoplastic invasion to visceral structures or by obstruction to any hollow viscus organ) and neuropathic pain (caused by injury to neural structures and may involve the peripheral nerves, spinal cord, plexuses, nerve roots). Treatment-related cancer pain syndromes include pain resulting from antineoplastic treatment such as chemotherapy, radiation, surgery, hormonal therapy. The most prevalent pain syndrome resulting from chemotherapy is Chemotherapy-Induced Peripheral Neuropathy (CIPN) characterized by damage of nerves that are distant from brain and spinal cord. These nerves are referred to as peripheral nerves. It is progressive, degenerating and often irreversible in nature characterized by numbness, tingling, and burning pain. The incidence of CIPN among cancer patients ranges from 30-40%.[28] In radiation therapy, the high-energy x-rays, gamma rays and charged particles are employed to kill malignant cells and can result in array of persistent painful syndromes such as plexopathies and

osteoradionecrosis.[20] Radiation often results in a burning sensation or painful scars. Surgery associated with cancer is painful and takes longer time to recover. Surgery has been known to produce persistent pain, such as phantom pain syndromes after limb amputation, post-mastectomy pain, post-thoracotomy pain. Hormonal therapies have also been documented to cause chronic pain particularly aromatase inhibitors. In order to prevent recurrence of breast cancer, aromatase inhibitors are often prescribed and can produce arthralgias.[29]

Table 1: Cancer Pain Syndromes

<table>
<tr><th colspan="3">Tumor-Related Cancer Pain Syndromes[9,30,31]</th></tr>
<tr><td colspan="3">I. Somatic nociceptive</td></tr>
<tr><td>(a) Tumor-related bone pain</td><td>(b) Tumor-related soft tissue pain</td><td>(c) Paraneoplastic pain syndrome</td></tr>
<tr><td rowspan="3">Base of skull metastases: Clivus syndrome, Jugular foramen syndrome, Middle cranial fossa syndrome, Orbital syndrome, Paraseller syndrome, sphenoid sinus syndrome</td><td>Eye and ear pain syndromes</td><td>Hypertrophic pulmonary osteoarthopathy</td></tr>
<tr><td>Headache and facial pain</td><td>Muscle cramps</td></tr>
<tr><td>Pleural pain</td><td>Oncogenic osteomalacia</td></tr>
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<tr><td>Paraneoplastic Raynaud’s phenomenon</td></tr>
<tr><td rowspan="2">Pain syndromes related to pelvis and hip: Hip joint syndrome, malignant piriformis, pelvic metastases</td><td>Tumor-related gynaecomastia</td></tr>
<tr><td rowspan="2"></td></tr>
<tr><td>Vertebral syndromes: Atalanto-axial destruction and odontioid fracture, C7-T1 syndrome, T12-L1 syndrome, Sacral syndrome, back pain</td></tr>
<tr><td colspan="3">II. Visceral nociceptive</td></tr>
<tr><td colspan="3">Adrenal pain syndrome</td></tr>
<tr><td colspan="3">Chronic intestinal obstruction</td></tr>
<tr><td colspan="3">Hepatic distention syndrome</td></tr>
<tr><td colspan="3">Malignant perineal pain</td></tr>
<tr><td colspan="3">Midline retroperitoneal syndrome</td></tr>
<tr><td colspan="3">Peritoneal carcinomatosis</td></tr>
<tr><td colspan="3">Ureteric obstruction</td></tr>
<tr><td colspan="3">III. Neuropathic pain syndrome</td></tr>
<tr><td>(a) Plexopathies</td><td>(b) Radiculopathies</td><td>(c) Miscellaneous</td></tr>
</table>

Cervical plexopathy	Cervical radiculopathy	Cranial neuralgias
Lower lumbosacral plexopathy	Lumbosacral radiculopathy	Leptomeningeal metastases
Malignant branchail plexopathy	Thoracic radiculopathy	Malignant painful radiculopathy
Malignant lumbosacral plexopathy		Paraneoplastic sensory neuropathy
		Peripheral mononeuropathies

Treatment-Related Cancer Pain Syndromes[9,32-34]			
I. Chemotherapy	II. Radiation	III. Surgery	IV. Hormonal
Chemotherapy induced peripheral neuropathy	Burning perineum syndrome	Stump pain	Arthralgia/myalgia
Bony complications of long-term steroids	Branchial plexopathy	Phantom pain	Osteoporotic compression fractures
Raynaud's syndrome	Chest pain/tightness	Postmastectomy pain	
	Cystitis	Post radical neck dissection	
	Enteritis and Proctitis	Post-thoracotomy pain	
	Fibrosis of skin	Post-thoracotomy frozen shoulder	
	Fistula formation	Postsurgery pelvic floor pain	
	Lymphoedema	Neuroma pain	
	Myelopathy		
	Osteoradionecrosis		
	Pelvic insufficiency fractures		
	Peripheral nerve entrapment		

1.2.3 Epidemiology of Cancer Pain

Cancer survivors can feel pain at any stage from diagnosis, during treatment and even after cure. In recent years, cancer pain has received attention and several studies have demonstrated cancer pain prevalence that varies widely by cancer pain type, site and staging. The pain prevalence estimates vary because of lack of standardized approach in pain definition, perception and management. Other contributing factors include heterogeneity of pain mechanism (nociceptive, neuropathic and mixed), heterogeneity of cancer diagnosis site and variation in treatment settings (pain clinic, hospice, oncology centers).

Furthermore, the published studies have varied sampling procedures, study design, inclusion and exclusion criteria that have limited the understanding of pain prevalence. For instance, many investigators included high risk population such as advanced cancer patients, palliative care, those receiving treatment at oncology unit. These samples are often chosen by convenience which truly does not represent larger population of cancer patients. The researchers have employed cross-sectional designs such as prospective questionnaire or retrospective chart reviews to examine epidemiology of cancer pain. The prospective survey approach can provide quality and complete clinical assessment data; however, they are still limited by the fact that cancer pain information obtained is at some particular point in the cancer trajectory. Similarly, retrospective chart reviews might not provide comprehensive data because researchers rely on existing data; in past, information on pain characteristics and related variables might be incomplete. Challenges arise as different instruments are employed by investigators to measure the pain limiting the ability of readers to compare estimates across studies. For instance, some studies have documented prevalence and severity of pain using visual analogue or numerical rating; others have reported pain more broadly capturing incidence, daily function, frequency, severity involving other functional variables using multidimensional questionnaire such as Memorial Symptom Assessment Scale, McGill Pain Questionnaire or Brief Pain Inventory (BPI).

1.2.3.1 Epidemiology by Type of Cancer Pain

Studies have documented tumor- or treatment-related cancer pain prevalence by diverse types such as breakthrough[35-42], episodic[26,43], incident[26], persistent and intermittent[44], nociceptive[40,45-49], neuropathic[40,45-50]. The occurrence rates reported ranges as high as from 13.0-100%[8,51-53]. Around 30.0%-55.0% reported pain due to tumor[11,12,54], 23.0%-59.0% because of treatment[11,12,54]. Breakthrough pain was experienced by 40.3% of patients as reported by Greco *et al*.[35] The episodic pain prevalence as reported by Zeppetella *et al*., was 19.0%-95.0% and its subtypes incident pain, idiopathic pain, and end-of-dose pain were 32.0%-94.0%, 28.0%-45.0% and 2.0%-29.0%, respectively.[26] Study conducted by Ovayolu *et al*., documented persistent and intermittent pain experienced by 32.3% (n=71) and 67.7% (n=149), respectively, of 220 cancer patients.[44] A systematic review conducted by Bennett *et al*., included 19 studies comprising 11,063 patients; approximately 59.4%, 19.0%, 20.1% and 1.5% experienced pain of nociceptive, neuropathic pain, mixed pain and unknown origin, respectively.[45] Petzke and team administered questionnaire among cancer patients admitted in pain clinic of which 39.0% reported transitory pain; by cancer-type the prevalence was 49.0% of nociceptive, 7.0% of neuropathic, 44.0% of nociceptive and neuropathic; by cancer treatment pain experienced by patient were 12.0% receiving no therapy, 68.0% of surgery, 55.0% of radiotherapy and 43.0% of Chemotherapy.[48] Table 2 briefly summarizes studies with cancer pain prevalence by cancer type.

Table 2: Epidemiology Of Cancer Pain Among Cancer Survivors Based On Type Of Cancer Pain

Source	Study design	Cancer pain type	Incidence or prevalence of pain
Ovayolu *et al,* 2015[44]	Cross-sectional and descriptive design using questionnaire and visual analogue scale	Persistent and intermittent pain	From total of 220 cancer patients, pain was reported in 32.3% (n=71) and 67.7% (n=149), respectively, experiencing persistent and intermittent pain
Bennett *et al,* 2012[45]	Systematic review	Nociceptive (visceral or somatic origin), neuropathic, mixed pain (nociceptive and neuropathic), and unknown/other mechanism	From 19 studies including 11,063 patients: (a) 59.4% (n=6569) had nociceptive pain (b) 19.0% (n=2102) had neuropathic pain (c) 20.1% (n=2227) of cancer patients are affected by mixed pain (d) 1.5% (n=165) experience pain of unknown cause .
Greco *et al,* 2011[35]	Multicenter, prospective, longitudinal, non-randomized study	Breakthrough cancer pain	Of 1,801 cases of cancer patients, 40.3% (n=723) had breakthrough pain of which 33% (n=239) reported pain of neuropathic origin
Fischer *et al,* 2010[54]	Cross-sectional study including subjects undergoing treatment for cancers of the lung, head/neck, or prostate at the Radiation Oncology Clinic using McGill Pain Questionnaire	Tumor- & treatment-related	Of 302 cancer patients, tumor-related pain reported was 30.8% (n=93), treatment-related 40.1% (n=121), both 13.2% (n=40)
Lema *et al,* 2010[50]	Review	Cancer-related neuropathic pain	Pain associated with direct tumor involvement reported was 78% of hospitalized patients and 62% of outpatients; whereas, treatment-related pain was 19% among hospitalized patients and 25% of outpatients
Shaheen *et al,* 2010[52]	Prospective survey	Cancer pain	Of 186 cancer patients, 63% (n=117) reported cancer pain
Breivik *et al,* 2009[55]	The European Pain in Cancer (EPIC) survey conducted in 11 European countries: Czech	Cancer-related pain	Of 5084 adult patients surveyed, 56% (n=2,864) suffered moderate-to-severe pain at least monthly

	Republic, Denmark, France, Finland, Ireland, Italy, Norway, Sweden, Romania, Switzerland, and the UK, and Israel		
Valeberg *et al,* 2008[53]	Questionnaire administered to cancer patients admitted to oncology outpatient clinic	Cancer pain	Of total 217 cancer patients who returned the questionnaire, 53% (n=115) reported cancer only related pain, of which 1%, 18.4%, 11.5% and 12.9% were receiving current treatment- surgery, radiation, chemotherapy, hormonal therapy, respectively
Holtan *et al,* 2007[36]	Survey questionnaire using Brief Pain Inventory QOL instrument	Cancer-related breakthrough pain	Of 857included hospitalized patients, 52% (n=453) stated having cancer-related pain
Teunissen *et al,* 2007[56]	Systematic review	Cancer pain	- Group I included studies with patients reporting cancer symptoms prevalence overall - Group II included studies with patients reporting cancer symptoms in the last one to two weeks of life The pooled pain prevalence among group 1 (including 37 studies and 21,917 patients) was 71% (95% CI: 67%-74%) and among group 2 (including 5 studies and 1,626 patients) was 45% (95% CI: 32% - 59%)
Van den Beuken *et al,* 2007[12]	Meta-analysis: Data from 52 studies were pooled to report cancer pain prevalence	Tumor- & treatment-related	Pain prevalence among cancer patients: (a) Receiving anticancer treatment (n=1,408): 59% (95% CI: 44.0 – 73.0) (b) Patients with all stages (n=8,088): 53% (95% CI: 43-63) (c) Cured of cancer (n=726): 33% (95% CI: 21.0 - 46.0)
Van den Beuken *et al,* 2007[11]	Prospective survey: A self-report patient questionnaire and medical data form filled in by the treating physician was developed	Tumor- & treatment-related	1,429 cancer patients were recruited over 5 months of study period, (a) 55% of study population experienced pain of which 44% of patients reported moderate to severe pain (b) 23% of study population reported treatment-related pain of 22% had moderate to severe pain
Sawyer *et al,* 2006[57]	Population-based, prospective observational study	Cancer pain	Total of 1,000 participants, 74% reported pain; among these, 52% experienced daily pain, with 26% reporting agonizing pain
Bradley *et al,* 2005[58]	Questionnaire administered to cancer patients admitted to	Cancer pain	Of the total 1,296 patients 1,137 had complete response on pain questionnaire, of which 28% (n=319), 32% (n=367), 17% (n=198), 78% (n=884) reported mild, medium, severe and total pain, respectively

	palliative radiotherapy clinic		
Goudas *et al,* 2005[51]	Review	Cancer pain	Pain prevalence reported among cancer survivor ranged from 14 – 100%
McGuire *et al,* 2004[8]	Review	Tumor- & treatment-related	(a) Occurrence rates ranges from 14.0 - 100% (b) Rates are higher 70.0 – 100% in palliative care or pain management settings
Davis *et al,* 2004[46]	Palliative Oncology Review	Tumor (somatic nociceptive pain, visceral nociceptive pain, neuropathic pain)- & treatment-related	(a) Pain type includes: i) somatic nociceptive pain – 50% ii) visceral nociceptive pain - 20% iii) neuropathic pain – 33% (b) 6 to 17% of patients with non-metastatic cancer reported pain directly attributable to cancer (c) 35 to 56% reported pain during cancer treatment with 20 to 34% experiencing severe pain
Pignon *et al,* 2004[59]	Cross-sectional survey conducted in radiotherapy oncologic unit	Cancer pain	Total of 126 patients, 93 completed the survey of which, 71% (n=66) reported pain
Hwang *et al,* 2003[37]	Prospective longitudinal study using Brief Pain Inventory QOL instrument	Cancer breakthrough pain	Of the 74 patients recruited: (a) On day one, 70% had breakthrough pain (somatic 42%, visceral 10% and neuropathic 48%) (b) After initiating the pain treatment, at week one, 36% had breakthrough pain (somatic 42%, visceral 2% and neuropathic 54%)
Fortner *et al,* 2002[38]	Telephonic survey	Breakthrough pain	Of the1000 patients surveyed, 53% (n = 527) had experienced pain since being diagnosed with cancer
Zeppetella *et al,* 2003[26]	Review	Episodic pain	The episodic pain prevalence reported was 19-95% and its subtypes incident pain, idiopathic pain, and end-of-dose pain were 32-94%, 28-45% and 2-29% respectively
Gomez-Batiste *et al,* 2002[39]	Observational and cross-sectional study	Breakthrough pain	Of 397 patients, 41% reported breakthrough pain
Swanwick *et al,* 2001[43]	Questionnaire administered to cancer patients admitted to in-patient unit	Episodic pain	Of the total 132 cancer patients with pain, 93% (n=123) reported at least one pain with a clear episodic nature in the preceding 24 hour
Zeppetella *et al,* 2000[40]	Prospective survey administered to cancer	Breakthrough pain	Of the 245 patients, 89% (n=218) reported breakthrough pain. The pathophysiology were classified as somatic 46%, visceral 30%,

	patients in a hospice		neuropathic 10% or mixed origin 16%
Caraceni *et al,* 1999[47]	Prospective, cross sectional, multicenter survey	Tumor-related: nociceptive (visceral or somatic origin), neuropathic, mixed pain (nociceptive and neuropathic), other and treatment-related	Of the 1095 patients: (a) Nearly 93% patients had one or more pains caused directly by the cancer (b) Around 21% of patients had one or more pains caused by cancer therapies (c) Somatic pain: 71.6%, visceral pain: 34.7%, and neuropathic pain 39.7% of the patients (d) 65% of patients reported breakthrough pain
Petzke *et al,* 1999[48]	Questionnaire administered to cancer patients admitted in pain clinic	Tumor (somatic nociceptive pain, visceral nociceptive pain, neuropathic pain)- & treatment-related	Total of 631 cancer patients admitted, 39% (n=243) reported transitory pain By cancer-type the prevalence reported was nociceptive 49%, neuropathic 7%, nociceptive and neuropathic 44% By treatment: No therapy 12%, Surgery 68%, Radiotherapy 55%, Chemotherapy 43%
Portenoy *et al,* 1999[41]	Survey questionnaire using Brief Pain Inventory QOL instrument	Breakthrough pain	Total of 164 patients who met the criteria, 51.2% (n=84) reported breakthrough pain, 75% (n=107) reported pain directly caused by neoplasm of which 38% was of nociceptive, 10% was of neuropathic and 52% was of nociceptive and neuropathic origin
Bernabei *et al,* 1998[60]	Retrospective cross-sectional study among elderly and minority cancer patients admitted to nursing homes	Daily cancer pain	Of total of 4,003 patients, 24%, 29%, and 38% of those aged 85 or older, 75 - 84 years and 65 - 74 years, respectively, reported daily pain
Fine *et al,* 1998[42]	Questionnaire administered to home-based terminally ill population	Breakthrough pain	Of 22 hospice patients, 86% experienced breakthrough pain
Grond *et al,* 1996[49]	Open prospective using self-assessment 6-point verbal rating scale	Tumor (somatic nociceptive pain, visceral nociceptive pain, neuropathic pain)- & treatment-related	Of 2,226 cancer patients: (a) 85% reported tumor-related pain and 17% reported pain due to anti-neoplastic treatment (b) Pain in bone and soft tissue (35% and 45%), visceral structures (33%), neuropathic origin (34%)
Brescia *et al,* 1992[61]	Prospective single center survey	Cancer pain	Of 1,103 patients admitted to hospital, 73% reported pain on admission and 38% reported severe pain

Portenoy *et al,* 1989[62]	Review	Cancer pain	The cancer pain prevalence reported was 50% (11% -75%)

1.2.3.2 Epidemiology of Cancer Pain by Cancer Site

Cancer pain is a complex phenomenon affecting somatic (muscles, joints, bones) and visceral structures (organ capsules, hollow viscus, myocardium). Somatic pain arises because of inflammation to soft tissue or metastatic bone disease. The underlying mechanism for somatic pain is either due to release in inflammatory mediators, simulation of nociceptors, or an increase in interoseal pressure associated with muscles, joints and tendons. In contrast to visceral pain, somatic is usually sharp in nature, well localized and increases with activities. Visceral pain results because of direct simulation of nerves arising due to either tumor penetration of the viscera or because of radiation and chemotherapy. The underlying mechanism includes distension, stretching or ischemia of the viscera. Often patients experience difficulties as visceral pain tends to be deep, poorly localized, aching or colicky type. Neuropathic pain may be by treatment or tumor invasion causing damage or injury to any part of nervous system. It is often described by patient as burning, electric shock-like in nature and associated with numbness or tingling sensation of site affected.

Although studies have published wide range of pain prevalence by cancer site, pain involving visceral and somatic structures is highest for the following tumors- breast 23.0%-92%, lung/respiratory 17.0%-86%, head and neck 16.0%-91%, genitourinary 58.0%-90%, prostate 13.0%-91%, colorectal 31.0%-85%, gastrointestinal 40.0%-88%, lymphoma 20.0%-87%, pancreas 72.0%-100%, sarcoma 39.0%-100%, gynecological 14.0%-90%, central nervous system 50.0%-90%, cervix/vagina 0-87%, ovary 39.0%-71%, bladder/kidney 83.0%-89%, hepatobiliary 29.0%-74%, leukemia 5.0%-66%, melanoma 20.0%-100%, esophagus 71.0%-77%, bone 49.0%-80%, stomach 75.0%, lung 11.0-72%.[48,61-63] A systematic review conducted by Van den Beuken and colleagues reported pooled pain prevalence for six type of cancer including head/neck 70.0%, gynecological 60.0%, gastrointestinal 59.0%, lung/bronchus 55.0%, breast 54.0%, urogenital 52.0%.[12] Table 3 briefly summarize studies with cancer pain prevalence by cancer site.

Table 3: Epidemiology Of Cancer Pain Among Cancer Survivors Based On Cancer Site/Location

Source	Study design	Settings	Pain prevalence
Ovayolu *et al,* 2015[44]	Cross-sectional and descriptive design using questionnaire and visual analogue scale for pain rating	Chemotherapeutic unit and adult oncology clinic	From total of 220 cancer patients, pain prevalence reported was head 11.4% (n=25), extremities 9.5% (n=21), abdomen 29.1% (n= 64), chest 17.3% (n=38), back and low back 18.6% (n=41), total body 14.1% (n=31)
Higginson *et al,* 2013[63]	Systematic literature review	Inpatient, outpatient, at home, hospice, referred to palliative care services	The prevalence of cancer pain by primary tumor site: Breast (23-92%), lung/respiratory (17-86%), head and neck (25-91%), genitourinary (58-90%), prostate (13-91%), colorectal (31-85%), gastrointestinal (40-88%), lymphoma (20-87%), pancreas (72-100%), sarcoma (39-100%), gynecological (14-90%), central nervous system (50-90%), cervix/vagina (0-87%), ovary (39-71%), bladder/kidney (83-89%), hepatobiliary (29-74%), leukemia (5-66%), melanoma (20-100%), esophagus (71-77%)
Greco *et al,* 2011[35]	multicenter, prospective, longitudinal, nonrandomized study	Outpatient clinic, hospice, hospital unit	Total of 1,801 cases of cancer patients, 40.3% (n=723) reported pain and based on primary tumor site the pain prevalence was lung 21% (n=152), breast 14.8% (n=107), colon-rectal 12.4% (n= 90), prostate 9.3% (n= 67), gynecologic 4.7% (n= 34), pancreas 5.4% (n=39), genitourinary 6.9% (n=50), stomach 5.4% (n=39), head and neck 5.9% (n=43), other 13% (n=94), missing 1.2% (n=8)
Fischer *et al,* 2010[54]	Cross-sectional study including subjects undergoing treatment for cancers of the lung, head/neck, or prostate using McGill Pain Questionnaire	Radiation oncology clinic	The total 302 cancer patients comprise of lung(n=146), head/neck (n=93) and prostate (n=63), the tumor and/or treatment-related or unknown origin was 87.7% (n=128), 95.7% (n=89), 81% (n=51) respectively
Harrington *et al,* 2010[64]	Systematic review	Ambulatory cancer patients	(a) For breast cancer: first six months' post-treatment: 26-47%, 6-12 months: 20-23%, 1-2 years:21-41%, 2-5 years: 19-41% (b) For prostate cancer: > 5 years: 54% (c) For colon-rectal cancer: > 5 years: 27.1%
Lema *et al,* 2010[50]	Review	Pain service	15%–20% of breast cancer patients reported brachial plexopathy, of which 30%–40% were of direct tumor involvement

Breivik *et al,* 2009[55]	The European Pain in Cancer (EPIC) survey conducted in 11 European countries: Czech Republic, Denmark, France, Finland, Ireland, Italy, Norway, Sweden, Romania, Switzerland, and the UK, and Israel	Patients managed by medical oncologists, general practitioner, palliative care specialist or a pain specialist	Of the 573 patients selected for phase II in-depth interview, the pain prevalence based on cancer site was: blood-borne cancer 2% (n=14), bone/muscle 7% (n=40), bowel/colorectal 11% (n= 68), brain tumor 1% (n=11), breast 27% (n=155), gynecological 9% (n=53), head & neck 5% (n=33), leukemia 2% (n=12), lung 8% (n=47), lymphoma 3% (n=19), non-Hodgkin's lymphoma 2% (n=12), pancreatic 2% (n=16), prostate 6% (n=36), testicular 1% (n=11), other 8% (n=46)
Valeberg *et al,* 2008[53]	Questionnaire administered to cancer patients	oncology outpatient clinic	Of total 217 cancer patients who returned the questionnaire, 53% (n=115) reported cancer only related pain; based on cancer site the pain prevalence was breast 24.3%, prostate 8.7%, gynecologic 7.8%, colorectal 9.6%, head and neck 14.8%, sarcoma 9.6%, other 25.2%
Holtan *et al,* 2007[36]	Survey questionnaire using Brief Pain Inventory QOL instrument	Hospitalized cancer patients	Of 453 included patients with cancer-related pain based on site prevalence was: GI 24.9% (n=113), urological 15.7% (n=71), hematological 14.1% (n=64), lung 12.6% (n=57), gynecological 11.0% (n=50), breast 8.2% (n=37), head and neck 4.4% (n=20), other 11.9% (n=54), missing 0.2% (n=1)
Van den Beuken et al, 2007[12]	Meta-analysis: Data from 52 studies were pooled to report cancer pain prevalence	Inpatient, outpatient, at home, hospice, referred to palliative care services	Pooled pain prevalence reported in six types of cancer was: head/neck 70%, gynecological 60%, gastrointestinal 59%, lung/bronchus 55%, breast 54%, urogenital 52%
Pignon *et al,* 2004[59]	Cross-sectional survey conducted in radiotherapy oncologic unit	Radiotherapy oncologic unit	Total of 126 patients, 93 completed the survey of which, n=66 (71%) reported pain. By cancer site the pain prevalence was head/neck 30% (n=20), brain 9% (n=6), breast 11% (n=7), chest 5% (n=3), pelvis 8% (n=5), bone metastases 1% (n=1), esophagus 6% (n=4), abdomen 11% (n=7)
Hwang *et al,* 2003[37]	Prospective longitudinal study using Brief Pain Inventory QOL instrument	Hematology/Oncology based Outpatient, inpatient unit	Locations and prevalence associated with breakthrough pain reported was- arm/shoulder, chest, abdomen, neck, leg, pelvis/hip, spine, anus, head at day 1 was 18%, 12%, 10%, 10%, 9%,9%,7%, 6%, 3%; after initiating the pain treatment, at week1, it was 18%, 5%, 7%, 7%, 13%, 13%, 13%, 0%, 0%, respectively
Lin *et al,* 2003[65]	Prospective survey administered to cancer patients	Inpatient at Oncology and outpatient radiotherapy clinics	Cancer sites in 233 patients with pain included oral 8%, colorectal 16%, breast 10%, lung 16%, nasopharyngeal 9%, liver 9%, cervical 8%, gastric 6%, prostate 5%, lymphoma 5%, brain 3%, and other 5%

Fortner *et al,* 2002[38]	Telephonic survey	Ambulatory cancer patients	Of the160 patients with breakthrough pain prevalence was: breast 11.3%, genitourinary 28.8%, gastrointestinal 19.4%, head/neck 7.5%, lung11.3%, sarcoma 1.9%, other 20%
Caraceni *et al,* 1999[47]	Prospective, cross sectional, multicenter survey	Inpatient, outpatient, hospice	Of the 1095 patients the pain prevalence was: lung 18.1%, breast 13.4%, head and neck 10.2%, pancreas/ stomach 9.6%, colon-rectum 9.5%, uterus 6.6%, prostate 6.0%, leukemia/lymphoma 3.9%, other 22.7%
Petzke *et al,* 1999[48]	Questionnaire administered to cancer patients	Pain clinic	Total of 631 cancer patients admitted, 39% (n=243) reported transitory pain By cancer-site the prevalence reported was: head/neck 16%, GI 26%, lung 11%, breast 12%, genitourinary 17%, lymphatic/hematopoietic 6%, skin/bone/connective tissue 4%, other 8%
Grond *et al,* 1996[49]	Open prospective using self-assessment 6-point verbal rating scale	Anesthesiology-based pain service of university hospital	Of 2,226 cancer patients, pain syndromes were located: head 17%, lower back 36%, thoracic region 23%, abdominal 27%, lower limbs 21% and pelvic 15%
Brescia *et al,* 1992[61]	Prospective single center survey	Inpatient hospitalization-	At admission, severe pain was reported among patients with cancer of cervix 68%, prostate 57%, colorectal 49%, bone metastasis 49%
Portenoy *et al,* 1989[62]	Review	Pain service	The epidemiology of cancer pain by cancer site reported was: bone 75%-80%, pancreas 79%, stomach 75%, uterus/cervix 75%, lung 72%, breast 70%, prostate 70%, colon 69%, lymphoma 58%, leukemia 52%

1.2.3.3 Epidemiology of Cancer Pain by Cancer Staging

Cancer produces pain by growing into or destroying adjacent tissues. These patients will experience higher cancer pain if tumor advances locally or is spread to distant organ or recurred. Early stage of lung, breast, ovarian or cervical rarely causes cancer pain; whereas, prostate and colon cancer can produce severe pain even in the early stages by urinary track and fecal stream obstruction, respectively.

A systematic review conducted by Higginson *et al*., reported weighted mean pain prevalence of 45.6% (range 21.4%–84.1%) in mixed- and early-stage cancer and 73.9% (range 53.0%–100 %) in advanced or metastatic cancer. A meta-analysis conducted by Van den Beuken and colleagues reported pooled pain prevalence of 64% (95% CI 58.0 – 69.0) among 9,763 cancer patients with metastatic or advanced form. Davis and colleagues investigated pain among cancer patients receiving palliative care of which 6.0% to 17.0% with non-metastatic cancer experienced pain directly attributable to cancer compared to 35.0% to 56.0% of those with metastatic disease.[46] Lin *et al*., included 233 cancer patients with pain and reported prevalence among 18.9% having localized and 81.1% with metastasized tumor. Caraceni and colleagues conducted prospective, cross sectional, multicenter survey to report pain prevalence based on extent of disease, categorized as none, local and metastatic of which 3.1%, 27.3% and 69.6% respectively, experienced pain. Table 4 briefly summarizes epidemiology of cancer pain by staging.

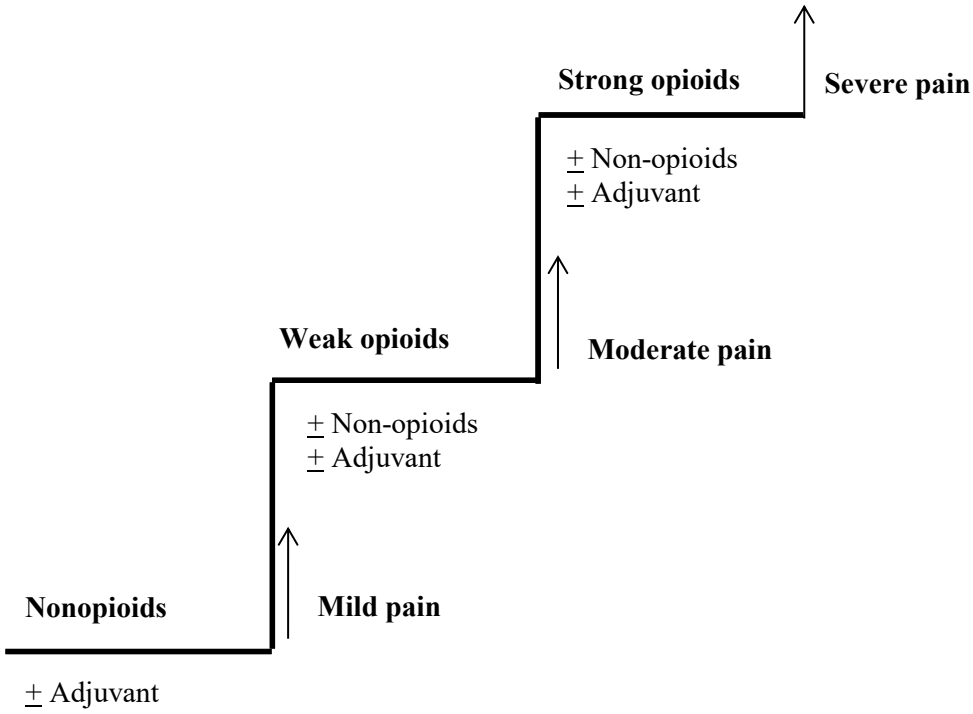
Table 4: Epidemiology of Cancer Pain Among Cancer Survivors Based On Cancer Staging

Source	Study design	Settings	Pain prevalence based on cancer staging
Higginson *et al,* 2013[63]	Systematic literature review	Inpatient, outpatient, at home, hospice, referred to palliative care services	The weighted mean pain prevalence reported: (a) In mixed- and early-stage cancer: 45.6% (range 21.4–84.1%) (b) In advanced or metastatic cancer: 73.9% (range 53–100 %)
Valeberg *et al,* 2008[53]	Questionnaire administered to cancer patients	oncology outpatient clinic	Of total 217 cancer patients who returned the questionnaire, 53% (n=115) reported cancer only related pain, of which 44.7% had metastatic form of tumor
Van den Beuken *et al,* 2007[12]	Meta-analysis: Data from 52 studies were pooled to report cancer pain prevalence	Inpatient, outpatient, at home, hospice, referred to palliative care services	Pain prevalence among 9,763 cancer patients with metastatic or advanced form was 64% (95% CI 58.0 – 69.0),
Davis *et al,* 2004[46]	Palliative oncology review	Inpatient, outpatient, hospice	Among advanced cancer patients: (a) 6 to 17% of patients with non-metastatic cancer reported pain directly attributable to cancer (b) 35 to 56% reported pain associated with metastatic disease
Lin *et al,* 2003[65]	Prospective survey administered to cancer patients	Inpatient at Oncology and outpatient radiotherapy clinics	Cancer staging in 233 patients with pain included localized, 18.9% (n=44) and metastasized 81.1% (n=189)
Caraceni *et al,* 1999[47]	Prospective, cross sectional, multicenter survey	Inpatient, outpatient, hospice	Pain prevalence based on extent of disease reported was: none 3.1%, local 27.3%, metastatic 69.6%
Petzke *et al,* 1999[48]	Questionnaire administered to cancer patients	Pain clinic	Of the total of 631 cancer patients admitted, 39% (n=243) reported transitory pain. By cancer staging the prevalence was: T_1 and T_2 20%, T_3 and T_4 41%, Unknown 39%, Metastasis 32%
Portenoy *et al,* 1989[62]	Review	Pain service	The epidemiology of cancer pain with advanced neoplasm was 71% (52%-96%)

1.3 Cancer Pain Management

Treatment of cancer pain largely depends upon it cause, severity, tumor location and comorbidities. In order to manage cancer pain, the WHO has outlined guidelines for the use of analgesics. The analgesic should preferably administered orally, with around-the-clock (ATC) dosing, as per analgesic ladder, considering individualized treatment based on pain severity, and with attention to detail.[2] Both pharmacological and non-medical approaches (physiotherapy and complementary therapies) are used to encounter cancer pain. To guide medical community worldwide, 3-step analgesic ladder was developed according to which if pain occurs prompt oral administration of drugs should begin with non-opioid analgesics followed by weak and strong opioids depending on pain intensity.[2] Adjuvant analgesics are routinely used in combinations with opioids and non-opioids for controlling cancer pain.[66]

Figure 1: WHO 3-Step Analgesic Pain Ladder



First Step: The first step in the analgesic ladder involves the use of non-opioids including NSAIDs and Salicylates with or without an adjuvant analgesic. NSAIDs are potent analgesics and antipyretic agents which makes them effective against cancer pain of musculoskeletal origin. The NSAIDs such as dicofenac, etodolac, fenoprofen, fulbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, celecoxib, sulindac, and tolmetin; the salicylates such as aspirin, choline magnesium trisalicylate, diflunisal are routinely used for treatment of mild pain. The mechanism of action is through nonspecific inhibition of cyclooxygenase (COX-I & COX-II) that mediates prostaglandin synthesis. Because of this non-selective nature, they have significant adverse effects such as gastric ulceration and bleeding. Therefore, NSAIDs may not be an optimal choice for those cancer patients with history of gastric bleeding, elderly and those with renal insufficiency. In order to overcome these side-effects non-narcotic analgesic combinations (naproxen/esomeprazole, acetaminophen/diphenhydramine, ibuprofen/famotidine) are preferred. When pain control is not achieved by other treatment such as systemic analgesics, adjuvant therapies or when intrathecal therapy is warranted miscellaneous non-opioids such as ziconotide is preferred.[36]

Second step: Weak opioids either alone or in combinations with non-opioid analgesic and/or adjuvant analgesic are used for the treatment of moderate pain and when pain control is not achieved by administration of non-opioids alone. Mild opioids such as codeine, fentanyl are routinely used for moderate pain. Other alternatives include hydrocodone, tramadol, and standardized opium. If the maximum prescribed dose of weak opioids does not achieve pain relief then it should be replaced with lower dose of morphine.

Third step: If pain persists or intensifies strong opioids such as morphine, hydromorphone and oxycodone should be prescribed alone or in combinations with non-opioid analgesic and/or adjuvant analgesic. While concerns exist about use of opioids as it is associated with drug dependence, tolerance and drug abuse. Several factors must be considered for effective use of opioids such as patient age, pain nature and severity, previous opioid exposure, cancer staging- particularly renal and hepatic involvement and

comorbidities. Notably, the use of opioid is limited or stopped if the cause of pain dealt with by anticancer treatment including chemotherapy or radiotherapy.

The adjuvant analgesics consists a diverse group of drugs with different primary indications. They are included along with opioid regime to enhance pain relief, address pain that has insufficiently responded and to encounter adverse effects by reducing the opioid dose.[31] The list includes antidepressants, anticonvulsants, neuroleptics, corticosteroids, local anesthetics. The selection of specific coanalgesic depends on wide variety of factors such as comprehensive assessment of patient (pain type & etiology, pain associated with tumor/treatment, relevant comorbidities and other symptoms), pharmacological characteristics, risk-benefit ratio. Adjuvant analgesics produces independent analgesic activity, may enhance the effect of other analgesic or counteract the adverse effect of NSAIDs or opioids.[31] Antidepressants and antiepileptic's are frequently administered coanalgesics to manage neuropathic pain.[2,33,66] To manage concomitant psychological disturbances like anxiety, depression, insomnia and seizures adjuvants of class anxiolytics, antidepressants, night sedatives and anticonvulsants, respectively are preferred. Corticosteroids are effective in managing pain for a variety of pain indications, including pain due to obstruction of visceral structures (bronchus, ureter, intestine), bone pain, neuropathic pain arising from nerve compression, spinal cord compression, headache due to raised intracranial pressure, and metastatic arthralgia. Other classes of adjuvants that are routinely used to manage cancer pain are local anesthetics for neuropathic pain, bisphosphonates and radiopharmaceuticals for bone pain, muscle relaxants for musculoskeletal pain; anti-cholinergic for pain from bowel obstructions. Table 5 briefly summarizes literature review on pain medication use among cancer survivors.

Table 5: Pain Medication Use Among Cancer Patients

Source	Study Design	Settings	Pain Medication Use
Henok Getachew Tegegn *et al,* 2017[67]	Questionnaire-based interview	Cancer patients admitted to oncology ward	From total of 83 cancer patients, No analgesics - 50 (60.2%) Nonopioids ± adjuvants - 15 (18.1%) Weak opioids ± nonopioids ± adjuvants - 14 (16.9%) Strong opioids ± nonopioids ± adjuvants - 4 (4.8%)
Ovayolu *et al,* 2015[44]	Cross-sectional design using questionnaire	Chemotherapeutic unit and adult oncology clinic	From total of 220 cancer patients, NSAIDs - 55(25%) Weak opioids - 9(4.1%) Strong opioids - 73 (33.2%) None - 83 (37.7%)
Breivik *et al,* 2009[55]	The European Pain in Cancer (EPIC) survey conducted in 11 European countries: Czech Republic, Denmark, France, Finland, Ireland, Italy, Norway, Sweden, Romania, Switzerland, and the UK, and Israel	Patients managed by medical oncologists, general practitioner, palliative care specialist or a pain specialist	From total 437 respondents, 24% (n=109) were taking WHO step 3opioids alone, 12% (n=53) were taking WHO step 2 opioids alone, 8% (n=39) were taking non-opioids alone
Valeberg *et al,* 2008[53]	Questionnaire administered to cancer patients	oncology outpatient clinic	Of total 217 cancer patients who could answer more than one and returned the questionnaire: No medication reported: 19.8% Non-opioid: 59.4% Mild opioid: 30.9% Strong opioid: 23.5%
Holtan *et al,* 2007[36]	Survey questionnaire	Hospitalized cancer patients	Of 453 patients having cancer related pain Paracetamol - 60.0% (n=272) NSAIDs - 19.6% (n=89) Weak opioids - 20.8% (n=94) Strong opioids - 62.0% (n=281) TCA & AE - 13.9% (n=63) Steroids - 23.8% (n=108) No analgesics - 36.9% (n=167)

Van den Beuken *et al,* 2007[11]	Prospective survey: A self-report patient questionnaire	Outpatient clinic of the medical institute	From total 1,383 cancer patients, WHO step 1 medication (NSAIDs) - 15%(n=202) WHO step 2 medications (weak opioids) - 6% (n=78) WHO step 3 (strong opioids) - 7% (n=95) Co-analgesics (anti-epileptics, tricyclic antidepressants) - 7% (n=95)
Bernabei *et* al,[60]	Retrospective cross-sectional study	Medicare-certified and/or Medicaid certified elderly and minority cancer patients admitted to nursing home	Of total of 4,003 patients who experienced daily pain, None - 1019 (26%) Any - 2984 (74%) WHO level 1 (Non-narcotic) - 659 (16%) WHO level 2 (Weak opiates) - 1293 (32%) WHO level 3 (Morphine or like substances) - 1029 (26%)

1.4 Barriers to Cancer Pain Management

The WHO guidelines to manage cancer pain have been widely published. Unfortunately, these recommendations are not universally applied and as a result the cancer pain management is often suboptimal. Evidence suggests that 85-90% of pain can be managed by following WHO guidelines; unfortunately, among the cancer survivors only 50% of cancer pain is controlled.[2] Often the patient encounters several barriers. Current challenges in adequate treatment include patient-, clinician-, and system-related barriers because of which cancer pain is not effectively treated.[21-24,68] The patient-related barriers constitute towards underreporting of cancer pain. A strict regulatory environment where physician prescribing patterns are closely monitored further contributes to undertreatment of cancer pain. The regulation on opioids widely varies among countries and interference with cancer pain management is more noticeable among countries with restrictive policy. Several factors contributing to patient-, health care professional- and system-related barriers are summarized in Table 6. These barriers have remarkable negative influence on the quality of cancer pain management and it is essential to identify the severity in order to eliminate the relevant barriers and manage cancer pain effectively.

Table 6: Barriers To Cancer Pain Management

I. Patient-Related Barriers
(a) Patient reluctance to report cancer pain
(b) Stoicism
(c) Lower cognitive performance
(d) Comorbidities
(e) Patient communication/language
(f) Ethnic minorities group
(g) Fear of addiction particularly to opioids
(h) Aging
(i) Patient concern for pain medication side effects
(j) Lower education level
(k) Cultural concept regarding pain and disease

(l) Patient attitude to accept pain as part of cancer
(m) Inability to pay for analgesics
(n) Patient history of drug, alcohol or controlled substance abuse
II. Health Care Professionals/Physician-Related Barriers
(a) Lack of comprehensive and clear guidelines on cancer survivors follow up care
(b) Lack of knowledge about cancer pain incidence, prevalence and management skills
(c) Administrative constraints
(d) Clinical inertia
(e) Reluctant to prescribe opioids even if necessary
(f) Inadequate pain assessments
(g) Concerns about polypharmacy and drug interactions
(h) Failure to identify cancer pain type (neuropathic, nociceptive)
(i) Low referral rate to pain specialists
(j) Ignoring pain with greater focus on treatment of cancer
(k) Concerns about tolerance, abuse, side-effects, legal regulations
(l) Perception of negative public impression for opioids
III. Health Care System-Related Barriers
(a) Lack of psychosocial support services
(b) Lack of availability to wide range of analgesics
(c) Lack of access particularly to wide range of opioids
(d) Lack of staff time to attend patient pain needs
(e) Lack of specialists
(f) Complex laws and regulation on opioids use since they are “controlled substances”
(g) Health insurance status
(h) Prior authorization for opioids

1.5 Gaps in Current Knowledge

Previous studies have examined cancer pain and type of analgesic medications among cancer patients through cross-sectional study design by administering questionnaire.[36,44,52,53] The survey approach can provide useful data; however, they are still limited by the fact that drug utilization information reported is at some particular point in the cancer trajectory. Similarly, study conducted through retrospective chart reviews might not provide comprehensive data because researchers rely on existing information. In order to measure incidence, prevalence of cancer pain and type of analgesic medications the optimal research design would be prospectively following cancer patients longitudinally for extended period of time through cancer trajectory. Unfortunately, because of expenses, feasibility, and loss to follow-up such studies are rarely conducted. Currently, little is known regarding pain medication use among cancer survivors. No study exists that has captured utilization and spending trends on pain prescriptions among cancer survivors. Despite extensive data on epidemiology of cancer pain, the distribution of pharmacological treatments to manage cancer pain by different socio-demographics, geographical, clinical and economic factors have never been explored.

The published studies may have selection bias since investigators included high risk population like advanced cancer patients, hospitalized, palliative care, those receiving treatment at oncology unit or similar specialized center. These samples are chosen by convenience; often are small or heterogeneous which truly does not represent larger pool of cancer patients. In addition, biases are also introduced by temporal factors such as demographics, clinical, geographical and economic, clinical settings, season and timings. For several reasons these biases are not controlled, defined or effectively measured.

The presence of long-term effects and emerging health problems secondary to the condition and treatment, are experienced by a number of cancer survivors for years following primary cancer treatment. Psychosocial and physical problems among cancer survivors are common and many studies have investigated HRQoL among cancer survivors.[69-72] Compared to those without a cancer history, cancer

survivors have poorer HRQoL on average and the estimates has been well documented. Nonetheless, HRQoL among cancer survivors stratified by different class of pain medication has never been investigated.

Identifying risk factors among post-treatment cancer survivors for pain, physical, mental and functional limitation is important in efforts to improve survivorship and decrease cancer burden. Previous studies have investigated physical, psychological and other concerns associated with post-treatment cancer survivors .[73,74] However, we do not yet have estimates of pain prescriptions claims on different socio-demographics, geographical, clinical and economic factors, with an emphasis on determining potential differential access to opioid medications.

It has been well documented that cancer survivors continue to experience significant levels of burden, poorer outcomes, functional limitations and diminished productivity.[75-77] Notably, no previous study has investigated association between type of pain medication and work productivity among post-treatment cancer survivors.

Furthermore, when study is conducted retrospectively using commercial database the patient related information obtained only represents insured employees and thus the results obtained may not be generalizable to the other population. Henceforth, when research is carried out with the aim to improve survivorship the optimal study design would be to examine cancer survivors identified from US civilian non-institutionalized population database that truly represents cancer survivors alive today.

1.6 Significance

The study is significant because it will contribute meaningful insight on pain medication utilization among cancer survivors in the following ways:

(1) This study is the first retrospective study to report trends in pain medication utilization, total expenditure and payer cost share among cancer survivors.

(2) The pharmacological treatment to manage cancer pain by different socio-demographics, geographical, clinical and economic factors will provide essential and critical information on pain medication utilization from health system perspective.

(3) This study will investigate HRQoL among cancer survivors by different socio-demographics, geographical, clinical and economic factors helping medical community appropriately target intervention with potential to improve cancer survivorship.

(4) This study is unique to summarize HRQoL among cancer survivors stratified by opioid exposure. It is critical to cancer survivors in terms of care, making treatment decisions and survival.

(5) Results from the study will help understand the reason for and the effects of pharmaceutical treatment of pain among post-treatment cancer survivors.

(6) This study provides estimates of pain prescription claims on different socio-demographics, geographical, clinical and economic factors among post-treatment cancer survivors.

(7) The findings of study will help determining potential differential claims for opioids prescription on different socio-demographics, geographical, clinical and economic factors among post-treatment cancer survivors.

(8) The study will explore the association between type of pain medication and work productivity among post-treatment cancer survivors which has never been explored earlier.

(9) The study is innovative and significant because it is first study that summarizes pain medication utilization among cancer survivors using US civilian non-institutionalized population database.

1.7 Objectives

Objective 1: To report recent trends in the pharmaceutical treatment of pain and HRQoL among cancer survivors in the United States.

Study 1a: To quantify annual trends in utilization, cost, and payer cost shares of pain medications and HRQoL among cancer survivors in the United States using MEPS, 2008 – 2013.

Study 1b: To explain the distribution of treatments and HRQoL among cancer survivors across different socio-demographics, geographical, clinical and economic factors in the United States using MEPS, 2008 – 2013.

Study 1c: To measure HRQoL among cancer survivors stratified by opioid exposure in the United States using MEPS, 2008 – 2013.

Objective 2: Among post -treatment cancer survivors, to understand better the reasons for and the effects of pharmaceutical treatment of pain in the United States.

Study 2a: To explain the distribution of pain prescriptions by different socio-demographics, geographical, clinical and economic factors among post -treatment cancer survivors using MEPS, 2010 – 2012.

Study 2b: To determine potential differential claims to opioid prescription across post -treatment cancer survivors on different socio-demographics, geographical, clinical and economic factors using MEPS, 2010 – 2012.

Objective 3: To assess relationship between use of pain medication and workers' productivity among post-treatment cancer survivors.

Study 3a: For post-treatment cancer survivors identified to explore association between pain medication use and work productivity (productivity measures obtained from SF-12) using MEPS, 2010 – 2012.

Study 3b: Among post-treatment cancer survivors who filled out Cancer Self-Administered Questionnaire to explore association between pain medication use and work productivity using MEPS, 2010 – 2012.

CHAPTER TWO:- METHODOLOGY

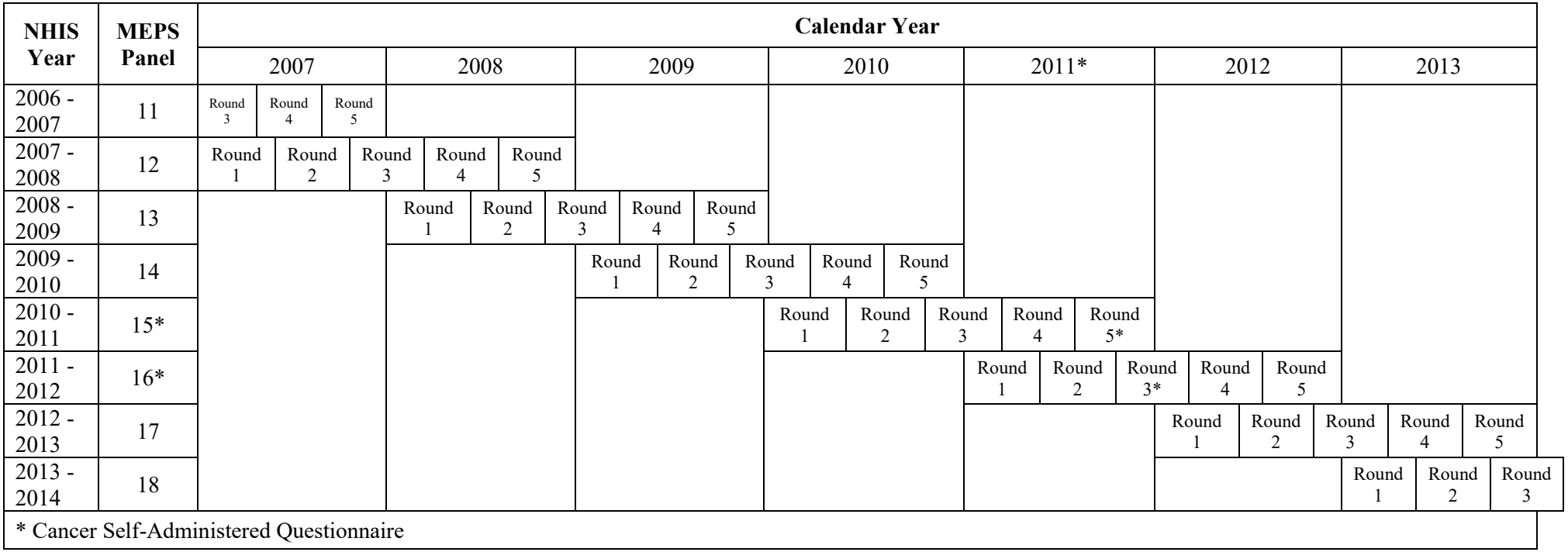
2.1 Data Overview

The MEPS is a set of ongoing large-scale surveys administered by the Agency for Healthcare Research and Quality (AHRQ) which are nationally representative sample of US civilian non-institutionalized population. The MEPS respondents are sub-sample from the previous year's National Health Interview Survey (NHIS) sponsored by National Center for Health Statistics (NCHS). The MEPS collects responses from individuals, families, pharmacists and health professionals on healthcare usage. The process includes obtaining data from one respondent per household with total of 5 in-person interviews using computer assisted personal interview (CAPI) technique over about 2 years of study period. This study period is referred as panel and each year a new panel is initiated as shown in fig 2.[78]

The MEPS comprise of household component (MEPS-HC), medical provider component (MEPS-MPC, medical providers survey linked to household component), insurance component (MEPS-IC, an independent employers and unions survey not linked to household component); of the three components, only the MEPS-HC data files are publicly released.

The MEPS-HC collects detailed data on various variables including demographics (age, sex, race and ethnicity, marital status, education; military services), geographical (MSA, region) and clinical (BMI, smoking status). Additionally, information on utilization of healthcare resources including all hospital (ER, inpatient and outpatient events), home health care, dental services, vision aids, physician services, clinical conditions and prescribed medicines is also recorded. Information on economic variables such as income, poverty status, employment status for all individuals above age 16 with hours worked, job tenure, types of business, whether health insurance both private and public status was offered throughout the reference period, health insurance coverage for each month, policy holder, the source of coverage, who is covered, whether or not it is an HMO, types of plan are recorded and publicly available in MEPS-HC.

Figure 2: Medical Expenditure Panel Survey Overlapping Panel Design



2.2 MEPS Sample Design

The first stage of sampling also known as Primary Sampling Units (PSUs) consists of county or group of adjacent counties. The whole US geographical area is patronized into many PSUs. The PSUs sampled for NHIS roughly half of which is used in MEPS. The second stage consists of Secondary Sampling Units (SSUs) which are cluster of housing units (Census blocks or tracts). Each sampled PSU is divided into SSUs. The final stage consists of sample of households from each selected SSUs. Notably, all families and persons within selected households are included. Oversampling of minorities is facilitated in MEPS to produce reliable estimates for subpopulation of interests- Asians, blacks, Hispanics and to increase variation in sampling weights.

For every individual participating in the MEPS, weight variable (also known as sampling weight or survey weight) has been assigned. These weights act as multipliers in order to produce national and regional estimates. Besides weight variable the complex sampling design also includes strata and PSU design variables. In order for results to be generalizable, performing weighted analysis and for reporting standard errors, mean, frequencies, and regression coefficients; this complex sample design using weights, strata, and PSU design variables must be taken into account.

Data from the MEPS can be pooled at condition level, event level, job level and even to person level. Data from two panels are combined to generate estimate for each calendar year and likewise each panel separately generates national estimates over two years.[78] Aggregation requires $\geq$ 100 unweighted cases or relative standard error < 30% to support national estimates. The MEPS data are routinely used for policy-related and behavioral research on the determinants of healthcare use, spending, access to care and insurance coverage.

2.3 IRB Approval Statement

This study (ID# 2015-8491) was approved by University of Cincinnati- Institutional Review Board (IRB). The study involves no recruitment of participants and the analysis is performed on publicly available data from MEPS-HC. For confidentiality purpose all the patient identifiers are removed from the released data files. However, it includes an encrypted ID number to allow longitudinal follow-up and merging patient data from multiple files. It was determined by UC-IRB that proposal does not require regulatory criteria for research involving human subjects and study was classified as exempt from human subject on Nov 25th, 2015.

2.4 Methodology: Objective 1

2.4.1 Data Source & Study Design

This observational study employs retrospective, descriptive, cross-sectional design covering the years 2008-2013 using a nationally representative survey database among participants aged 18 years and older ever diagnosed with cancer. To conduct analyses the study measures were derived from the full-year consolidated, medical conditions and prescribed medicines files of the MEPS-HC.

(a) Full-year consolidated data file: The variables of interest obtained from this file were:

I. Demographic variables: It provides detail information about the demographic characteristics of each respondent. The characteristics include age, sex, race/ethnicity, education and marital status.

II. Geographic variables: It comprise of census region and Metropolitan Statistical Area (MSA).

III. Clinical variables: Variables such as smoking, BMI, ever diagnosed of cancer, cancer type, age when cancer diagnosed.

IV. Economic variables: such as employment status, family income as % of poverty line, health insurance coverage was employed.

V. Health status variables: The Mental Component Summary (MCS) scores and the Physical Component Summary (PCS) scores of HRQoL were obtained from the data file.

(b) Medical conditions file: MEPS-HC respondents during interview are asked open-ended questions about their own medical conditions and of other family members. The file contains information on variables describing medical conditions, ICD-9-CM diagnosis, procedure and Clinical Classification Code (CCC). For confidentiality reasons, ICD-9-CM diagnosis codes are collapsed from fully-specified codes to 3-digit category code. Similarly, the procedure codes are collapsed from fully-specified codes to 2-digit category code. Notably, ICD-9-CM codes for similar conditions have been aggregated into clinically meaningful, homogenous and mutually exclusive categories known as

CCCs. These CCCs were used in study to identify individuals with cancer. In addition, comorbidities in terms of priority conditions were obtained from medical conditions file.

(c) Prescribed medicines file:

The prescribed medicines file of MEPS-HC provides detail information for each drug event.

File includes drug name, National Drug Codes (NDC), quantity of the prescribed medicine dispensed, form of prescribed medicine, dosage strength, number of times acquired in the round, date first used, pharmacy info, payment sources, amount of payment for each source and medicines if obtained free.

In addition, each record on this file contains Multum Lexicon variables such as therapeutic classification variable assigns a drug to one or more therapeutic categories; can have up to three categories per drug; therapeutic sub-classification variable assigns one or more sub-categories to a more general therapeutic class category given to a drug and therapeutic sub sub-classification variable assigns one or more sub subcategories to a more general therapeutic class category and sub-category given to a drug.

The utilization, total expenditure and payment share associated with each pain medications were obtained from prescribed medicine file.

Annual datasets were created for each year from 2008-2013. The full-year consolidated data file were linked to the medical conditions file to identify cancer survivors; were subsequently linked to the prescribed medicine files to report annual utilization, total expenditure and payment share. In order to report pooled estimates over six years study period these annual datasets were merged to create final dataset that contains information about study population, variables of interest (demographical, geographical, clinical and economic), pain medications and outcome measures (HRQoL, utilization, total expenditure and patient cost share).

2.4.2 Study Population: Cancer Survivors

Records from the medical conditions file and full-year consolidated data file were linked in order to identify study population and the comparison group. An algorithm was developed to identify cancer survivors and individuals without cancer history using CCCs and cancer diagnosis related questions.

From the total respondents within a given year (N=36,940 in year 2013), children (age<18, n=10,624) were excluded from the analysis. Of the adult respondents (n=26,316), individuals with incomplete information on MEPS question *"Whether a doctor or health professional had ever told them that they had cancer or malignancy of any kind?"* (n=54) were excluded. Adult respondents with known response (yes/no, n=26,262) on cancer diagnosis question were screened for mention of cancer diagnosis using CCC=011-047, excluding other non-epithelial cancer of skin, CCC=023. Notably, individuals solely diagnosed with non-melanoma skin cancer (CCC=023) were not recognized as cancer survivors and in algorithm were navigated as individuals without cancer history. Individuals with no mention of cancer diagnosis (n=24,872) were further grouped into individuals with (n=1,175) and without history of cancer (n=23,697). Among individuals with history of cancer they were further screened for what type of cancer they experienced in past. Those with bladder, blood, bone, brain, breast, cervix, colon, esophagus, gall bladder, kidney, larynx, leukemia, liver, lung, lymph, melanoma of skin, mouth, muscle, ovary, pancreas, prostate, rectum, stomach, testis, throat, thyroid, uterus and miscellaneous were categorized into cancer survivors (n=748); with history of solely non-melanoma or unknown type skin cancer (n=427) were channeled into individuals without cancer history.

In this research, study population were ***cancer survivors*** defined as any adult individuals ever been diagnosed with cancer, identified by mention of cancer diagnosis code (n=1,390) or with history of cancer (n=748).

The comparison group were ***individuals without cancer history*** identified as adult respondents with no mention of cancer diagnosis code and no history of cancer in past (n=23,697); however, including those solely reported non-melanoma or unknown type skin cancer (n=427).

Thereby, inclusion and exclusion criteria to identify:

I. Cancer survivors:

Inclusion criteria:

(a) Adult individuals age≥18

(b) Mention of cancer diagnosis code or history of cancer

(c) Diagnosed with one or more cancer type

(d) Type of cancer includes head & neck, gastrointestinal, lung/bronchus, breast, urogenital, gynecological, prostate, hematological, bone, skin and other/unspecified

Exclusion criteria:

(a) Adult respondents with missing data on cancer question "Ever been diagnosed with cancer?"

(b) Individuals diagnosed solely with non-melanoma skin cancer

II. Individuals without cancer history

Inclusion criteria:

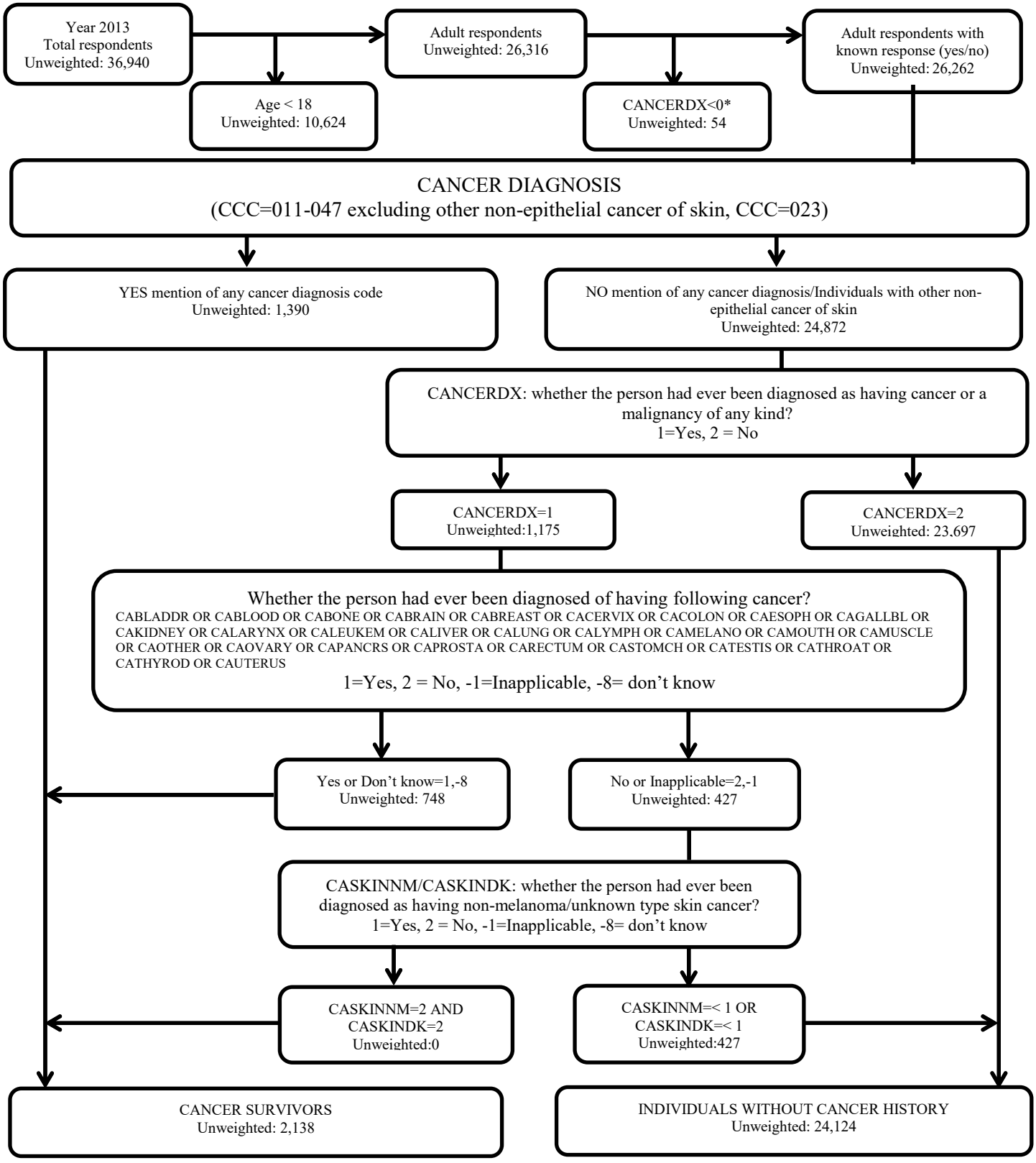
(a) Adult individuals age≥18

(b) No mention of cancer diagnosis code or history of cancer except those diagnosed solely with non-melanoma skin cancer

Exclusion criteria:

(a) Adult respondents with missing data on cancer question "Ever been diagnosed with cancer?"

Figure 3: Flowchart Identifying Cancer Survivors & Individuals Without Cancer History For Year 2013



2.4.3 Variables

The variables related to demographic, geographical, clinical and economic obtained from MEPS-HC were:

I. Demographic variables:

(a) Age: Date of birth for every household members of the participant is asked, and age is recorded during each round of the interview. In MEPS, variable age is available as continuous variable and for confidentiality purpose it is top-coded at 85 years. From 2008-2013, age variables AGE08X, AGE09X, AGE10X, AGE11X, AGE12X AND AGE13X were employed to categorize individuals into following age-groups, Age $\leq$ 55, Age 56-65, Age 66-75, Age $\geq$ 76.

(b) Sex: Categorical variable SEX (male/female) available in MEPS-HC was used to determine gender-based pain medication utilization among cancer survivors.

(c) Race/Ethnicity: Race based analysis were performed using variable RACEX/RACEV1X. Variable RACEV1X replaced RACEX starting 2012. Combination of variables RACEX/RACEV1X and HISPANX were employed to categorize individuals into race/ethnicity categories such as non-Hispanic White, non-Hispanic Black, Hispanic and non-Hispanic other/multiple race (Asian, Alaska native/American Indian, Native Hawaiian/Pacific Islander).

(d) Education status: In MEPS-HC, highest degrees of education gained by individual was captured using variable HIDEG. Starting 2013 variable HIDEG was removed and EDUYRDG was introduced. Education based analysis was performed using variable HIDEG/EDUYRDG by grouping individual into categories such as less than high school diploma, high school graduate, some college degree or more.

(e) Marital status: The variables MARRY08X, MARRY09X, MARRY10X, MARRY11X, MARRY12X, and MARRY13X for year 2008-2013, respectively, were used. Individuals were grouped into following three categories married, widowed/divorced/separated and never married.

II. Geographic variables:

(a) Region: Census region was coded as categorical variable and grouped into Northeast, Midwest, South and West. For year 2008-2013, REGION08, REGION09, REGION10, REGION11, REGION12 and REGION13, respectively, were used to determine region-based pain medication utilization among cancer survivors.

(b) MSA: Whether an individual resides in urban or rural was captured through variable MSA08, MSA09, MSA10, MSA11 and MSA12 respectively for year 2008-2012. Starting 2013, the MSA status variables are no longer released for public use due to confidentiality reasons.

III. Clinical variables:

(a) Smoking: Whether an individual is smoking or not is captured in MEPS-HC by the variable ADSMOK42. This variable was used to check pain medication utilization by smoking status.

(b) BMI: The Body Mass Index (BMI) calculated based on individual reported height and weight of every adult respondents (age>17) was released by continuous variable BMINDX53. A categorical variable was created with four distinct classes- Obese, $\geq$ 30.0; Overweight, 25.0 – 29.9; Normal, 18.5 – 24.9; Underweight, < 18.5.

(c) Pain perception: One of the questions that SF-12 comprises of is *"During past 4 weeks, pain interfered with normal work outside the home and housework?"* and in MEPS-HC the response was captured through variable ADPAIN42. The individuals were categorized based on the response including extremely/quite a bit, moderately, a little bit and no pain.

(d) Chronic condition: Some of the chronic conditions are designated as priority condition in MEPS, because of their prevalence, policy relevance; expenditure, long-term and life-threatening in nature. It includes arthritis, asthma, cancer, chronic bronchitis, diabetes, heart disease (such as coronary atherosclerosis, congestive heart failure, and myocardial infraction), hypertension, stroke, high cholesterol. These conditions were incorporated to describe the pain medication use. List of CCCs used to identify these conditions are summarized in Appendix C.

(e) Number of other known MEPS priority conditions, excluding cancer: Individuals based on number of chronic conditions were grouped into the following categories greater or equal to 3, 2, 1 or none.

(a) Type of cancer: Cancer survivors were identified using CCCs (Appendix A) and during interview from a question about *"Whether a doctor or health professional had ever told them that they had cancer or malignancy of any kind?"* If answered yes, the response to follow-up question *"what type of malignancy?"* was captured using variables CABLADDR, CABLOOD, CABONE, CABRAIN, CABREAST, CACERVIX, CACOLON, CAESOPH, CAGALLBL, CAKIDNEY, CALARYNX, CALEUKEM, CALIVER, CALUNG, CALYMPH, CAMELANO, CAMOUTH, CAMUSCLE, CAOTHER, CAOVARY, CAPANCRS, CAPROSTA, CARECTUM, CASTOMCH, CASKINNM, CASKINDK, CATESTIS, CATHROAT, CATHYROD, CAUTERUS indicates selection of bladder, blood, bone, brain, breast, cervix, colon, esophagus, gallbladder, kidney, larynx, leukemia, liver, lung, lymph, melanoma, mouth, muscle, other, ovary, pancreas, prostate, rectal, stomach, non-melanoma skin cancer, unknown skin cancer, testis, throat, thyroid, uterus (Appendix B).

Cancer survivors were classified based on tumor site including head & neck, gastrointestinal, lung/bronchus, breast, gynecological, prostate, hematological, bone, skin, urogenital and other/unspecified to describe pain medication utilization among cancer survivors.

(f) Cancer status: Individual's cancer status was categorized into any of the following categories:

(1) Currently diagnosed: Cancer condition was defined as current if individuals currently experiencing the condition identified with mention of cancer diagnosis code determined from medical conditions file.

(2) Previously diagnosed: Individuals answered yes to ever been told by doctor or health professional that they have cancer condition (CANCERDX=1); however, no mention of cancer diagnosis code.

(b) Years since first cancer diagnosis: Individuals who answered yes to cancer question "ever being diagnosed with cancer" were further asked kind of cancer and age of diagnosis. The variables BLDRAGED, BLODAGED, BONEAGED, BRAIAGED, BRSTAGED, CERVAGED, COLOAGED, ESPHAGED, KIDNAGED, LRNXAGED, LEUKAGED, LIVRAGED, LUNGAGED, LYMPAGED, MELAAGED, MOUTAGED, MUSCAGED, OTHRAGED, OVRYAGED, PANCAGED, PRSTAGED, RECTAGED, STOMAGED, TSTSAGED, THRTAGED, THYRAGED, UTERAGED, respectively, indicates age at which cancer of indicates cancer selection of bladder, blood, bone, brain, breast, cervix, colon, esophagus, kidney, larynx, leukemia, liver, lung, lymph, melanoma, mouth, muscle, other, ovary, pancreas, prostate, rectal, stomach, testis, throat, thyroid, uterus were diagnosed.

Time since first cancer diagnosis was calculated as the difference between age at the interview year and age at first cancer diagnosis. Cancer survivors were categorized into one of the following >10, 6-10, 2-5, < 2 years to describe pain medications utilization.

IV. Economic variables:

(a) Employment status: Information on employment status was asked for all the respondent household members age 16 or older. Allowable responses captured through variables EMPST31, EMPST42, EMPST53 were, currently employed, has job to return and not employed. Individual ever employed during year was identified and grouped into binary categorical variable if employed or not. The variables employment status was incorporated to describe pain medication use among cancer survivors.

(b) Family income as % of poverty line: For every respondents, family income was derived by bringing together every household member total income comprising annual earnings from wages, salaries, business and firm profit and loss, interest and dividends, bonuses, tips, commissions, unemployment and workers compensation, private cash transfers, pensions, IRA withdrawals,

child support, alimony, temporary assistance for needy families, rent, royalties, social security and other source of income.

Variables POVCAT08, POVCAT09, POVCAT10, POVCAT11, POVCAT12 and POVCAT13 respectively for year 2008-2013, classifies income into one of the five poverty categories including high income (greater than or equal to 400%), middle income (200% to less than 400%), low income (125% to less than 200%), near poor (100% to less than 125%), negative or poor (less than 100%). The family income as % of poverty line was used to describe pain medication use among cancer survivors.

(c) Health insurance coverage: Health insurance status was obtained from variables, INSCOV08, INSCOV09, INSCOV10, INSCOV11, INSCOV12 and INSCOV13, respectively, for year 2008-2013. The individuals were grouped into the following classes any private, public only or uninsured.

The above mentioned different socio-demographics, geographical, clinical and economic variables were used describe pain medication utilization, HRQoL among cancer survivors and individuals without cancer history.

2.4.4 Drug Selection

To determine pain medication use among cancer survivors and its comparison group- individuals without cancer history, the pain medications were broadly categorized into four major class, non-opioids, narcotic analgesic combinations, opioids and adjuvant analgesics. The list of pain medication belonging to different class were obtained from eFacts and Comparisons 4.0.[21] As shown in Table 7, the pain medications are summarized with their name, both branded and generic, mechanism of action and route of administration. They are:

1. Non-opioids: It consists of NSAIDs, salicylates, non-narcotic analgesic combinations and miscellaneous class of analgesics. The list includes:
    (a) NSAIDs: acetaminophen, dicofenac, etodolac, fenoprofen, fulbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, celecoxib, sulindac, and tolmetin
    (b) Salicylates: aspirin, choline magnesium trisalicylate, diflunisal, magnesium salicylate, salsalate
    (c) Non-narcotic analgesic combinations: diclofenac/misoprostol, ibuprofen/famotidine, naproxen/esomeprazole, acetaminophen/aspirin/caffeine, acetaminophen/butalbital, acetaminophen/butalbital/caffeine, acetaminophen/diphenhydramine, acetaminophen/isometheptene/caffeine**,** acetaminophen/pamabrom/pyridoxine, acetaminophen/phenyltoloxamine, acetaminophen/salicylamide/phenyltoloxamine, acetaminophen/salicylamide/phenyltoloxamine/caffeine, acetaminophen/aspirin/salicylamide/caffeine, acetaminophen/aspirin/salicylamide /caffeine/ phenyltoloxamine, aspirin/butalbital/caffeine, aspirin/meprobamate
    (d) Miscellaneous non-opioids: ziconotide
2. Narcotic analgesic combinations: These are the combination product that contains opioid with one or more other non-opioid analgesics such as acetaminophen, aspirin, or ibuprofen. The list comprise of

acetaminophen/codeine, acetaminophen/caffeine/dihydrocodeine, aspirin/codeine, aspirin/caffeine/dihydrocodeine, codeine phosphate/acetaminophen/caffeine/butalbital, codeine phosphate/aspirin/caffeine/butalbital, hydrocodone/guaifenesin, hydrocodone bitartrate/acetaminophen, hydrocodone bitartrate/ibuprofen, meperidine-promethazine, belladonna/opium, oxycodone/aspirin, oxycodone/ibuprofen, oxycodone/naloxone, oxycodone/acetaminophen, propoxyphene/acetaminophen, tramadol/acetaminophen, buprenorphine/naloxone, pentazocine/naloxone, morphine/naltrexone, pentazocine/acetaminophen.

3. Opioids: Such as alfentanil, buprenorphine, butorphanol, codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, nalbuphine, opium, oxycodone, oxymorphone, pentazocine, propoxyphene, remifentanil, sufentanil, tapentadol, tramadol.
4. Adjuvants for neuropathic pain: As per WHO guidelines, antidepressants and anticonvulsants are drug of choice to manage cancer pain of neuropathic origin.[2] These two classes of drugs are most frequently used adjuvants in presence of neuropathic pain.[66] Based on guidelines recommendation the following adjuvant analgesics were selected:
    (a) Antidepressants:
        (1) Tricyclic antidepressants: amitriptyline, nortriptyline, desipramine
        (2) Selective Serotonin Reuptake Inhibitors (SSRI): paroxetine, citalopram
        (3) Serotonin Norepinephrine Reuptake Inhibitors (SNRI): venlafaxine, duloxetine
    (b) Anticonvulsants: gabapentine, pregabalin

The drugs belonging to different class of adjuvant analgesics such as corticosteroids (dexamethasone, prednisone), neuroleptics (olanzapine), local anesthetics (lidocaine, mexiletine), bisphosphonates (zoledronic acid), radiopharmaceuticals (strontium, samarium), muscle relaxants (cyclobenzaprine, orphenadrine), benzodiazepines (diazepam, lorazepam), anticholinergics (hyoscine, glycopyrrolate) were excluded from the analysis.

Table 7: Drugs Used In Management Of Pain Among Cancer Survivors

Generic Name	Trade Name(s)	Mechanism of Action	Class	Route of Administration
Non-opioid analgesics				
Acetaminophen	Acephen, Febrol, Feverall, Mapap, Maxapap, Nortemp, Pharbetol, Q-PAP, Tactinal, Tylenol	Cox I and -II inhibitors	Weak NSAIDs	oral, inj, rectal
Diclofenac	Cambia, Cataflam , Voltaren, Zipsor, Zorvolex	Cox-I inhibitors	NSAIDs	oral
Etodolac	Lodine	Cox-I inhibitors	NSAIDs	oral
Fenoprofen	Nalfon	Cox-I inhibitors	NSAIDs	oral
Flurbiprofen	Ansaid	Cox-I inhibitors	NSAIDs	oral
Ibuprofen	Addaprin, Advil, Caldolor, Motrin, Dyspel, Genpril, Midol, Provil	Cox-I inhibitors	NSAIDs	oral, iv
Indomethacin	Indocin	Cox-I inhibitors	NSAIDs	oral, rectal
Ketoprofen	Ketoprofen	Cox-I inhibitors	NSAIDs	oral
Ketorolac	Sprix, Toradol	Cox-I inhibitors	NSAIDs	oral, inj, im, nasal
Meclofenamate	Meclofenamate	Cox-I inhibitors	NSAIDs	oral
Mefenamic acid	Ponstel	Cox-I inhibitors	NSAIDs	oral
Meloxicam	Mobic	Cox-I inhibitors	NSAIDs	oral
Nabumetone	Relafen	Cox-I inhibitors	NSAIDs	oral
Naproxen	Aleve, Anaprox, Mediproxen, Naprosyn, Naprelan, Midol ER	Cox-I inhibitors	NSAIDs	oral
Oxaprozin	Daypro	Cox-I inhibitors	NSAIDs	oral
Piroxicam	Feldene, Therafeldamine	Cox-I inhibitors	NSAIDs	oral
Celecoxib	Celebrex	Cox-II inhibitors	NSAIDs	oral
Sulindac	Clinoril	Cox-II inhibitors	NSAIDs	oral
Tolmetin		Cox-II inhibitors	NSAIDs	oral
Aspirin	Aspirtab, Ecotrin, EcPirin, Halfprin, Miniprin,	Cox I and -II inhibitors	Salicylates	oral, rectal
Choline Magnesium Trisalicylate	Choline Magnesium Trisalicylate	Cox I and -II inhibitors	Salicylates	oral
Diflunisal	Dolobid	Cox I and -II inhibitors	Salicylates	oral
Magnesium Salicylate	DeWitts Pain Relieve, Doans Pills	Cox I and -II inhibitors	Salicylates	oral
Salsalate	Disalcid	Cox I and -II inhibitors	Salicylates	oral
Diclofenac/Misoprostol	Arthrotec	NSAID/mucosal protective	Non-narcotic analgesic combinations	oral
Ibuprofen/Famotidine	Duexis	NSAID/H_2-receptor antagonist	Non-narcotic analgesic	oral

			combinations	
Naproxen/Esomeprazole	Vimovo	NSAID/proton pump inhibitor	Non-narcotic analgesic combinations	oral
Acetaminophen/Aspirin/ Caffeine	Excedrin, Extraprin, Headrin, Pamprin, PainAid ESF	Cox I and -II inhibitors/CNS stimulant	Non-narcotic analgesic combinations	oral
Acetaminophen/Butalbital	Bupap, Cephadyn, Orbivan	Cox I and -II inhibitors/ Barbiturate/ CNS stimulant	Non-narcotic analgesic combinations	oral
Acetaminophen/Butalbital/Caffeine	Alagesic LQ, Dolgic plus, Esgic, Fioricet, Margesic, Vanatol LQ, Zebutal	Cox I and -II inhibitors/ Barbiturate/ CNS stimulant	Non-narcotic analgesic combinations	oral
Acetaminophen/Diphenhydramine	Aceta-Gesic, Percogesic	Cox I and -II inhibitors/anti-histamine	Non-narcotic analgesic combinations	oral
Acetaminophen/Isometheptene/Caffeine	Prodrin, MigraLam, Migra Ten	Cox I and -II inhibitors /Sympathomimetic amine/CNS stimulant	Non-narcotic analgesic combinations	oral
Acetaminophen/Pamabrom/Pyridoxine	Vitelle Lurline	Cox I and -II inhibitors/diuretic/vitmin B6 supplement	Non-narcotic analgesic combinations	oral
Acetaminophen/Phenyltoloxamine	Biphenox, Zflex, Acuflex, BP Poly-650, Rhinoflex	Cox I and -II inhibitors/anti-histamine	Non-narcotic analgesic combinations	oral
Acetaminophen/Salicylamide/Phenyltoloxamine	Duraxin, Ed-Flex plus, Be-Flex plus	Cox I and -II inhibitors/anti-histamine	Non-narcotic analgesic combinations	oral
Acetaminophen/Salicylamide/Phenyltoloxamine/ Caffeine	Durabac, Cafgesic	Cox I and -II inhibitors/anti-histamine/CNS stimulant	Non-narcotic analgesic combinations	oral
Acetaminophen/Aspirin/ Salicylamide/Caffeine	Saleto	Cox I and -II inhibitors/CNS stimulant	Non-narcotic analgesic combinations	oral
Acetaminophen/Aspirin/ Salicylamide /Caffeine/ Phenyltoloxamine	Levacet	Cox I and -II inhibitors/ CNS stimulant/ anti-histamine	Non-narcotic analgesic combinations	oral
Aspirin/Butalbital/Caffeine	Fiorinal	Cox I and -II inhibitors/ Barbiturate/ CNS stimulant	Non-narcotic analgesic combinations	oral
Aspirin/Caffeine	Anacin	Cox I and -II inhibitors/ CNS stimulant	Non-narcotic analgesic combinations	oral
Aspirin/Meprobamate	Equagesic	Cox I and -II	Non-narcotic	oral

		inhibitors/ GABA receptors	analgesic combinations	
Ziconotide	Prialt	N-type voltage-gated calcium channel blocker	Miscellaneous	intrathecal
Narcotic analgesics combinations				
Acetaminophen/Codeine	Tylenol-Codeine	Centrally and peripherally acting	Opioid analgesics combinations	oral
Acetaminophen/Caffeine /Dihydrocodeine	Trezix, APAP-Caff-Dihydrocodeine	Centrally and peripherally acting	Opioid analgesics combinations	oral
Aspirin/Codeine	Empirin	Centrally and peripherally acting	Opioid analgesics combinations	oral
Aspirin/Caffeine/Dihydr ocodeine	Synalgos-DC	Centrally and peripherally acting	Opioid analgesics combinations	oral
Codeine Phosphate/Acetaminoph en/Caffeine/Butalbital	Floricet/Codeine	Centrally and peripherally acting	Opioid analgesics combinations	oral
Codeine Phosphate/Aspirin/Caffe ine/Butalbital	Fiorinal/Codeine ASCOMP/Codeine	Centrally and peripherally acting	Opioid analgesics combinations	oral
Hydrocodone/Guaifenesi n	Codotuss, Flowtuss, Obredon	Centrally and peripherally acting	Opioid analgesics combinations	oral
Hydrocodone Bitartrate/Acetaminophe n	Hycet, Lortab, Vincodin, Norco, Lorcet, Panlor	Centrally and peripherally acting	Opioid analgesics combinations	oral
Hydrocodone bitartrate/Ibuprofen	Reprexain, Vicoprofen, Xylon	Centrally and peripherally acting	Opioid analgesics combinations	oral
Meperidine-Promethazine	Mepergan Fortis, Meprozine	Centrally and peripherally acting	Opioid analgesics combinations	oral
Belladonna/Opium		Centrally and peripherally acting	Opioid analgesics combinations	rectal
Oxycodone/Aspirin	Percodan, Endodan	Centrally and peripherally acting	Opioid analgesics combinations	oral
Oxycodone/Ibuprofen	Combunox	Centrally and peripherally acting	Opioid analgesics combinations	oral
Oxycodone/Naloxone	Targiniq ER	Centrally and peripherally acting	Opioid analgesics combinations	oral
Oxycodone/Acetaminop hen	Endocet, Magnacet, Percocet, Primelev, Roxicet, Tylox, Xartemis XR, Xolox	Centrally and peripherally acting	Opioid analgesics combinations	oral
Propoxyphene/ Acetaminophen	Darvocet, Balacet, Propacet, Propoxacet	Centrally and peripherally acting	Opioid analgesics combinations	oral
Tramadol/Acetaminophe n	Ultracet	Centrally and	Opioid analgesics combinations	oral

		peripherally acting		
Buprenorphine/Naloxone	Suboxone, Zubsolv	Mixed agonists/antagonists	Opioid analgesics combinations	oral
Pentazocine/Naloxone	Talwin NX	Mixed agonists/antagonists	Opioid analgesics combinations	oral
Morphine/Naltrexone	Embeda	Mixed agonists/antagonists	Opioid analgesics combinations	oral
Pentazocine/Acetaminophen	Talacen	Mixed agonists/antagonists	Opioid analgesics combinations	oral
Opioid analgesics				
Alfentanil	Alfenta	Full opioid agonists	Opioids	inj
Buprenorphine	Buprenex, Butrans	Mixed agonists/antagonists	Opioids	oral, im, iv, trasdermal
Butorphanol	Stadol	Mixed agonists/antagonists	Opioids	inj, nasal
Codeine		Full opioid agonists	Opioids	oral
Fentanyl	Abstral, Actiq, Duragesic, Fentora, Lazanda, Sublimaze, Subsys	Full opioid agonists	Opioids	oral, nasal, inj
Hydrocodone	Hysingla ER, Zohydro ER	Full opioid agonists	Opioids	oral
Hydromorphone	Dilaudid, Exalgo,	Full opioid agonists	Opioids	oral, inj, rectal
Levorphanol	Levo-Dromoran	Full opioid agonists	Opioids	oral
Meperidine	Demerol, Meperitab	Full opioid agonists	Opioids	oral, inj
Methadone	Dolphine, Methadose,	Full opioid agonists	Opioids	oral, inj
Morphine	Avinza, DepoDur, Duramorph, Infumorph, Kadian, MS Contin, Oramorph SR	Full opioid agonists	Opioids	oral, inj, epidural, iv, im, rectal
Nalbuphine	Nubain	Mixed agonists/antagonists	Opioids	oral
Opium	Paregoric	Full opioid agonists	Opioids	oral
Oxycodone	Oxecta, Oxycontin, Roxicodone, ETH-Oxydose, Oxy IR	Full opioid agonists	Opioids	oral
Oxymorphone	Opana	Full opioid agonists	Opioids	oral, inj
Pentazocine	Talwin	Mixed agonists/antagonists	Opioids	inj
Propoxyphene	Darvon	Weak agonist	Opioids	oral
Remifentanil	Ultiva	Full opioid agonists	Opioids	iv
Sufentanil	Sufenta	Full opioid agonists	Opioids	iv
Tapentadol	Nucynta	Atypical opioids	Opioids	oral
Tramadol	ConZip, Rybix ODT, Ryzolt, Synapryn FusePag, Ultram	Atypical opioids	Opioids	oral
Adjuvant analgesics (For neuropathic pain)				

Amitriptyline	Elavil	Tricyclic antidepressants	Antidepressants	oral
Nortriptyline	Pamelor	Tricyclic antidepressants	Antidepressants	oral
Desipramine	Norpramin	Tricyclic antidepressants	Antidepressants	oral
Paroxetine	Paxil, Brisdelle, Paxeva	SSRI	Antidepressants	oral
Citalopram	Celexa	SSRI	Antidepressants	oral
Venlafaxine	Effexor	SNRI	Antidepressants	oral
Duloxetine	Cymbalta, Irenka	SNRI	Antidepressants	oral
Gabapentin	Fanatrex, Gralise, Horizant, Neurontin,	alpha-2-delta modulators	Anticonvulsants	oral
Pregabalin	Lyrica	alpha-2-delta modulators	Anticonvulsants	oral

SSRI = Selective Serotonin Reuptake Inhibitors,
SNRI = Serotonin-Norepinephrine Reuptake Inhibitors
(Source: eFacts & Comparisons)

2.4.1 Outcome Measures

2.4.1.1 Utilization of Pain Prescription

Utilization was defined as obtaining or purchasing pain prescription in the year of interest (annually from 2008-2013 or pooled estimate over six years of study period). Original prescriptions as well as refills were included in calculating utilization estimates. The prescribed medicines file of MEPS-HC provides detail information on prescription drug use data and the variable drug name (RXNAME) was used to determine utilization of pain prescriptions.

The cancer survivor was considered to be using pain medication if claims on pain prescription were identified from the non-opioids, narcotic analgesics combinations, opioids and adjuvant analgesics class of drugs as mentioned in Table 7. The utilization of pain medications was reported by different class among cancer survivors and the individuals without cancer history annually from 2008-2013 and pooled estimates over six years of study period. The analyses were also performed to determine pain medication utilization stratified by socio-demographic, geographical, clinical and economic variables.

2.4.1.2 Total Expenditure

Expenditure was defined as total direct payments from all the sources to drug store for the pain prescriptions reported by respondents in the MEPS-HC.

The total expenditure associated with each pain medications were obtained from the prescribed medicine file. The file supply information on different payment sources; the amount of payment from each of these sources, which were used to calculate total expenditure associated with each prescription. The different source includes:

(a) Out-of-pocket by user (self) or family

(b) Private Insurance

(c) Medicare

(d) Medicaid

(e) Veterans Administration/CHAMPVA

(f) TRICARE

(g) Other Federal sources such as military treatment facilities, Indian Health Service

(h) Other State/Local source: State and local health programs, neighborhood and community clinics

(i) Workers compensation

(j) Other unclassified/miscellaneous or unknown sources: such as homeowners, automobile, and liability insurance

The MEPS-HC provide information on sum of payments variables, RXXP08X, RXXP09X, RXXP10X, RXXP11X, RXXP12X, and RXXP13X respectively for year 2008-2013. The variable sums all the expenditures from the different sources of payment for each prescription. These variables were used to report estimates of the total cost associated with pain prescription annually and pooled over six years of study period. Expenditures were reported in US dollars. The cost estimates were not adjusted and reported in the year they were obtained.

2.4.1.3 Patient Cost Share

The patient cost share was defined as percent of payment share of total expenditure that is paid out-of-pocket (self or family) to pharmacy for the pain prescriptions. The out-of-pocket costs associated with each pain medications were obtained from the prescribed medicine file. The file provides itemized expenditures from each source which are used to calculate total expenditure associated with each prescription. The patient cost share was calculated as:

$$\text{Patient cost share (\%)} = \left(\frac{\text{Out-of-pocket costs}}{\text{Total Expenditure}}\right)\text{x}100$$

The MEPS-HC provide information on amount paid by self or family through variables, RXSF08X, RXSF09X, RXSF10X, RXSF11X, RXSF12X, and RXSF13X, respectively, for year 2008-2013. The variable captures out-of-pocket costs that individual pays for each prescription. These variables were used

to calculate estimates of the patient cost share associated with pain prescription annually and pooled over six years of study period. The out-of-pocket costs were in US dollars. The cost estimates were not adjusted, and calculation was facilitated using cost value in the year they were obtained.

2.4.1.4 Health-Related Quality-of-Life

The information on cancer survivor's health status can be obtained from Short Form-12 version 2 (SF-12v2) available in full-year consolidated data file of MEPS-HC. The SF-12v2 measures the following eight domains: general health, physical functioning, role limitation, bodily pain, vitality, social functioning, emotional problems, and mental health. An algorithm was developed to generate the physical component summary (PCS) and mental component summary (MCS) scores.[79] The mean score is set to 50, thereby scores > 50 represents better physical or mental health; mean scores < 50 are interpreted as clinically lower than average health status. The variables PCS42 and MCS42 available in MEPS-HC were used to obtain PCS and MCS scores. These variables incorporate information from all twelve items of SF-12v2. Notably, the scores for PCS42 and MCS42 were coded negative value if the response on any of the twelve items were incomplete or missing.

Identifying who in the cancer survivor's population is at risk of poor health status is important first step in direction to develop appropriate target interventions with potential to improve cancer survivorship and reduce cancer burden. This study investigated US civilian non-institutionalized population to: (a) compare the PCS and MCS scores of cancer survivors to individuals without cancer history (b) compare the PCS and MCS scores by stratifying study population and the comparison group according to socio-demographics, geographical, clinical and economic variables (c) measure HRQoL among cancer survivors stratified by opioid exposure.

The cancer survivors and individuals without cancer history with the negative values on variables PCS42 and MCS42 were excluded from all HRQoL related analyses.

2.4.2 Other Study Measures

2.4.2.1 Percent Taking Pain Medication

The percent taking pain medication was defined as proportion among all the cancer survivors/ individuals without history identified with atleast one claims of pain prescription belonging to class of non-opioids, narcotic analgesic combinations, opioid and/or adjuvants.

Percent taking pain medication (%) = $\left(\frac{n}{N}\right)$ x100

Where,

n= number of cancer survivors/individuals without cancer history identified with claims of atleast one pain prescription

N = total number of cancer survivors/ individuals without cancer history

2.4.2.2 Opioid Exposure

The HRQoL among cancer survivors and individuals without cancer history were analyzed based on their opioid prescription claims. The assumption is extreme pain interference will be associated with the claims of opioid prescription and worst PCS and MCS scores. Based on opioid exposure, individuals were grouped into following three broad categories:

(a) Any opioid use: Individuals identified with claims of atleast one prescription of opioid or narcotic analgesic combinations.

(b) No opioid use but with claims of atleast one prescription for pain medication: Individuals identified with no claims of opioid/narcotic analgesic combinations but atleast one pain prescription claims.

(c) No pain medication: Individuals identified with no claims of pain prescription.

2.5 Methodology: Objective 2

2.5.1 Data Source & Study Design

This observational study employs retrospective, longitudinal research design covering the panel 15 (Jan 2010- Dec 2011) and panel 16 (Jan 2011- Dec 2012) using a nationally representative survey database among participants aged 18 years and older ever diagnosed with cancer.

Figure 4 represents MEPS overlapping panel design where individuals in the panel 15 and 16 are followed upto 2 years. Each bar represents five separate rounds of in-person interview. The individual characteristics changes over two-year time period. These changes in characteristics are recorded through the information obtained from respondents and are publicly released in form of the indicators that may be captured monthly, annually, each five rounds or in separate rounds of interview.

(a) Monthly indicators (24 measures): Insurance coverage if covered by private (PRIJAY1, PRIJAY2, PRIFEY1, PRIFEY2, PRIMAY1, PRIMAY2, PRIAPY1, PRIAPY2, PRIMYY1, PRIMYY2, PRIJUY1, PRIJUY2, PRIJLY1, PRIJLY2, PRIAUY1, PRIAUY2, PRISEY1, PRISEY2, PRIOCY1, PRIOCY2, PRINOY1, PRINOY2, PRIDEY1, PRIDEY2).

(b) Annual indicators (2 measures): Family income as % of poverty line (POVCATY1 and POVCATY2).

(c) Each round (5 measures): Marital status (MARRY1X, MARRY2X, MARRY3X, MARRY4X and MARRY5X), Region, MSA.

(d) Separate rounds (2 measures): Certain questions, measures or instrument sections are only asked in certain round.

    a. Round 2 and 4: Smoking (ADSMOK2 & ADSMOK4), the last numerical digit at the end of variable signifies the round in which information was collected. As in above example smoking status was derived in round 2 of panel 15 and round 4 of panel 16.

    b. Round 3 and 5: BMI (BMINDX3 & BMINDX5).

Figure 4: Panel 15 & 16, MEPS Panel Design: Data Reference Periods

Sample Size (N)	Panel	2010				2011*				2012				Cancer Survivors (n)
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
16,221	**Panel 14** Round 3 Round 4 Round 5													
14,541	**Panel 15** Round 1 Round 2 Round 3 Round 4 Round 5													$n_{Panel15}$= 1,104
18,512	**Panel 16** Round 1 Round 2 Round 3 Round 4 Round 5													$n_{Panel16}$ = 1,489
17,923	**Panel 17** Round 1 Round 2 Round 3													
*Cancer Self-Administered Questionnaire														

To accomplish research objective, panel 15 and panel 16 were selected to maximize the utility of the available data. Since, panel 15 and 16 incorporates information on Cancer-Self Administered Questionnaire (CSAQ) administered only once in year 2011. Eligible individuals interviewed during round 5 of panel 15 and round 3 of panel 16 answered the questionnaire.

The following different files were used, and seven datasets were created with variables of interest:

(1) Longitudinal data file: Records from panel 15 (n=14,541) and 16 (n=18,512) were obtained containing following variables of interest:

I. Demographic variables: It provides detail information about the demographic characteristics of each respondent. The characteristics include age, sex, race/ethnicity, education and marital status.

II. Geographic variables: comprise of census region and MSA.

III. Clinical variables: such as smoking, BMI, ever diagnosed of cancer, cancer type, age when cancer diagnosed.

IV. Economic variables: such as employment status, family income as % of poverty line, health insurance coverage was employed from this file.

V. Health status variables: SF-12 question "during past 4 weeks, pain interfered with normal work outside the home and housework?"

(2) Medical conditions file: The relevant CCCs were used to obtain list of painful conditions, mental illness and substance abuse from medical conditions file.

(3) Prescribed medicines file:

The utilization in terms of number of pain medications and opioids prescription were obtained from prescribed medicine file.

(4) Outpatient visits file: The file contains information associated with the outpatient visit such as date of visit, type of services provided, ICD-9CM, procedure and CCCs associated with service, care received, expenditure and source of payment. Up to 4 variables were provided mentioning conditions code (both ICD-9CM and CCCs) and 2 variables mentioning procedure code. Any chemotherapy, radiation, or cancer-related surgeries performed during outpatient visits were obtained from this file.

(5) Office-based medical provider visits file: The file provides information associated with the office-based visit such as date of visit, type of treatment and services provided, ICD-9CM, procedure and CCCs associated with service, expenditure and source of payment. Up to 4 variables were provided mentioning conditions code (both ICD-9CM and CCCs) and 2 variables mentioning procedure code. Any chemotherapy, radiation, or cancer-related surgeries performed during office-based visits were obtained from this file.

(6) Hospital inpatient stays file: The file contains characteristics associated with inpatient hospitalization such as date of hospital inpatient stay, reason for stay, type of treatment and services received, ICD-9CM, procedure and CCCs associated with service, expenditure and source of payment. Up to 4 variables were provided mentioning conditions code (both ICD-9CM and CCCs) and 2 variables mentioning procedure code. Any cancer-related operation or surgeries performed during hospitalization were obtained from this file.

(7) Objective 1 dataset: A dataset was created identifying cancer survivors annually for years 2010, 2011 and 2012 (study population for objective 1).

Individuals identified as cancer survivors in objective 1 were linked to outpatient department, office-based or hospital inpatient stays file to differentiate subjects receiving cancer treatment. Those identified not receiving treatment were linked to longitudinal data files (panel 15 and 16), medical conditions file and prescribed medicines file to create final dataset (N=33,053) that contains information about post-treatment cancer survivors, comorbidities, predictor variables (demographical, geographical, clinical and economic) and outcome variables (number of pain and opioid prescriptions). Longitudinal weight (LONGWT) produces national estimates for persons in two consecutive years. It is derived for respondents who are in scope for entire period during two years of follow-up. Longitudinal weight together with strata and PSU design variable were used to conduct weighted analysis.

2.5.2 Study Population: Post-Treatment Cancer Survivors

Cancer survivors identified annually in year 2010, 2011 and 2012 (flowchart outlined in figure 3) were screened in longitudinal files for information on panel using MEPS variable name PANEL and those individuals interviewed during panel 14 and 17 were excluded. Thereby, of all the respondents (N=33,053) from panel 15 and 16, the cancer survivors (N_{Total}=2,593) identified, respectively belonging to panel 15 and 16 were $n_{Panel15}$=1,104 and $n_{Panel16}$ = 1,489. Whether cancer survivors were receiving current treatment was identified from outpatient department, office-based or hospital inpatient stays file using variables CHEMOTH (Did patient received chemotherapy during visit?), RADIATTH (Did patient received radiation therapy during visit?), ANYOPER and SURGPROC (Was cancer-related surgery or operation performed on patient during visit?). Cancer-related surgery or operations were identified by mention of cancer CCCs excluding non-melanoma skin cancer using the variables IPCCC1X, IPCCC2X, IPCCC3X, IPCCC4X from hospital inpatient stays file; OPCCC1X, OPCCC2X, OPCCC3X, OPCCC4X from outpatient visits file and OBCCC1X, OBCCC2X, OBCCC3X, OBCCC4X from office-based medical provider visits file. From total of 2,593 cancer survivors, 801 patients were currently receiving treatment and were excluded. Of 1,792 cancer survivors not receiving treatment, 348 subjects were excluded for incomplete information (120 patient lost to follow-up, 42 were deceased during study period, 37 persons were not in-scope because of weight equals zero, 6 cancer survivors were adolescent and 143 individuals had missing information on covariates such as education, smoke, obese, pain perception and survival).

As shown in figure 5, final sample consists of total 1.444 post-treatment cancer survivors with complete information on predictor and outcome variables to incorporate in weighted regression.

The ***post-treatment cancer survivors*** included in the study were defined as adult individuals ever diagnosed with cancer excluding solely non-melanoma skin cancer; have not received active treatment in terms of chemotherapy, radiation therapy or cancer-related surgery or operation within two years of their longitudinal follow-up.

Thereby, inclusion and exclusion criteria to identify post-treatment cancer survivors are:

Inclusion criteria:

(a) Adult individuals age≥18

(b) Mention of cancer diagnosis code or history of cancer

(c) Diagnosed with one or more cancer type

(d) Type of cancer includes head & neck, gastrointestinal, lung/bronchus, breast, urogenital, gynecological, prostate, hematological, bone, skin and other/unspecified

(e) Have not received active treatment in terms of chemotherapy, radiation therapy or cancer-related surgery/operation within two years of their longitudinal follow-up

Exclusion criteria:

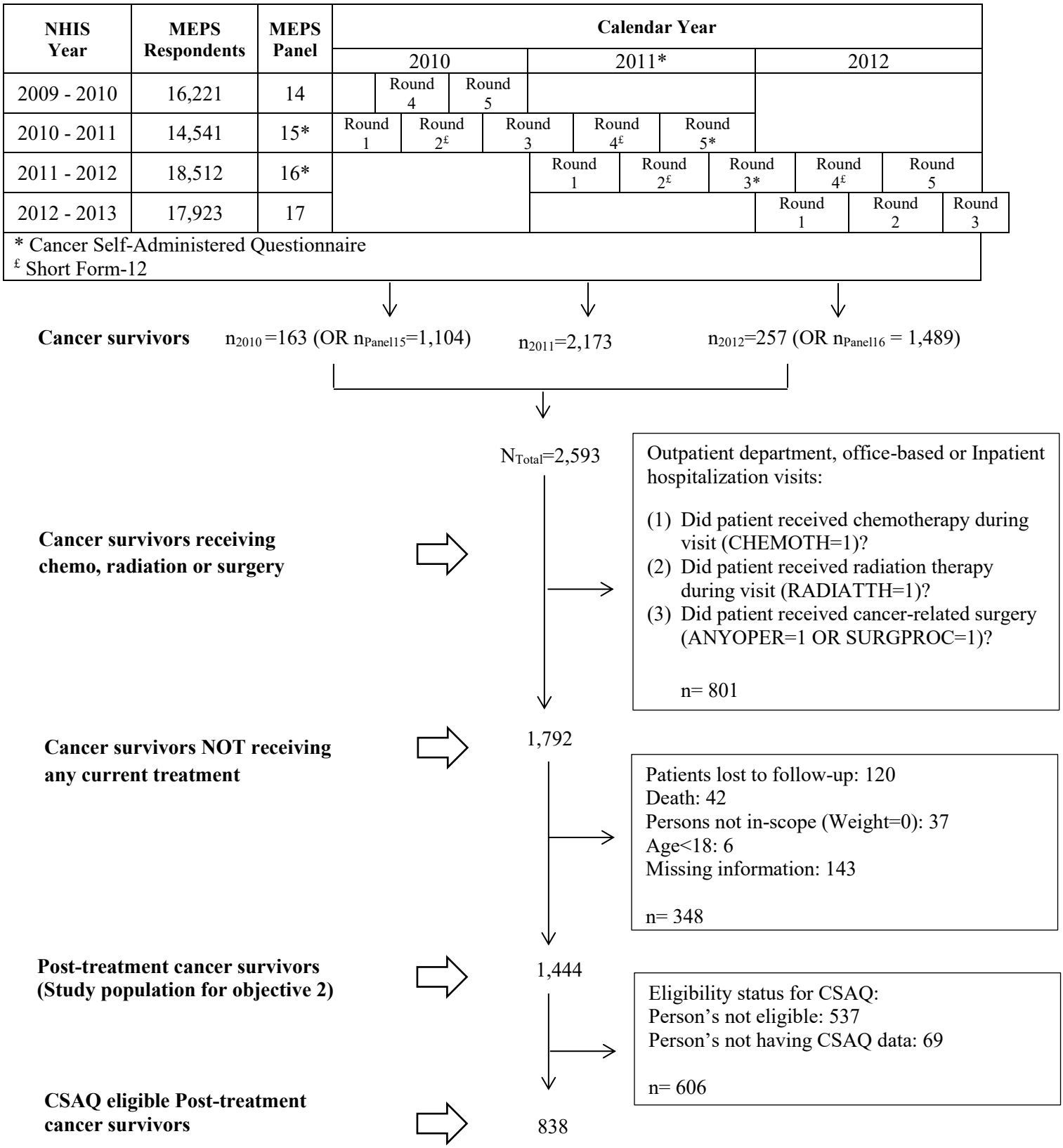
(a) Adult respondents with missing data on cancer question "Ever been diagnosed with cancer?"

(b) Individuals diagnosed solely with non-melanoma skin cancer

(c) Patient lost to follow-up, not in-scope or deceased within two years of their longitudinal follow-up

(d) Individuals with incomplete/missing information on covariates

Figure 5: Flowchart Identifying Post-Treatment Cancer Survivors



2.5.3 Predictor Variables

The demographic, geographical, clinical and economic predictor variables obtained from MEPS-HC were regressed to check their association with number of pain/opioids prescription:

I. Demographic variables:

(a) Age: The information on age is collected from respondent during each round of the interview and publicly released through age variables AGE1X, AGE2X, AGE3X, AGE4X and AGE5X. It is available as continuous variable and for confidentiality reasons top-coded at 85 years. Individuals with Age $\geq$ 85 were excluded from analysis, since; biased estimate would be generated in calculating years since first cancer diagnosis. The variable AGE1X were employed to categorize post-treatment cancer survivors into the following age-groups, Age 18-34, Age 35-44, Age 45-54, Age 55-64, Age 65-74, Age 75-84. Age category 18-34 was used as reference category in the model to determine their association with outcome variable.

(b) Sex: Categorical variable SEX (male/female) for both panels were used to check association between gender and number of pain/opioids prescription. Male was used as reference category in the model to determine their association with outcome variable.

(c) Race/Ethnicity: Combination of variables RACEX/RACEV1X and HISPANX were employed to categorize individuals into race/ethnicity categories such as non-Hispanic White, non-Hispanic Black, Hispanic and non-Hispanic other/multiple race (Asian, Alaska native/American Indian, Native Hawaiian/Pacific Islander). Non-Hispanics Whites category was used as reference in the regression model to determine their association with outcome variable.

(d) Education status: Education based analysis was performed using variable HIDEG by distributing individuals into more (college degree or more) or less education. To determine the association of education with number of pain prescription/opioids less education was used as reference category in the regression model.

(e) Marital status: During five rounds of the interview, variables MARRY1X, MARRY2X, MARRY3X, MARRY4X and MARRY5X captures information on marital status. Depending upon the marital status in most of the panel individuals were grouped into categories married or not (widowed/ divorced/ separated and never married). i.e respondent were categorized as married if the marital status was married in atleast 3 rounds of the interview. Not married was used as reference category.

(f) Panel: The panel in which respondent begins the interview process were used as independent variable; panel 15 was used as reference category in the regression model.

II. Geographic variables:

(a) Region: Information on Census region was captured during every round of interview and publicy released through variables REGION1, REGION2, REGION3, REGION4, and REGION5, respectively. Depending upon region where respondent reside the most (atleast 3 out of 5 rounds) during 2 years of the follow-up, they were grouped into Northeast, Midwest, South and West. Category Northeast was used as reference category.

(b) Urban status: Whether an individual resides in urban or rural was captured through variable MSA1, MSA2, MSA3, MSA4 and MSA5, respectively, for 5 rounds of the interview. Depending where respondent reside the most during 2 years of the follow-up, they were grouped into either urban or rural. Residing in rural was used as reference category in the regression model.

III. Clinical variables:

(a) Smoking: Whether an individual is smoking or not is captured by the round variables ADSMOK2 and ADSMOK4. An individual was considered to be smoker if he ever smokes during 2 years of follow-up period. The variable smoking status was incorporated in the model as predictor variable with non-smokers as reference category.

(b) BMI: In MEPS-HC, the Body Mass Index (BMI) was calculated based on individual reported height and weight of every adult respondents (age>17) and was released by continuous variable BMINDX3 and BMINDX5. An individual was considered to be obese if the BMI was $\geq$ 30.0

anytime during 2-years of follow-up. A categorical variable was created that classifies individual into either of the two distinct classes obese and non-obese (normal/underweight/overweight). The variable was regressed to check the association with total number of pain medications /opioids with non-obese as reference category.

(c) Pain perception: One of the questions that SF-12 comprises of is *"During past 4 weeks, pain interfered with normal work outside the home and housework?"* and the response was captured through round variables ADPAIN4 and ADPAIN2. These variables were used to determine pain perception and the response includes extremely, quite a bit, moderately, a little bit, no pain and unknown/not ascertained/inapplicable.

Using the response on both the variables individual were categorized into the following: (i) No pain: individual experiencing no pain during 2 years of follow up, (ii) Mild/moderate pain: those individual experiencing little bit or moderate pain during 2 years of follow up, (iii) High /severe pain: characterized by individual experiencing quite a bit or extreme pain during 2 years of follow up; (iv) Pain changes over the panel: individual experiencing fluctuating pain that changes over time. Category no pain was used as reference category.

(d) Type of cancer: Cancer survivors were identified using CCCs (Appendix A) and through cancer history self-report question about *"Whether a doctor or health professional had ever told them that they had cancer or malignancy of any kind?"* If answered yes, the response to follow-up question *"what type of malignancy?"* was captured using variables CABLADY1, CABLADY2, CABLOOY1, CABLOOY2, CABONEY1, CABONEY2, CABRAIY1, CABRAIY2, CABREAY1, CABREAY2, CACERVY1, CACERVY2, CACOLOY1, CACOLOY2, CAESOPY1, CAESOPY2, CAKIDNY1, CAKIDNY2, CALARYY1, CALARYY2, CALEUKY1, CALEUKY2, CALIVEY1, CALIVEY1, CALUNGY1, CALUNGY2, CALYMPY1, CALYMPY2, CAMELAY1, CAMELAY2, CAMOUTY1, CAMOUTY2, CAMUSCY1, CAMUSCY2, CAOTHEY1, CAOTHEY2, CAOVARY1, CAOVARY2, CAPANCY1, CAPANCY2, CAPROSY1, CAPROSY2, CARECTY1, CARECTY2,

CASTOMY1, CASTOMY2, CATESTY1, CATESTY2, CATHROY1, CATHROY2, CATHYRY1, CATHYRY2, CAUTERY1, and CAUTERY2 indicates cancer selection of bladder, blood, bone, brain, breast, cervix, colon, esophagus, kidney, larynx, leukemia, liver, lung, lymph, melanoma, mouth, muscle, other, ovary, pancreas, prostate, rectal, stomach, testis, throat, thyroid, uterus. (Appendix B). Post-treatment cancer survivors were classified based on cancer site including head & neck, gastrointestinal, lung/bronchus, breast, urogenital, gynecological, prostate, hematological, bone, skin, and other/unspecified. A variable multi-cancer was created categorizing individuals with more than one cancer.

Types of cancer based on tumor site along with multi-cancer were used as predictor variables in the regression model with category absence of cancer as reference category.

(e) Years since first cancer diagnosis: Individuals who answered yes to cancer question were asked kind of cancer and age of diagnosis. The variables BLDRAGY1, BLDRAGY2, BLODAGY1, BLODAGY2, BONEAGY1, BONEAGY2, BRAIAGY1, BRAIAGY2, BRSTAGY1, BRSTAGY2, CERVAGY1, CERVAGY2, COLOAGY1, COLOAGY2, ESPHAGY1, ESPHAGY2, KIDNAGY1, KIDNAGY2, LRNXAGY1, LRNXAGY2, LEUKAGY1, LEUKAGY2, LIVRAGY1, LIVRAGY2, LUNGAGY1, LUNGAGY2, LYMPAGY1, LYMPAGY2, MELAAGY1, MELAAGY2, MOUTAGY1, MOUTAGY2, MUSCAGY1, MUSCAGY2, OTHRAGY1, OTHRAGY2, OVRYAGY1, OVRYAGY2, PANCAGY1, PANCAGY2, PRSTAGY1, PRSTAGY2, RECTAGY1, RECTAGY2, STOMAGY1, STOMAGY2, TSTSAGY1, TSTSAGY2, THRTAGY1, THRTAGY2, THYRAGY1, THYRAGY2, UTERAGY1, UTERAGY2, respectively, indicates age at which cancer of bladder, blood, bone, brain, breast, cervix, colon, esophagus, kidney, larynx, leukemia, liver, lung, lymph, melanoma, mouth, muscle, other, ovary, pancreas, prostate, rectal, stomach, testis, throat, thyroid, uterus was diagnosed.

Time since first cancer diagnosis was calculated as the difference between age at the interview year and age at first cancer diagnosis. Individuals were categorized into one of the followings

>20, 16-20, 11-15, 6-10, 1-5, < 1 years. The category less than one year was used as reference category.

(f) Types of painful conditions: Conditions such as arthritis, neck and back pain, chest pain, connective tissue disease, diabetes, fracture, headache, pelvic/abdominal pain were incorporated in the model as predictors. The list of painful conditions was obtained from prior research conducted by White *et al*.[80] The painful conditions were included as covariates based on previous research that has shown that failure to control comorbidities adequately may lead to substantial upward bias.[81] A variable multi-pain conditions was created categorizing individuals with more than one painful conditions. Types of painful condition along with multi-pain were used as predictor variable with the absence of disease as reference category. The CCCs were used to identify different painful conditions and the details are summarized in Appendix D.

(g) Mental conditions: Comorbidities including mental health such as major depressive disorder, adjustment disorder, anxiety, bipolar, conduct disorder were incorporated in the model. A variable multi-mental disorder was created categorizing individuals with more than one mental conditions. Types of mental conditions along with variable multi-mental commodities were used as predictor variable with the absence of disease as reference category. The CCCs were used to identify different mental conditions. The lists of mental conditions with details are summarized in Appendix E.

(h) History of drug/substance abuse:

Having history of alcohol and drugs abuse and dependence was incorporated in model to examine the association with outcome variables. The CCCs were used to identify history of drug/substance abuse. The lists of conditions with details are summarized in Appendix F.

IV. Economic variables:

(a) Employment status: Information on employment status was asked for all the respondent household members age 16 or older during every round of the interview. Allowable response includes if currently employed, has job to return and not employed; captured through variables

EMPST1, EMPST2, EMPST3, EMPST4 and EMPST5. Individuals were considered to be employed if they had job to return or were employed during most of the panel (atleast 3 out of 5 rounds). Individual ever employed during year were identified and grouped into binary categorical variable employed versus unemployed with unemployed as reference category.

(b) Family income as % of poverty line: For every respondents, family income was derived by bringing together every household members total income comprising annual earnings from different sources including wages, salaries, business and firm profit and loss, interest and dividends, bonuses, tips, commissions, unemployment and workers compensation, private cash transfers, pensions, IRA withdrawals, child support, alimony, temporary assistance for needy families, rent, royalties, social security and other source of income.

The MEPS classifies income into one of the five poverty categories including high income (greater than or equal to 400%), middle income (200% to less than 400%), low income (125% to less than 200%), near poor (100% to less than 125%), negative or poor (less than 100%). Annual variables POVCATY1 and POVCATY2, respectively, for two years of panel 15 and 16 were used to differentiate family income into higher, lower or change in income. Individuals with higher income were defined as the family income as % of poverty line with middle or high income during 2 years of follow-up. Lower income was used as reference category defined as individuals with family income as % of poverty line with low, near poor or poor income during 2 years of follow-up. Individuals for whom if the family income changed over time from higher to lower or vice-versa were classified into change income category.

(c) Health insurance coverage: The health insurance coverage variables available in MEPS-HC were used to differentiate individuals into one of the following mutually exclusive categories:

(i) Private only: Individuals were considered privately insured if they had coverage through private insurance sources for atleast 18 out of 24 months follow-up. The variables PRIJAY1, PRIFEY1, PRIMAY1, PRIAPY1, PRIMYY1, PRIJUY1, PRIJLY1, PRIAUY1, PRISEY1, PRIOCY1, PRINOY1, PRIDEY1, PRIJAY2, PRIFEY2,

PRIMAY2, PRIAPY2, PRIMYY2, PRIJUY2, PRIJLY2, PRIAUY2, PRISEY2, PRIOCY2, PRINOY2 and PRIDEY2 were used to determine individual's private insurance coverage.

Individuals with only private insurance coverage were included in this category.

(ii) Medicaid only: Individuals were considered Medicaid beneficiary if they had coverage through Medicaid program for atleast 18 out of 24 months follow-up. The variables MCDJAY1, MCDFEY1, MCDMAY1, MCDAPY1, MCDMYY1, MCDJUY1, MCDJLY1, MCDAUY1, MCDSEY1, MCDOCY1, MCDNOY1, MCDDEY1, MCDJAY2, MCDFEY2, MCDMAY2, MCDAPY2, MCDMYY2, MCDJUY2, MCDJLY2, MCDAUY2, MCDSEY2, MCDOCY2, MCDNOY2 and MCDDEY2 were used to determine individual's insurance coverage through Medicaid.

Individuals with only Medicaid insurance coverage were included in this category.

(iii) All Medicare beneficiaries (including Medicare only, Medicare and Medicaid, Medicare and private): Individuals were considered Medicare beneficiary if they had coverage through Medicare program for atleast 18 out of 24 months follow-up. The variables MCRJAY1, MCRFEY1, MCRMAY1, MCRAPY1, MCRMYY1, MCRJUY1, MCRJLY1, MCRAUY1, MCRSEY1, MCROCY1, MCRNOY1, MCRDEY1, MCRJAY2, MCRFEY2, MCRMAY2, MCRAPY2, MCRMYY2, MCRJUY2, MCRJLY2, MCRAUY2, MCRSEY2, MCROCY2, MCRNOY2 and MCRDEY2 were used to determine individual's insurance coverage through Medicare.

(iv) Uninsured: Individuals were considered to be uninsured if they lack any private, any public (Medicaid, All Medicare) health insurance coverage during 24 months of follow-up. The response to annual variables UNINSY1 & UNINSY2 were used to determine if individuals were uninsured.

(v) Change in health insurance status: Individuals not classified in above four distinct categories representing intermittently insured pattern were included in this category.

2.5.4 Outcome Variables

2.5.4.1 Total Number of Pain Prescription Claims

The variable drug name (RXNAME) obtained from prescribed medicines file of MEPS-HC for years 2010, 2011 and 2012 were used to identify pain prescriptions. The total numbers of pain prescriptions were calculated based on individuals' claim of analgesics belonging to non-opioids, narcotic analgesic combinations, opioids and adjuvants class of drugs as mentioned in Table 7. Original prescription as well as refills were included in calculating the estimates.

Total number of pain prescription claims (N_T) = N_1+ N_2 + N_3 +N_4

Where,

N_1 = Total number of non-opioids prescription

N_2 = Total number of narcotic analgesic combinations prescription

N_3 = Total number of opioids prescription

N_4 = Total number of adjuvants prescription

Thus, the regression model consists of outcome variable in terms of count data [0,1,2,3, 4,……n] characterized by non-negative integers greater or equal to zero ($N_T \geq 0$). An individual was considered to be using pain medication if atleast one claim on pain prescription was identified from the non-opioids, narcotic analgesic combinations, opioids or adjuvant analgesics class of drugs ($N_T \geq 1$). The total number of pain prescriptions was used as dependent variable and estimates were reported for different covariates stratified by socio-demographic, geographical, clinical and economic characteristics.

2.5.4.2 Total Number of Opioids Prescription Claims

The variable drug name (RXNAME) obtained from prescribed medicines file of MEPS-HC for years 2010, 2011 and 2012 were used to identify opioids prescriptions. The total numbers of opioid prescriptions were calculated based on individuals' claim of drugs belonging to class of opioids and narcotic analgesic combinations. Both, the original prescriptions as well as refills were included in calculating the estimates.

Total number of opioids prescription claims (N_O) = N_1+ N_2

Where,

N_1 = Total number of opioids prescription

N_2 = Total number of narcotic analgesic combinations prescription

Thus, the regression model consists of outcome variable in terms of count data [0,1,2,3, 4,……n] characterized by non-negative integers greater or equal to zero ($N_O \geq 0$). An individual was considered to be using opioids if atleast one prescription claim was identified from the narcotic analgesic combinations or opioids class of drugs ($N_O \geq 1$). The total number of opioid prescriptions was used as dependent variable and estimates were reported for different covariates stratified by socio-demographic, geographical, clinical and economic characteristics.

2.6 Methodology: Objective 3

2.6.1 Data Source & Study Design

This observational study was conducted among post-treatment cancer survivors and the relationship between productivity measures and pain medication use were explored using retrospective, longitudinal exploratory study design covering the panel 15 (Jan 2010- Dec 2011) and panel 16 (Jan 2011- Dec 2012). The panel 15 and 16 were selected because individuals ever diagnosed with cancer were asked to complete one-time CSAQ questionnaire administered during year 2011.

The change in work productivity and pain mediation use over time were assessed through the respondent's data on productivity measures obtained from longitudinal file and the pain medication use data derived from prescribed medicines file, respectively. The work-related productivity measures were obtained from questions asked during interview through Short-form 12 and among eligible respondents completing cancer experiences questionnaire.

2.6.1.1 Short Form-12

The MEPS has several measures of HRQoL, including the 12-item Short Form Health Survey version 2 (SF-12v2). The person's health status on eight domains including general health, physical functioning, role limitation, bodily pain, vitality, social functioning, emotional problems, and mental health can be assessed through the following constructs[82]:

1. General health today
2. During a typical day, limitations in moderate activities
3. During a typical day, limitations in climbing several flights of stairs
4. During past 4 weeks, as result of physical health, accomplished less than would like
5. During past 4 weeks, as result of physical health, limited in kind of work or activities
6. During past 4 weeks, as result of mental health, accomplished less than would like
7. During past 4 weeks, as result of mental problems, did work or other activities less carefully than usual
8. During past 4 weeks, pain interfered with normal work outside the home and housework
9. During past 4 weeks, felt calm and peaceful
10. During past 4 weeks, had a lot of energy
11. During past 4 weeks, felt downhearted and depressed
12. During past 4 weeks, physical health or emotional problems interfered with social activities

Using the above 12-items, an algorithm was developed to generate the PCS and MCS scores.[79] The mean score is set to 50, thereby scores > 50 represents better physical or mental health; mean scores < 50 are interpreted as clinically lower than average health status.

2.6.1.2 Cancer-Self Administered Questionnaire

The CSAQ was developed by AHRQ in collaboration with NCI, CDC and ACS administered to around 1,800 cancer survivors. The paper-and-pencil questionnaire was fielded only once during calendar year 2011 (i.e. round 5 of panel 15 and round 3 of panel 16) among individuals who answered yes to cancer question "Ever been told by doctor or health professional that (person) had malignancy of any kind?"

The CSAQ asked respondents about cancer-related history and long-lasting effects, disease burden, financial impacts, employment outcomes for cancer survivors and care givers through several sections outlined below:

(1) Cancer history:

The section comprises of questions confirming respondents are adult (Age $\geq$ 18), diagnosed with cancer and its treatment related information.

(2) Changes to your work schedule:

This section incorporated questions on work-related changes made due to cancer or its treatment. Such as extended paid time off from work, unpaid time off from work, change from working full-time to part-time, change to less demanding job, change to flexible work schedule, decided not to pursue promotion or change in retirement plans.

(3) Other aspects of work:

This section included questions to ascertain cancer survivors' experiences at work from the time they were diagnosed with cancer till now, ever felt that cancer or treatment interfered with ability to perform physical tasks required by job, interfered with ability to perform mental tasks required by job, less productive at work, worried to retire early, concern about losing health insurance.

(4) Caregivers:

This section incorporated questions related to caregivers, if they changed their work-related schedules (paid time off, unpaid time off, from full-time to part-time, change to less demanding

job and flexible work schedule), helped with doctor visit, making appointments, decision about treatment, other types of care and support during treatment.

(5) Experience with health insurance:

From the time the cancer survivors were first diagnosed with cancer to now, this section included questions on health insurance coverage that paid for all or only part of medical care, cancer treatment, tests, doctor visits or ever denied coverage.

(6) Effects of cancer and its treatment on finances:

This section ascertains respondents' financial burden that they encountered because of cancer, its treatment or lasting effects of that treatment.

(7) Medical care for cancer:

The respondents' experiences with receiving medical care including topics discussed with doctors or healthcare providers, whether received all necessary care and reasons for not receiving necessary care are captured in this section.

(8) Effects of cancer and its treatment on life:

The last section included questions about how cancer, its treatment and lasting effects of that treatment influenced the person's life. The questions are on limitations on activities and tasks, help getting to healthcare provider, understanding medical bills, worrying about cancer coming back or getting worse, overall experience with cancer.

2.6.2 Patient Selection: CSAQ Eligible Post-Treatment Cancer Survivors

As shown in figure 5, total of 1.444 post-treatment cancer survivors were identified (sample for objective 2) and the variables CELIGI5 and CELIGI3 were used to determine CSAQ eligibility status. Based on the eligibility question, 537 respondents were excluded since they were not eligible and 69 were excluded as the CSAQ data were not available. The final sample consists of total 838 CSAQ eligible post-treatment cancer survivors with CSAQ data.

The ***CSAQ eligible post-treatment cancer survivors*** included in the study were defined as any adult individuals ever diagnosed with cancer excluding non-melanoma skin; have not received active treatment in terms of chemotherapy, radiation therapy or cancer-related surgery or operation within two years of their longitudinal follow-up and were eligible for cancer experiences questionnaire with relevant data.

The inclusion and exclusion criteria to identify CSAQ eligible post-treatment cancer survivors are:

Inclusion criteria:

(a) Adult individuals age≥18
(b) Mention of cancer diagnosis code or history of cancer
(c) Diagnosed with one or more cancer type
(d) Type of cancer includes head & neck, gastrointestinal, lung/bronchus, breast, urogenital, gynecological, prostate, hematological, bone, skin and other/unspecified
(e) Have not received active treatment in terms of chemotherapy, radiation therapy or cancer-related surgery/operation within two years of their longitudinal follow-up
(f) Eligible for CSAQ with relevant data

Exclusion criteria:

(a) Adult respondents with missing data on cancer question “Ever been diagnosed with cancer?”
(b) Individuals diagnosed solely with non-melanoma skin cancer
(c) Patient lost to follow-up, not in-scope or dead within two years of their longitudinal follow-up
(d) Individuals with no data on CSAQ

2.6.3 Productivity Measures

In order to explore association between productivity measures and pain medication use, the work-related productivity indicators were obtained from questions asked during interview through SF-12v2 and from paper-pencil cancer experiences questionnaire. Post-treatment cancer survivors during the 2 years of the longitudinal follow-up experienced CSAQ once in year 2011 and the SF-12v2 twice in round 4 and round 2. Depending upon their source the measures included in the study are summarized below:

(a) Productivity measures obtained from SF-12v2:

One of the questions that SF-12 comprises of is *"During past 4 weeks, as result of physical health, limited in kind of work or other activities?"* and in MEPS-HC it was captured through round variables ADPWLM4 & ADPWLM2. The response includes all the time, most of the time, some of the time, little of the time, none of the time.

Using the response on both the variables, individual was categorized into the following:

(i) None of the time: individual experiencing no work limitation during 2 years of follow up

(ii) Little/some of the time: individual experiencing little bit or some work limitation during 2 years of follow up

(iii) Most/all of the time: characterized by individual experiencing work limitation most or all the time during 2 years of follow up

(iv) Work limitation changes over time: individual experiencing fluctuating work limitation that changes over time.

The other three productivity measures questions obtained from SF-12 were similarly coded. The questions asked to respondents *were:*

"During past 4 weeks, as result of mental problems, did work or other activities less carefully than usual?;

During past 4 weeks, as result of physical problems, accomplished less than would like?;

During past 4 weeks, as result of mental problems, accomplished less than would like?"

The responses to these questions were publicly released through variables ADMWLM4 & ADMWLM2; ADPALS4 & ADPALS2; ADMALS4 & ADMALS2, respectively.

(b) Productivity measures obtained from CSAQ:

From the cancer experiences questionnaire, the section 2- changes in work schedule and section 3- other aspects of work were extensively exploited to obtain productivity measures. The questions include cancer survivors employed at any time since the diagnosis, changes in work schedule (such as paid time off, unpaid time off, less demanding job), because of cancer or its treatment limitations in physical and mental tasks at work, decreased work productivity and early retirement than planned. The detail list of productivity measures along with the MEPS variables included in the study is summarized in Table 8. To all the questions obtained from CSAQ, respondents with distinct response in terms of yes/no were only included in data analysis.

Table 8: Indicators Of Productivity Measures

Productivity Measures			
	Source	**MEPS Variable**	**Description**
1.	SF-12	ADPWLM4 & ADPWLM2	During past 4 weeks, as result of physical health, limited in kind of work or other activities?
2.	SF-12	ADMWLM4 & ADMWLM2	During past 4 weeks, as result of mental problems, did work or other activities less carefully than usual?
3.	SF-12	ADPALS4 & ADPALS2	During past 4 weeks, as result of physical problems, accomplished less than would like?
4.	SF-12	ADMALS4 & ADMALS2	During past 4 weeks, as result of mental problems, accomplished less than would like?

5.	CSAQ, Q9	CWRKP5 & CWRKP3	At any time from when you were first diagnosed with cancer until now, were you working for pay at a job or business?
6.	CSAQ, Q10	CTMOFF5 & CTMOFF3	At any time since your first cancer diagnosis, did you take extended paid time off from work, unpaid time off, or make a change in your hours, duties or employment status?
7.	CSAQ, Q14	CEXTM5 & CEXTM3	Did you ever take extended time off from work?
8.	CSAQ, Q18	CNPTOF5 & CNPTOF3	Did you ever take unpaid time off from work?
9.	CSAQ, Q26	CCNGPT5 & CCNGPT3	Did you ever change from working full-time to working part-time?
10.	CSAQ, Q32	CNGLDJ5 & CNGLDJ3	Did you ever change to a less demanding job?
11.	CSAQ, Q38	CERET5 & CERET3	Because of your cancer, its treatment, or the lasting effects of that treatment, did you retire earlier than planned?
12.	CSAQ, Q40	CPTASK5 & CPTASK3	Did you ever feel that your cancer, its treatment, or the lasting effects of that treatment interfered with your ability to perform any physical tasks by your job?
13.	CSAQ, Q41	CMTASK5 & CMTASK3	Did you ever feel that your cancer, its treatment, or the lasting effects of that treatment interfered with your ability to perform any mental tasks required by your job?
14.	CSAQ, Q42	CLPROD5 & CLPROD3	Did you ever feel that, because of your cancer, its treatment, or the lasting effects of that treatment, you were less productive at work?
Source: Medical Expenditure Panel Survey – SF-12, Cancer Experience Questionnaire			

2.6.4 Pain Medication Use

The prescribed medicines file provides detail information for each drug event including the number of times prescriptions acquired in the round (PURCHRD); this variable was used to define pain medication use among post-treatment cancer survivors. Based on individuals' claim of analgesics belonging to non-opioids, narcotic analgesic combinations, opioids and adjuvants class of drugs as mentioned in Table 7, the claims for the pain prescriptions were checked in each round of the panel. Both, original prescriptions as well as refills were included in determining pain medication use among post-treatment cancer survivors. The pain medication use was defined in terms of no user, acute, moderate and chronic.

(a) Total pain prescriptions: Drugs belonging to non-opioids, narcotic analgesic combinations, opioids and adjuvants class were included in analysis.
    (i) None: individuals with no claim of pain prescription were defined as no users.
    (ii) Acute: individuals with claim of at least one pain prescription on one round only were defined as acute users.
    (iii) Moderate: individuals with claim of pain prescription on 2-3 rounds were defined as moderate users of pain prescriptions.
    (iv) Chronic/long-term: individuals with claim of pain prescription on atleast 4 rounds were chronic users of pain medications.

(b) Total opioids prescriptions: Drugs belonging to narcotic analgesic combinations and opioids were included in analysis.
    (i) None: individuals with no claim of opioids prescription were defined as no users.
    (v) Acute: individuals with claim of opioids on one round only were defined as acute users.
    (ii) Moderate: individuals with claim of opioids on 2-3 rounds were defined as moderate users of opioids prescriptions.

(iii) Chronic/long-term: individuals with claim of opioids on atleast 4 rounds were chronic users of opioid medications.

In order to assess the relationship between pain medication use and workers' productivity, descriptive statistics for these categorical variables was reported in form of frequency tables, which displays the number and percentage of post-treatment cancer survivors.

CHAPTER THREE:- STATISTICAL ANALYSIS

3.1 Objective 1: Data Analyses

3.1.1 SAS Survey Procedures

The survey procedures (SURVEYMEANS, SURVEYFREQ) were predominantly used to analyze complex survey data. These survey procedures take into account multi-stage or single-stage designs, with or without unequal weighting, and with or without stratification. These survey procedures generate estimates using weights (PERWT08F, PERWT09F, PERWT10F, PERWT11F, PERWT12F and PERWT13F, respectively, from year 2008 to 2013), strata (VARSTR) and PSU (VARPSU) design variables.

Study 1a:

For each year of study period from 2008 to 2013, annual utilization of pain prescription by different class including non-opioids, narcotic analgesic combinations, opioids and adjuvant analgesics were reported in terms of weighted estimates using SURVEYFREQ procedure. Annual total costs and out-of-pocket costs for different class of pain prescriptions were obtained in terms of weighted mean expenditure using SURVEYMEANS procedure. Total expenditure was not inflated to current year and reported in actual years. For patient share, frequencies in terms of percentage share were reported. For HRQoL, an estimate of PCS and MCS scores in terms of weighted mean along with standard error was reported using SURVEYMEANS procedure. Individuals with the negative values on variables PCS42 and MCS42 were excluded from all HRQoL related analyses. Pooled value in terms of average estimates over the 6-years of study period was determined by creating pooled weight variable (POOLWT) obtained by dividing weight with number of years pooled.

Study 1b:

Among cancer survivors and individuals without cancer history, in order to analyze the distribution of treatment and HRQoL across different socio-demographics, geographical, clinical and economic factors, SURVEYFREQ and SURVEYMEANS procedure were respectively used. Since, data were pooled across six years study period estimates were reported incorporating POOLWT, strata, and PSU design variables.

Study 1c:

The HRQoL among cancer survivors stratified by opioid exposure was measured by mean PCS and MCS scores using SAS SURVEYMEAN procedure. Since, data were pooled across six years study period estimates were reported incorporating POOLWT, strata, and PSU design variables.

3.1.2 Statistical Significance

The differences in the utilization of pain medications among cancer survivors and individuals without cancer history by different class of drugs including non-opioids, narcotic analgesic combinations, opioids and adjuvants was assessed using Rao-Scott modified chi-square test (χ^2) using PROC SURVEYFREQ procedure.

The difference in health status among cancer survivors and individuals without cancer history was assessed by comparing weighted mean PCS and MCS scores across two group through two sample t- test using PROC TTEST sas command. The statistical significance was evaluated at the 5% level.

3.1.3 Statistical Package

The SAS software (version 9.4, SAS Institute Inc., Cary North Carolina)[83] was used for data analyses. All the statistical analyses adhered to analytical techniques mentioned in AHRQ documentation to account for the weighting and generating national estimates.

Microsoft Excel 2010 was used to generate graphical representation of numbers in terms of charts.

3.2 Objective 2: Data Analyses

3.2.1 Multicollinearity

Multicollinearity occurs when two or more covariates are correlated in the model and provide misleading results. The consequences of high multicollinearity are increased standard error and less reliable estimates. To detect multicollinearity, VIF (variance inflation factors) was employed. It's called VIF because it determines how much the variance of coefficient is inflated due to linear dependence with other independent variables.

The VIF was calculated for each covariate by linear regression of that variable on all the other predictor variables and obtaining R^2 from that regression. The VIF is just $1/(1-R^2)$. For predictor variable, VIF ≥ 10 implies multicollinearity problem.

Unfortunately, the VIF test that applies to complex survey data accounting for stratified multistage probability sample is not available. For this study, multicollinearity was checked using unweighted sample count.

3.2.2 Zero-Inflated Poisson Regression

The characteristics of the outcome variables, total number of pain prescription claims and total number of opioids prescription were in terms of counts which are positive integers greater or equal to zero. These outcome variables with non-negative integer value arise from counting in terms of pain prescription claims rather than ranking. For the count data that are normally distributed, the OLS regression can be used and for highly non-normal count data Poisson regression is preferred. However, Poisson regression makes a big assumption of equidispersion meaning the mean and variance are the equal. Unfortunately, this criterion is not true in many situations identified by overdispersion where variance is greater than mean. The overdispersion arises due to excess zeros in count data or heterogeneity of population. The presence of overdispersion demands the use of zero-inflated Poisson (ZIP) model that accounts for excess zeroes in the data. The model divides the population into two groups: (i) with non-zero outcomes and (ii)

population with zero outcomes. Thus, the ZIP model generates separate estimates involving two different model, Poisson regression predicting non-zero outcomes and logit regression for predicting excess zero.

The zeros (no claims of pain prescription) in the dataset were due to the two clinical situations arising either because patient are not in pain or they are not receiving pain prescriptions even with ongoing pain possibly due to patient-, physician-, system-related barriers as outlined in Table 6. In context to this study, the zero-inflated Poisson regression generates estimates involving two separate models. Firstly, by fitting Poisson regression for non-zero outcomes (the count of pain prescriptions when prescribed); secondly, it accounts for additional zeroes by fitting logistic regression to predict the likelihood of not prescribing pain medications.

The output generated from both the models were reported in terms of regression estimates, its exponentiated value with 95% CI and $p \leq 0.05$ as level of significance. The positive regression coefficient for the Poisson model implies higher counts of pain medication by exp^ β among post-treatment cancer survivors who were prescribed (population with non-zero outcomes). The positive regression coefficient for the logit model implies the characteristic is associated with higher odds of "not" receiving pain prescriptions among post-treatment cancer survivors who were not prescribed (population with certain zero outcomes). The 95% CI for each coefficient implies that for a given predictor, we are 95% confident that the regression coefficient lies between the upper and lower limit of the interval. The advantage of 95% CI is that it provides information on effect size and direction. The null hypothesis that the regression coefficient equals zero was tested through 2-tailed p-values using alpha of 0.05.

3.2.3 Statistical Package

The STATA (version 14) was used for data analyses involving multicollinearity and zero-inflated Poisson regression.[63]

Multicollinearity was assessed using regress command among subpopulation of interest.

An analytical command SVYSET was written in STATA that identifies survey design characteristics in order to obtain weighted estimates. The regression procedure adhered to analytical techniques mentioned in AHRQ documentation to account for the complex sample design, weighting and reporting the estimates incorporating weights (LONGWT), strata (VARSTR) and PSU (VARPSU) design variables.

3.3 Objective 3: Data Analyses

3.3.1 Frequency Table

The descriptive statistics for categorical variables can be obtained using frequency tables, which displays the number and percentage of observed cases for each categories of a variable. The frequency table generated through crosstabulation includes cell frequencies, cell percentage of total, cell percentages of row frequencies and cell percentages of column frequencies. If there are cases with missing values for the variable, the total frequency of missing observations are displayed below the table.

Study 3a:

The SAS procedure PROC FREQ was used to obtain number and percent of post-treatment cancer survivors across different categories of SF-12 productivity measure and pain medication use. In order to describe relationship between the categorical variables- workers' productivity (none of the time, little/some of the time, most of the time, work limitation changes over time) and pain medication use (none, acute, moderate, and chronic), a 4x4 contingency table with frequency distribution was summarized.

Study 3b:

The SAS procedure PROC FREQ was used to obtain number and percent of post-treatment cancer survivors across different categories of CSAQ productivity measure and pain medication use. In order to describe relationship between the categorical variables- workers' productivity/work-related changes (yes/no) and pain medication use (none, acute, moderate, and chronic), a 2x4 contingency table with distribution of frequency was summarized.

3.3.2 Statistical Significance

The relationship between pain medication use and workers' productivity among post-treatment cancer survivors was assessed through Rao-Scott modified chi-square test (χ^2) using PROC SURVEYFREQ procedure. The chi-square test assumes that the expected value for each cell is five or higher. The Fisher's Exact test was used in the situations when the assumption was not met.

The Fisher's Exact test has no such assumption and can be used regardless of how small the expected frequency is. Also, Fisher's Exact tests does not apply to complex survey data accounting for stratified multistage probability sample. It computes probabilities using only unweighted sample count.

The statistical significance was evaluated at the 5% level. When p-value $\leq$0.05 we reject the null hypothesis that two variables are independent and conclude that there is significant association between column and row variables.

3.3.3 Statistical Package

The SAS software (version 9.4, SAS Institute Inc., Cary North Carolina)[83] was used for data analyses. All the statistical analyses adhered to analytical techniques mentioned in AHRQ documentation to account for the complex sample design of the MEPS, weighting and reporting estimates.

CHAPTER FOUR:- RESULTS

4.1 Results: Objective 1

4.1.1 Study 1a

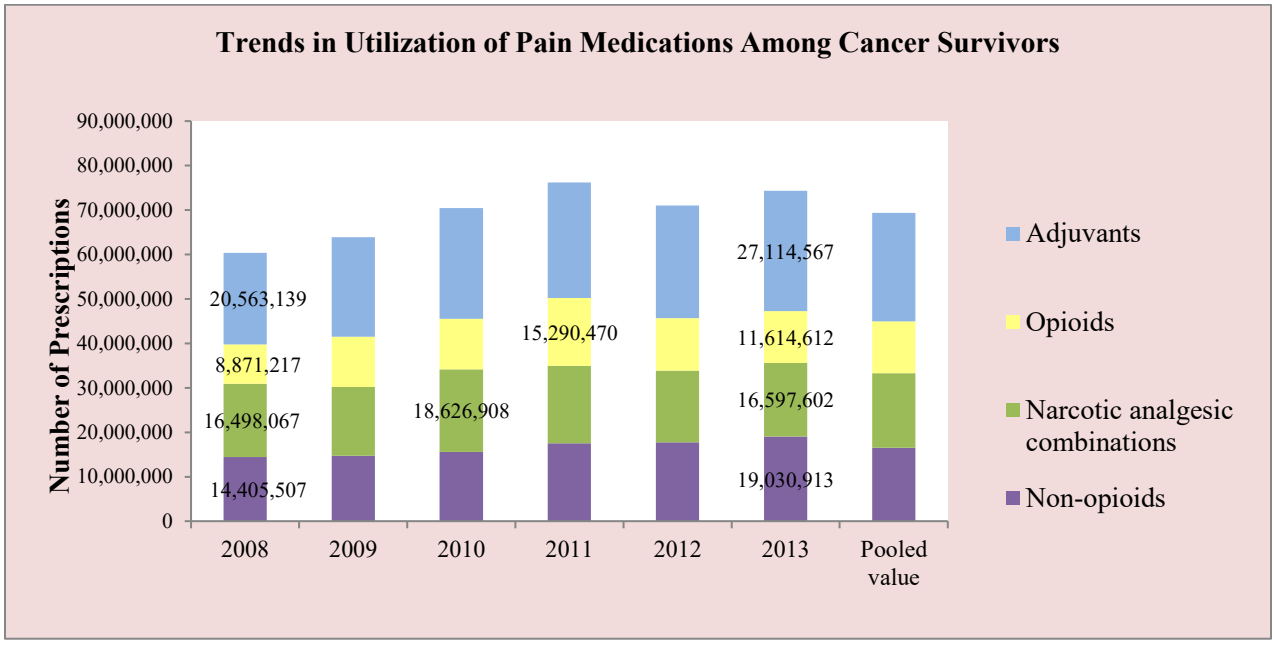
I. Trends in Utilization of Pain Prescriptions

As shown in Table 9, from year 2008 to 2013, the number of cancer survivors (weighted count) identified, respectively, were 23.4 million, 24.1million, 23.6 million, 25.2 million, 25.1 million, 24.8 million persons/year; individuals without cancer history identified were 203.9 million, 205.1 million, 207.5 million, 209.3 million, 211.9 million and 214.4 million persons/year respectively.

From year 2008, both, the number and the percent of cancer survivors taking pain medications increased in year 2013.The percent of cancer survivors taking pain medications, respectively, were 40.8%, 41.1%, 42.4%, 42.0%, 41.6% and 44.0% over the six years of study period. These percentages exceeded compared to individuals without a history of cancer (Table 9 & 10). The percent of individuals taking pain medications among the individuals without cancer history were 22.7%, 22.9%, 22.9%, 22.7%, 21.7% and 23.7%, respectively from 2008 to 2013.

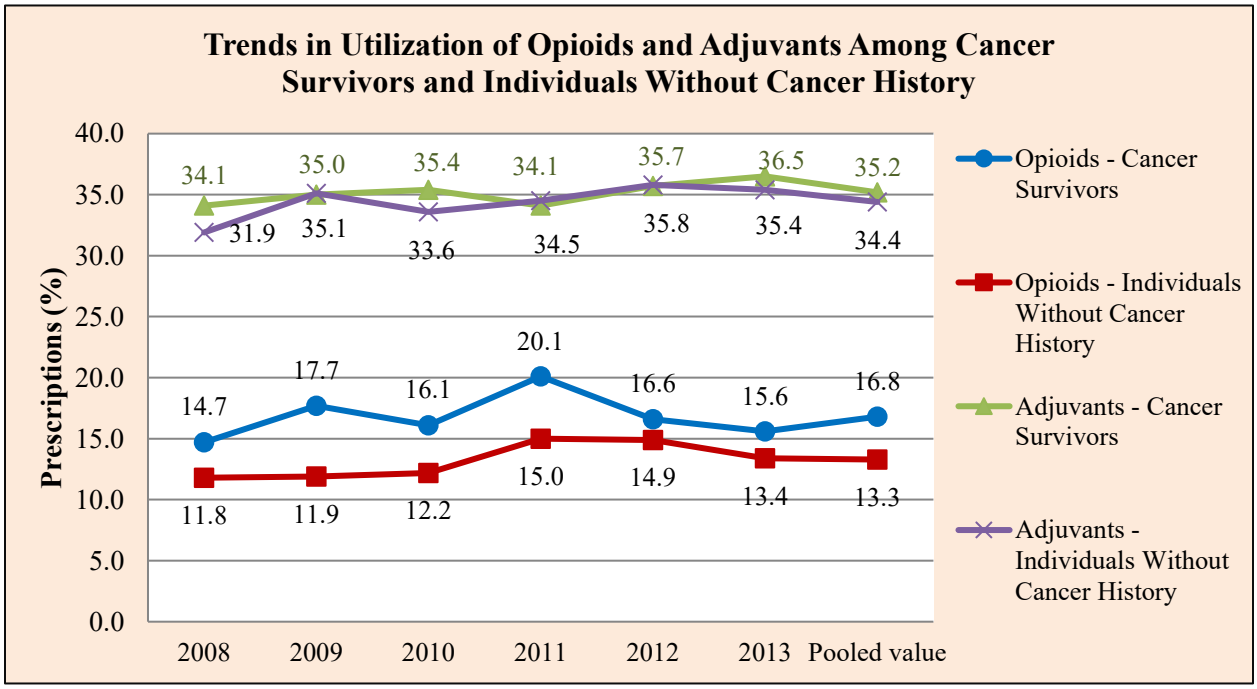
The utilization of pain prescription among the cancer survivors from 2008 to 2013, respectively, was 60.3 million, 63.9 million, 70.5 million, 76.2 million, 70.9 million and 74.4 million. The total number of prescriptions for pain medications prescribed to cancer survivors increased from 60.3 million in 2008 to 74.4 million in 2013 (Figure 6). The number of prescriptions for non-opioids and adjuvant analgesics increased from 14.4 million and 20.6 million, respectively, in 2008, to 19.0 million and 27.1 million, respectively, in 2013. There were approximately 16.5 million prescriptions for narcotic analgesic combinations in year 2008, the utilization peaked in year 2010 with 18.6 million and then decreased each year through 2013. From 8.9 million opioid prescriptions in year 2008, the utilization peaked in year 2011 to 15.3 million and then decreased each year through 2013.

Figure 6: Trends In Utilization Of Pain Medications Among Cancer Survivors, MEPS 2008-2013



Over the six years of study period, the total number of pain prescriptions use (pooled estimate) among cancer survivors was 69.4 million; for non-opioids, narcotic analgesic combinations, opioids and adjuvant, respectively, was 16.5 million, 16.8 million, 11.7 million and 24.4 million. Among the cancer survivors, the utilization of opioids and adjuvant analgesics was significantly ($p<0.0001$) higher 16.8% and 35.2%, respectively, compared to individuals without cancer history with utilization 13.3% and 34.4%, respectively (Figure 7).

Figure 7: Trends In Utilization Of Opioids & Adjuvants Among Cancer Survivors, MEPS 2008-2013

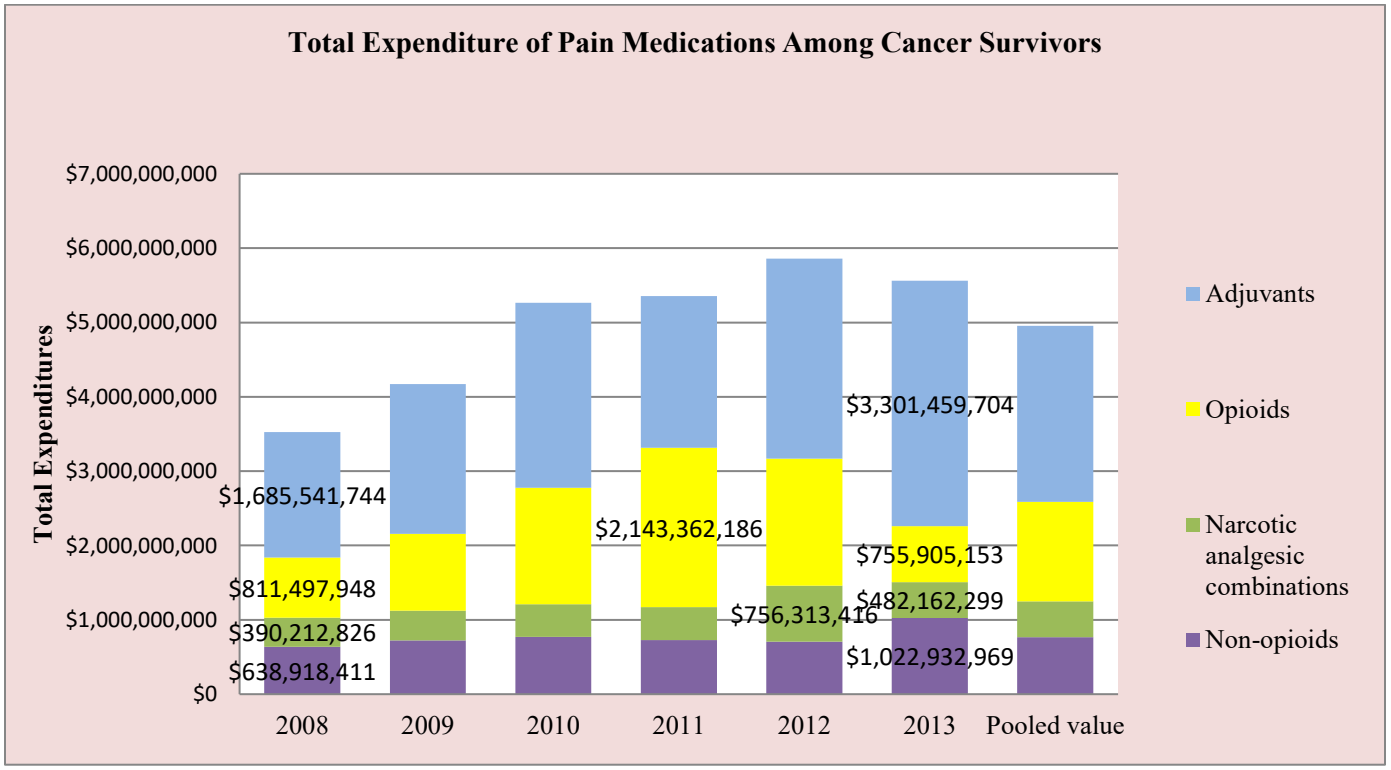


II. Total Expenditure of Pain Prescriptions

The total costs (not adjusted for inflation) of pain medications from 2008 to 2013, respectively, was $3.5 billion, $4.2 billion, $5.3 billion, $5.4 billion, $5.9 billion and $5.6 billion.

The total expenditure increased from $3.5 billion in 2008 to $5.6 billion in 2013 (Figure 8). The cost of prescriptions for adjuvant analgesics and non-opioids increased from $1.6 billion and $638.9 million, respectively, in 2008, to $3.3 billion and $1.0 billion, respectively, in 2013. The cost of opioid prescriptions increased from $811.5 million in 2008 to $2.1 billion in 2011, followed by decline to $755.9 million in 2013. Similar trend was observed for narcotic analgesics combination class where the expenditure increased from $390.2 million in 2008 to $756.3 million in 2012, followed by decline to $482.2 million in 2013.

Figure 8: Trends in Total Expenditure of Pain Medications Among Cancer Survivors, MEPS 2008-2013

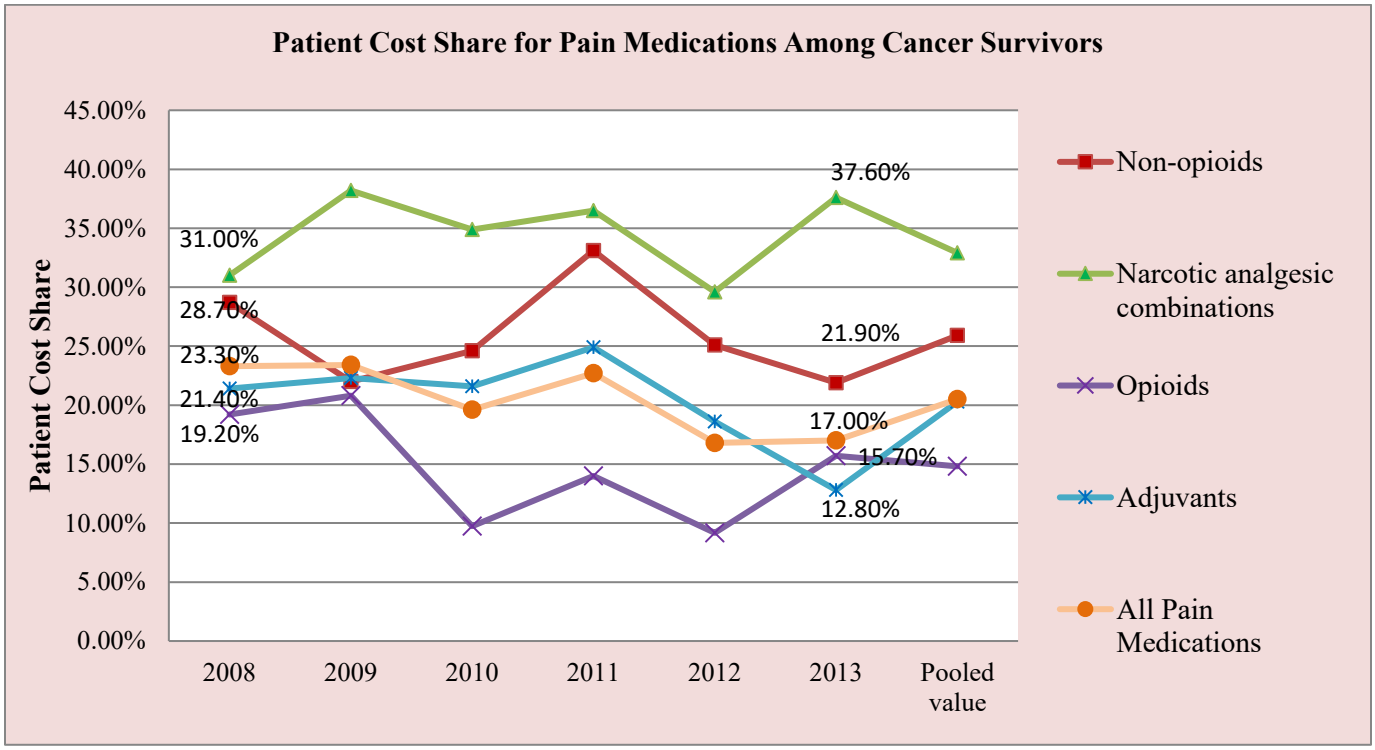


Over the six years of study period, the total expenditure of pain prescriptions (pooled estimate) among cancer survivors was $5.0 billion and among individuals without cancer history was $16.4 billion. The total expenditure for non-opioids, narcotic analgesic combinations, opioids, adjuvants class of pain medications, respectively, was 15.4%, 9.8%, 26.9%, 47.8% of $5.0 billion among cancer survivors; was 17.0%, 13.4%, 18.5%, 51.1% of $16.4 billion among individuals without cancer history (Table 9 & 10). When compared to individuals without cancer history, the total expenditure associated with opioids prescription was higher among cancer survivors.

III. Patient Cost Share

From year 2008 to 2013, the patient cost share for pain medications, respectively, was 23.3%, 23.4%, 19.6%, 22.7%, 16.8% and 17.0% among cancer survivors. The patient cost share decreased from 23.3% in 2008 to 17.0% in 2013 (Figure 9). The patient cost share for adjuvants, non-opioids, and opioids class of pain medications decreased from 21.4%, 28.7% and 19.2%, respectively, in 2008 to 12.8%, 21.9% and 15.7%, respectively, in 2013. Whereas, the patient cost share for narcotic analgesic combinations class increased from 31.0% to 37.6%.

Figure 9: Trends in Patient Cost Share for Pain Medications Among Cancer Survivors, MEPS 2008-2013



Compared to individuals without cancer history, overall the spending in terms of patient share was lower among cancer survivors. Overall, the out-of pocket costs among cancer survivors was 20.5% of $5.0 billion and among individual without cancer history was 22.4% of $16.4 billion. For different class of pain medication, the spending for non-opioids, opioids, adjuvants class of drugs was lower except for the narcotic analgesic combinations among the cancer survivors. The patient costs share for non-opioids, narcotic analgesic combinations, opioids, adjuvants class of pain medications, respectively, was 25.9%, 32.9%, 14.8%, 20.3% among cancer survivors; was 26.6%, 31.6%, 17.7%, 20.9% among individuals without cancer history.

IV. HRQOL

The cancer survivors with complete information on HRQoL scores identified from 2008 to 2013, respectively, were 22.2 million, 23.0 million, 22.7 million, 23.8 million, 24.0 million and 23.2 million persons/year; individuals without cancer history, respectively, were 189.6 million, 190.8 million, 192.1 million, 193.8 million, 199.0 million and 196.1 million as shown in Table 9 & 10.

Among the cancer survivors, respectively, from year 2008 to 2013, the HRQoL measure in terms of PCS scores, respectively, were 44.0 (0.35), 43.8 (0.36), 43.8 (0.40), 44.3 (0.37), 43.6 (0.38), 44.2 (0.38); MCS scores, respectively, were 50.2 (0.28), 50.1 (0.30), 50.4 (0.32), 50.1 (0.26), 49.9 (0.27), 50.7 (0.32). Among individuals without cancer history, from year 2008 to 2013, the HRQoL measure in terms of PCS scores, respectively, were 50.2 (0.11), 50.1 (0.11), 50.1 (0.12), 49.9 (0.11), 49.7 (0.11), 49.9 (0.12); MCS scores, respectively, were 51.0 (0.10), 51.0 (0.09), 51.2 (0.11), 51.0 (0.09), 51.2 (0.09), 51.8 (0.10).

The overall PCS and MCS scores (pooled estimate) reported by cancer survivors was 43.9(SE=0.20) and 50.2(SE=0.16) compared to individuals who never had cancer, 50.0(SE=0.07) and 51.2(SE=0.05) respectively (Figure 10 and 11). This difference obtained in PCS and MCS scores across both the group was significant.

Figure 10: HRQoL–Physical Component Summary Scores Among Cancer Survivors & Individuals Without Cancer History, MEPS 2008 - 2013

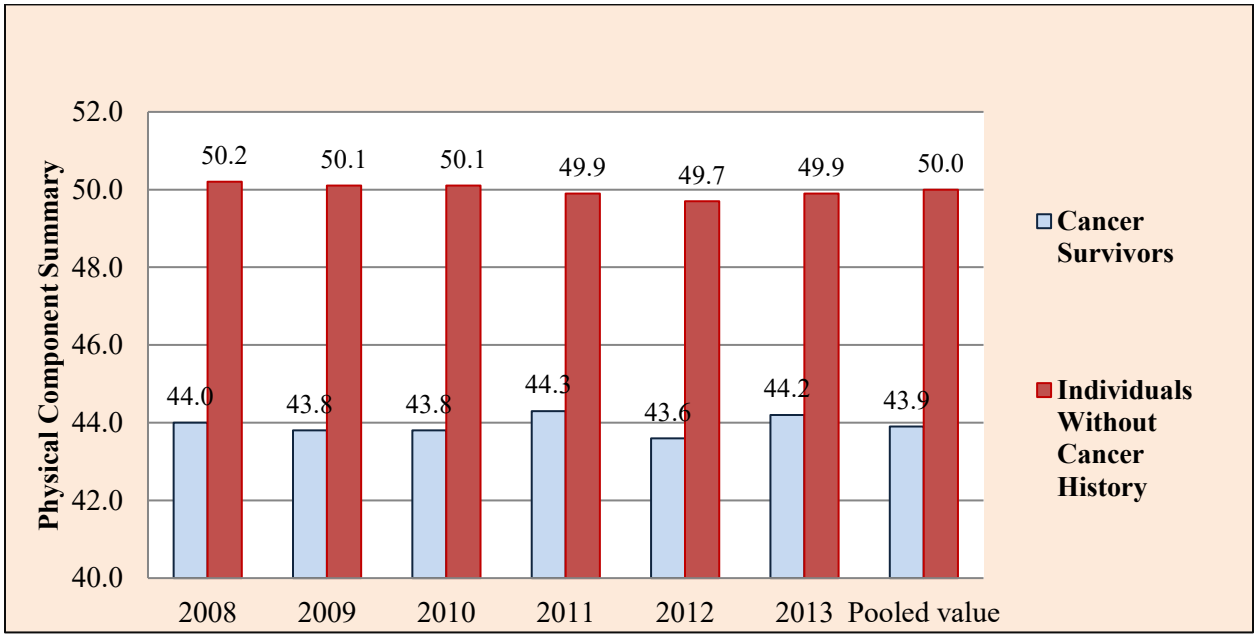
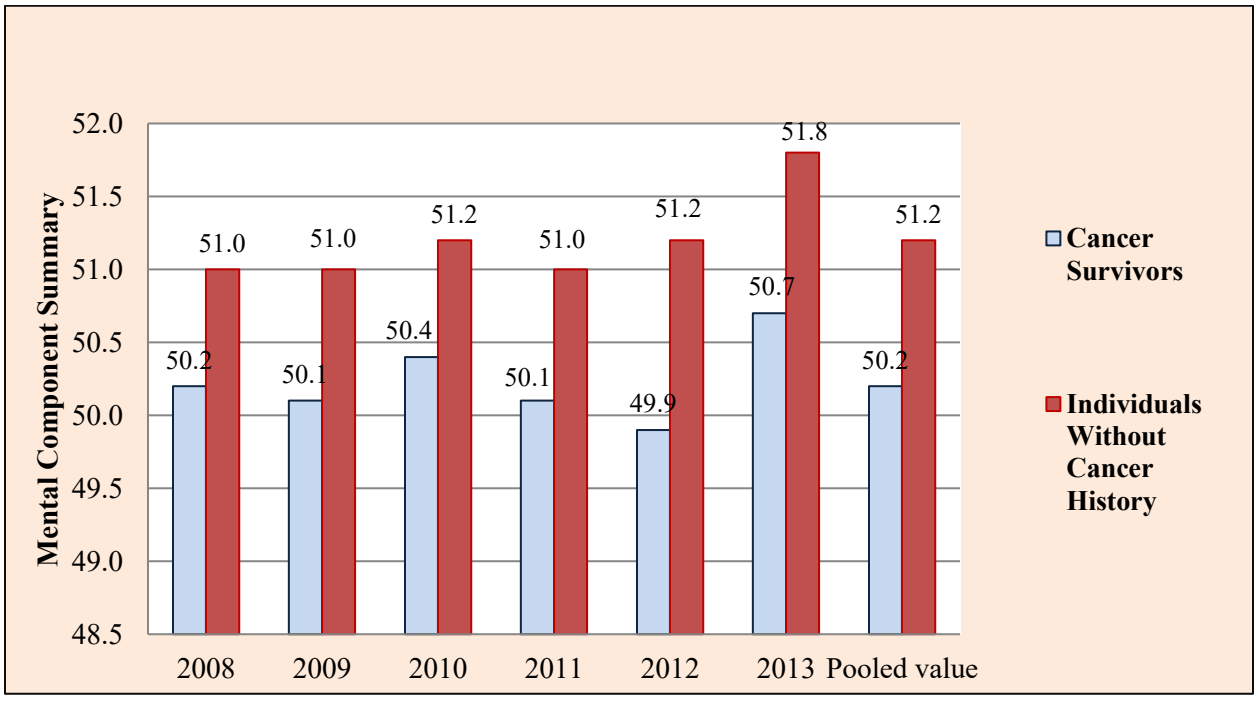


Figure 11: HRQoL–Mental Component Summary Scores Among Cancer Survivors & Individuals Without Cancer History, MEPS 2008 – 2013



4.1.2 Study 1b

Over the six years of the study period, the total of 69.4 million and 284.9 million of pain prescriptions was reported by cancer survivors and individuals without cancer history, respectively. For HRQoL measure, 23.2 million cancer survivors and 193.6 million individuals without cancer history were identified with complete information on PCS and MCS scores.

I. Demographic factors:

(a) Age group:

Among the cancer survivors stratified by age groups, Age $\leq$ 55, Age 56-65, Age 66-75, Age $\geq$ 76, from total of 69.4 million the distribution of pain prescriptions, respectively, was 26.6 million (38.4%), 19.2 million (27.6%), 13.8 million (19.9%) and 9.7 million (14.1%). Among individuals without cancer history, from total of 284.9 million, distribution of pain prescriptions, respectively, was 161.1 million (56.5%), 63.1 million (22.1%), 36.9 million (13.0%) and 23.9 million (8.4%). As shown in table 11 &12, when compared to individuals without cancer history, total pain medication use was higher among cancer survivors with age group, Age 56-65, Age 66-75, Age $\geq$ 76.

Among cancer survivors with age group, Age $\leq$ 55, the narcotic analgesic combinations and opioid use reported was 28.2%, and 16.8% of 26.6 million; for age group, Age 56-65, the narcotic analgesic combinations and opioid use reported was 22.6%, and 16.8% of 19.2 million; for age group, Age 66-75, the narcotic analgesic combinations and opioid use reported was 20.8%, and 16.6% of 13.8 million; for age group, Age $\geq$ 76, the opioid use reported was 17.7% of 9.7 million; these percentages exceeded when compared to individual without cancer history.

Stratified by age group, the cancer survivors with complete information on HRQoL scores identified were 35.5%, 23.0%, 21.8%, 19.8% of 23.2 million, respectively, for Age $\leq$ 55, Age 56-65, Age 66-75, Age $\geq$ 76. Individuals without cancer history, respectively, were 71.6%, 14.8%, 7.9%, 5.8% of 193.6 million. Among the cancer survivors, the HRQoL measure in terms of PCS scores stratified by age group were

48.0 (0.31), 44.2 (0.41), 42.9 (0.33), 37.4 (0.37), respectively; MCS scores were 48.3 (0.24), 50.2 (0.34), 52.2 (0.29), 51.5 (0.30), respectively. Among individuals without cancer history, stratified by age group, PCS scores were 52.1 (0.06), 46.8 (0.16), 44.2 (0.20), 39.2 (0.22), respectively; MCS scores were 50.8 (0.06), 51.4 (0.12), 53.1 (0.16), 51.7 (0.22), respectively.

(b) Sex:

Based on gender, the pain medication use reported by female cancer survivors was 47.5 million (68.5% of 69.4 million); the narcotic analgesic combinations and opioids use reported was 23.8%, and 16.1% of 47.5 million. As shown in table 11 &12, when compared to individuals without cancer history, the utilization of pain medications, narcotic analgesic combinations and opioids was higher among female cancer survivors.

Around 38.5% were male and 61.5% were female cancer survivors with complete information on HRQoL scores. Individuals without cancer history comprise of 51.0% female. Stratified by sex, among male cancer survivors, the PCS and MCS scores, respectively, were 43.5 (0.32) and 51.3 (0.25); among female cancer survivors, 44.2 (0.25) and 49.6 (0.19), respectively. Among male individuals without cancer history, stratified by sex, the PCS and MCS scores, respectively, were 50.7 (0.07) and 52.0 (0.06), among female individuals without cancer history, 49.3 (0.09) and 50.4 (0.07), respectively.

(c) Race/Ethnicity:

Among the cancer survivors stratified by race/ethnicity including non-Hispanic Whites, non-Hispanic Blacks, Hispanic, non-Hispanic Other/Multiple race, of total 69.4 million, the distribution of pain prescriptions, respectively, was 56.9 million (82.0%), 5.6 million (8.0%), 4.3 million (6.2%) and 2.6 million (3.8%). Among individuals without cancer history, from total of 284.9 million, distribution of pain prescriptions, respectively, was 209.3 million (73.4%), 31.3 million (11.0%), 30.3 million (10.6%) and 14.1 million (5.0%). As shown in table 11 &12, when compared to individuals without cancer

history, total pain medications use was lower among cancer survivors belonging to non-Hispanic Blacks, Hispanic, non-Hispanic Other/Multiple race group.

Among cancer survivors for non-Hispanic Whites, the narcotic analgesic combinations and opioid use reported was 24.0%, and 16.7% of 56.9 million; for non-Hispanic Blacks, the narcotic analgesic combinations and opioid use reported was 28.2%, and 15.6% of 5.6 million; for Hispanics, the narcotic analgesic combinations and opioid use reported was 22.8%, and 17.8% of 4.3 million; for non-Hispanic Others/Multiple, the narcotic analgesic combinations and opioid use reported was 22.4%, and 20.7% of 2.6 million. When compared to individuals without cancer history, opioids use was higher among cancer survivors across all race groups.

The cancer survivors identified were 82.9%, 7.9%, 5.8%, 3.4% of 23.2 million, respectively, for race/ethnicity categories, non-Hispanic Whites, non-Hispanic Blacks, Hispanic, non-Hispanic Other/Multiple race. Individuals without cancer history, respectively, were 65.6%, 11.8%, 15.3%, 7.3% of 193.6 million. Among the cancer survivors, the PCS scores stratified by race/ethnicity were 44.1 (0.23), 41.6 (0.45), 44.4 (0.44), 43.9 (0.71), respectively; MCS scores were 50.5 (0.18), 48.9 (0.33), 47.6 (0.47), 49.7 (0.65), respectively. Among individuals without cancer history, stratified by race/ethnicity, PCS scores were 49.9 (0.08), 48.9 (0.14), 51.0 (0.13), 50.6 (0.16), respectively; MCS scores were, 51.1 (0.07), 51.4 (0.11), 50.9 (0.11), 51.6 (0.16), respectively.

(d) Education:

The distribution of pain prescriptions stratified by education including less than high school, high school graduate, some college or more, respectively, was 9.8 million (14.1%), 30.5 million (43.9%), 17.3 million (24.9%) among cancer survivors. Among individuals without cancer history, the distribution of pain prescriptions, respectively, was 43.7 million (15.3%), 122.9 million (43.1%) and 68.1 million (23.9%). As shown in table 11 &12, when compared to individuals without cancer history, total pain medications use was higher among cancer survivors with high school graduates and some college or more.

The distribution of narcotic analgesic combinations and opioids among cancer survivors with lower education, respectively, was 29.2% and 18.4% of 9.8 million; high school graduate, respectively, was 25.9% and 18.0% of 30.5 million; some college or more, respectively, was 20.1% and 14.4% of 17.3 million. When the percentages are compared to individual without cancer history the utilization of opioids was higher among cancer survivors across all education categories.

The cancer survivors identified were 10.9%, 39.5%, 40.7% of 23.2 million, respectively for education categories, less than high school, high school graduate, some college or more. Individuals without cancer history, respectively, were 14.1%, 40.3%, 36.3%, of 193.6 million. Among the cancer survivors, the PCS scores stratified by education status were 38.2 (0.41), 42.4 (0.27), 47.1 (0.24), respectively; MCS scores were 47.5 (0.40), 49.7 (0.25), 51.6 (0.21), respectively. Among individuals without cancer history, stratified by education status, PCS scores were 47.6 (0.17), 49.4 (0.08), 51.8 (0.08), respectively; MCS scores were, 49.9 (0.12), 51.0 (0.07), 52.0 (0.07), respectively.

(e) Marital Status:

The distribution of pain prescriptions stratified by marital status including married, widowed/divorced/separated and never married, respectively, was 37.7 million (54.3%), 24.9 million (36.0%), 6.7 million (9.7%) among cancer survivors. Among individuals without cancer history, the distribution of pain prescriptions, respectively, was 144.9 million (50.8%), 94.3 million (33.1%) and 45.8 million (16.1%). As shown in table 11 &12, when compared to individuals without cancer history, total pain medications use was higher among married cancer survivors and among divorced/separated/widowed.

The distribution of narcotic analgesic combinations and opioids among married cancer survivors, respectively, was 22.8% and 16.6% of 37.7 million; among widowed/divorced/separated, respectively, was 25.5% and 17.4% of 24.9 million; among cancer survivors who never married, respectively, was

26.9% and 16.5% of 6.7 million. When the percentages are compared to individual without cancer history the utilization of opioids was higher among cancer survivors across all categories of marital status.

The cancer survivors identified were 58.8%, 30.4%, 10.8% of 23.2 million, respectively for marital status, married, widowed/divorced/separated and never married. Individuals without cancer history, respectively, were 52.7%, 19.2%, 28.1%, of 193.6 million. Among the cancer survivors, the PCS scores stratified by marital status were 44.9 (0.26), 40.8 (0.33), 47.1 (0.54), respectively; MCS scores were 51.3 (0.19), 49.1 (0.28), 47.6 (0.45), respectively. Among individuals without cancer history, stratified by marital status, PCS scores were 50.0 (0.07), 45.9 (0.16), 52.8 (0.08), respectively; MCS scores were, 52.1 (0.06), 49.4 (0.11), 50.8 (0.09), respectively.

II. Geographical factors:

(a) Region:

The distribution of pain prescriptions stratified by region including northeast, midwest, south, and west, respectively, was 10.9 million (15.7%), 17.2 million (24.8%), 27.3 million (39.3%) and 14.0 million (20.2%) among cancer survivors. Among individuals without cancer history, the distribution of pain prescriptions, respectively, was 44.6 million (15.7%), 67.6 million (23.7%), 110.9 million (38.9%) and 61.9 million (21.7%). As shown in table 13 &14, when compared to individuals without cancer history, pain medications use was higher among cancer survivors residing in midwest and south.

The distribution of narcotic analgesic combinations and opioids among cancer survivors residing in northeast, respectively, was 19.0% and 12.0% of 10.9 million; among cancer survivors residing in Midwest, respectively, was 23.6% and 18.8% of 17.2 million; among cancer survivors residing in south, respectively, was 27.3% and 16.3% of 27.3 million; among cancer survivors residing in west, respectively, was 22.9% and 19.4% of 14.0 million. When the percentages are compared to individual without cancer history the utilization of narcotic analgesic combinations was higher among cancer

survivors residing in south; opioids utilization was higher among cancer survivors residing in midwest, south and west.

The cancer survivors identified were 18.5%, 23.4%, 37.2%, 20.9% of 23.2 million, respectively, for region categories northeast, midwest, south, and west. Individuals without cancer history, respectively, were 17.9%, 21.6%, 37.2%, 23.3% of 193.6 million. Among the cancer survivors, the PCS scores stratified by region were 44.9 (0.60), 43.7 (0.42), 43.1 (0.31), 44.6 (0.34), respectively; MCS scores were 50.7 (0.41), 50.5 (0.38), 49.9 (0.24), 49.9 (0.30), respectively. Among individuals without cancer history, stratified by region, PCS scores were 50.4 (0.16), 50.1 (0.17), 49.5 (0.11), 50.4 (0.14), respectively; MCS scores were, 51.4 (0.15), 51.1 (0.11), 51.3 (0.09), 50.9 (0.11), respectively.

(b) Metropolitan Statistical Area:

Based on MSA, the pain medication use reported by cancer survivors residing in urban area was 52.0 million (75.0% of 69.4 million); among the individuals without cancer history was 213.6 million (75.0% of 284.9 million). As shown in table 13 &14, the utilization of pain medications was nearly similar across both study groups.

The narcotic analgesic combinations and opioids use among cancer survivors residing in urban area, respectively, was 23.8%, and 17.2% of 52.0 million; among cancer survivors residing in rural area, respectively, was 25.2%, and 16.0% of 14.3 million. When compared to individuals without cancer history, the utilization of narcotic analgesic combinations was higher among cancer survivors residing in rural and opioids use was higher across both categories of MSA.

The cancer survivors with complete information on HRQoL scores identified were 68.9%, 14.3% of 23.2 million, residing in urban and rural, respectively. Individuals without cancer history, respectively, were 70.2%, 12.9% of 193.6 million. Among the cancer survivors, stratified by MSA, the PCS scores were 44.3 (0.24), 41.9 (0.51), respectively; MCS scores were 50.2 (0.19), 49.7 (0.42), respectively. Among

individuals without cancer history, stratified by MSA, the PCS scores were 50.3 (0.07), 48.3 (0.21), respectively; MCS scores were 51.1 (0.06), 50.8 (0.15), respectively.

III. Clinical factors:

(a) Smoking status:

Based on smoking status, the pain medication use reported by cancer survivors currently smoking was 18.2 million (26.2%) and among non-smoker was 47.8 million (68.9%); these percentages were nearly similar across individuals without cancer history (Table 15 & 16).

The narcotic analgesic combinations and opioids use among cancer survivors currently smoking, respectively, was 29.6%, and 18.8% of 18.2 million; among non-smoker, respectively, was 22.1%, and 15.9% of 47.8 million. When compared to individuals without cancer history, the utilization of narcotic analgesic combinations was higher among cancer survivors currently smoking and opioids use was higher across both categories of smoking status.

Among 23.2 million cancer survivors, 15.3% were currently smoking and 83.2 % were non-smokers. Among 193.6 million individuals without cancer history, 18.4% were currently smoking and 80.4% were non-smokers. Among the cancer survivors, stratified by smoking status, the PCS scores were 41.6 (0.46), 44.4 (0.21), respectively among smokers and non-smokers; MCS scores were 45.5 (0.43), 51.2 (0.16), respectively. Among individuals without cancer history, stratified by smoking status, the PCS scores were 48.4 (0.14), 50.4 (0.07), respectively; MCS scores were 48.4 (0.11), 51.9 (0.05), respectively.

(b) Body Mass Index:

The distribution of pain prescriptions stratified by BMI including obese, overweight, normal and underweight, respectively, was 29.8 million (42.9%), 20.4 million (29.5%), 15.5 million (22.3%) and 1.3 million (1.9%) among cancer survivors. Among individuals without cancer history, the distribution of

pain prescriptions, respectively, was 121.6 million (42.7%), 87.4 million (30.7%), 65.5 million (23.0%) and 4.5 million (1.6%).

The distribution of narcotic analgesic combinations and opioids among obese cancer survivors, respectively, was 25.0% and 13.8% of 29.8 million; among overweight cancer survivors, respectively, was 22.8% and 16.6% of 20.4 million; among normal cancer survivors, respectively, was 24.8% and 20.2% of 15.5 million; among underweight cancer survivors, respectively, was 30.8% and 35.2% of 1.3 million. As shown in table 15 &16, when the percentages are compared to individual without cancer history the utilization of narcotic analgesic combinations was higher among obese cancer survivors; opioids utilization was higher among cancer survivors across all BMI categories.

Among cancer survivors, 30.4%, 33.4%, 31.5%, 1.4%, respectively, were obese, overweight, normal and underweight. Individuals without cancer history, respectively, were 29.2%, 33.6%, 33.2% and 1.7%. Among the cancer survivors, the PCS scores stratified by BMI were 40.7 (0.31), 45.2 (0.32), 46.4 (0.30), 41.6 (1.34), respectively; MCS scores were 49.7 (0.26), 51.0 (0.27), 50.3 (0.24), 48.7 (0.97), respectively. Among individuals without cancer history, stratified by BMI, PCS scores were 47.0 (0.10), 50.6 (0.08), 52.2 (0.09), 49.4 (0.39), respectively; MCS scores were, 50.4 (0.08), 51.7 (0.07), 51.5 (0.07), 49.6 (0.35), respectively.

(c) Pain perception:

The distribution of pain prescriptions stratified by pain perception including extremely, moderately, little bit, no pain, respectively, was 32.9 million (47.4%), 12.5 million (18.1%), 12.8 million (18.4%) and 8.6 million (12.4%) among cancer survivors. Among individuals without cancer history, the distribution of pain prescriptions, respectively, was 117.7 million (41.3%), 45.9 million (16.1%), 56.4 million (19.8%) and 53.9 million (18.9%). As shown in table 15 &16, when compared to individuals without cancer history, utilization of pain medications was higher among cancer survivors experiencing extreme and moderate pain.

The distribution of narcotic analgesic combinations and opioids among cancer survivors experiencing extreme pain, respectively, was 27.6% and 22.3% of 32.9 million; among cancer survivors experiencing moderate pain, respectively, was 21.5% and 16.4% of 12.5 million; among cancer survivors experiencing little pain, respectively, was 19.6% and 7.7% of 12.8 million; among cancer survivors experiencing no pain, respectively, was 20.8% and 10.2% of 8.6 million. When the percentages are compared to individual without cancer history, opioids utilization was higher among cancer survivors experiencing extreme and moderate pain.

Among cancer survivors, 18.8%, 15.1%, 28.6%, 37.3%, respectively, reported experiencing extremely, moderately, little bit, no pain, during past 4 weeks. Individuals without cancer history, respectively, were 10.3%, 9.6%, 24.0% and 55.9%. Among the cancer survivors, the PCS scores stratified by pain perception, were 26.5 (0.21), 37.4 (0.25), 46.2 (0.18), 53.7 (0.14), respectively; MCS scores were 43.5 (0.39), 48.9 (0.36), 51.2 (0.25), 53.4 (0.15), respectively. Among individuals without cancer history, stratified by pain perception, PCS scores were 30.0 (0.13), 40.6 (0.11), 49.0 (0.06), 55.7 (0.04), respectively; MCS scores were, 43.8 (0.17), 48.1 (0.14), 50.4 (0.09), 53.4 (0.05), respectively.

(d) Chronic conditions

The distribution of pain prescriptions stratified by presence of chronic conditions among cancer survivors was 48.0 million (69.2%), 12.5 million (18.0%), 13.3 million (19.1%), 16.3 million (23.5%), 12.9 million (18.5%), 38.7 million (55.8%), 0.6 million (0.9%), 34.1 million (49.2%), respectively, for arthritis, asthma, chronic bronchitis, diabetes, heart disease, hypertension, stroke and high cholesterol. Among individuals without cancer history was 179.6 million (63.0%), 37.3 million (13.1%), 37.6 million (13.2%), 61.1 million (21.4%), 38.9 million (13.6%), 139.8 million (49.0%), 1.4 million (0.5%), 113.8 million (39.9%), respectively. As shown in table 15 &16, the pain medication use was higher among cancer survivors compared to Individual without cancer history presenting same comorbidities.

The distribution of narcotic analgesic combinations and opioids among cancer survivors with arthritis, respectively, was 24.1% and 18.9% of 48.0 million; among cancer survivors with asthma, respectively, was 22.7% and 18.3% of 12.5 million; among cancer survivors with chronic bronchitis, respectively, was 24.1% and 18.3% of 13.3 million; among cancer survivors with diabetes, respectively, was 20.5% and 18.3% of 16.3 million; among cancer survivors with heart disease, respectively, was 22.1% and 21.2% of 12.9 million; among cancer survivors with hypertension, respectively, was 23.2% and 16.3% of 38.7 million; among cancer survivors with stroke, respectively, was 22.4% and 1.0% of 0.6 million; among cancer survivors with high cholesterol, respectively, was 22.6% and 15.8% of 34.1 million. When these percentages are compared to individual without cancer history, narcotic analgesic combinations utilization was higher among cancer survivors with hypertension, stroke and high cholesterol; opioids utilization was higher among cancer survivors with arthritis, asthma, chronic bronchitis, diabetes, heart disease, hypertension, and high cholesterol.

The cancer survivors identified with chronic conditions were 9.7 million (41.7%), 2.0 million (8.8%), 2.6 million (11.4%), 3.9 million (17.0%), 3.4 million (14.6%), 10.9 million (47.5%), 0.1 million (0.6%), 9.6 million (41.3%), respectively, for arthritis, asthma, chronic bronchitis, diabetes, heart disease, hypertension, stroke and high cholesterol. Individuals without cancer history, respectively, identified were 45.4 million (23.5%), 11.3 million (5.8%), 10.8 million (5.6%), 17.9 million (9.3%), 10.4 million (5.4%), 47.9 million (24.8%), 0.3 million (0.2%), 39.4 million (20.4%). Among the cancer survivors, the PCS scores, respectively, were 38.4 (0.28), 36.2 (0.59), 35.6 (0.50), 37.1 (0.39), 35.2 (0.46), 39.9 (0.28), 35.5 (2.43), 40.8 (0.30); MCS scores, respectively, were 48.8 (0.27), 46.7 (0.44), 47.5 (0.47), 49.2 (0.38), 49.4 (0.41), 50.1 (0.23), 51.0 (1.58), 50.3 (0.25). Among individual without cancer history, the PCS scores, respectively, were 42.1 (0.14), 43.8 (0.27), 41.9 (0.29), 41.2 (0.19), 37.6 (0.27), 43.4 (0.14), 40.3 (1.02), 44.1 (0.15); MCS scores, respectively, were 48.9 (0.11), 48.2 (0.20), 47.8 (0.23), 49.4 (0.18), 48.7 (0.24), 50.3 (0.10), 49.5 (0.86), 50.5 (0.11).

(e) Number of MEPS priority conditions (excluding cancer):

The distribution of pain prescriptions stratified by number of chronic conditions including atleast 3, 2, 1 or none, respectively, was 34.3 million (49.4%), 15.7 million (22.6%), 11.3 million (16.2%) and 8.2 million (11.8%) among cancer survivors. Among individuals without cancer history, the distribution of pain prescriptions, respectively, was 113.1 million (39.7%), 55.6 million (19.5%), 64.5 million (22.6%) and 51.8 million (18.2%). As shown in table 15 &16, when compared to individuals without cancer history, pain medications use was higher among cancer survivors with 2 or atleast 3chronic conditions.

The distribution of narcotic analgesic combinations and opioids among cancer survivors with atleast 3 chronic conditions, respectively, was 22.7 % and 17.8% of 34.3 million; among cancer survivors with 2 chronic conditions, respectively, was 23.4% and 17.9% of 15.7 million; among cancer survivors with 1 chronic conditions, respectively, was 25.5% and 15.6% of 11.3 million; among cancer survivors with no chronic conditions, respectively, was 29.9% and 13.0% of 8.2 million. When the percentages are compared to individual without cancer history the utilization of narcotic analgesic combinations was higher among cancer survivors with presence of no, 1 or 2 chronic conditions; opioids utilization was higher across all categories of chronic conditions among cancer survivors.

Around 32.3%, 20.2%, 21.6%, 25.9% cancer survivors, respectively, were identified with atleast 3, 2, 1 or no chronic conditions. Individuals without cancer history, respectively, were 13.8%, 11.8%, 21.0% and 53.2%. Among the cancer survivors, the PCS scores stratified by number of chronic conditions were, 36.7 (0.30), 43.0 (0.34), 46.7 (0.30), 51.2 (0.23), respectively; MCS scores were 49.2 (0.28), 50.4 (0.34), 50.5 (0.28), 51.2 (0.24), respectively. Among individuals without cancer history, stratified by number of chronic conditions, PCS scores were 39.1 (0.16), 45.7 (0.16), 49.5 (0.11), 54.0 (0.04), respectively; MCS scores were, 48.8 (0.15), 50.7 (0.13), 50.6 (0.10), 52.1 (0.06), respectively.

(f) Types of cancer

As shown in table 15, the distribution of pain prescriptions stratified by type of cancer was 3.8 million (5.5%), 4.6 million (6.7%), 2.2 million (3.2%), 10.8 million (15.6%), 10.3 million (14.8%), 4.9 million (7.2%), 4.4 million (6.3%), 3.2 million (4.7%), 0.8 million (1.2%), 4.4 million (6.4%), 23.5 million (33.9%), respectively, for head & neck, gastrointestinal, lung/bronchus, breast, gynecological, prostate, urogenital, hematological, bone, skin, and other/unspecified.

The distribution of narcotic analgesic combinations and opioids among survivors with head/neck type, respectively, was 22.7% and 12.2% of 3.8 million; among survivors with gastrointestinal type, respectively, was 26.8% and 20.5% of 4.6 million; among survivors with lung/bronchus type, respectively, was 30.4% and 24.8% of 2.2 million; among survivors with breast cancer , respectively, was 20.1% and 15.0 % of 10.8 million; among survivors with gynecological type, respectively, was 26.8% and 18.1% of 10.3 million; among survivors with prostate type, respectively, was 22.4% and 15.6 % of 4.9 million; among survivors with urogenital type, respectively, was 27.8% and 24.7% of 4.4 million; among survivors with hematological type, respectively, was 23.2% and 26.2% of 3.2 million; among survivors with bone type, respectively, was 22.8% and 35.3% of 0.8 million; among survivors with skin type, respectively, was 26.3% and 8.8% of 4.4 million; among survivors with unspecified cancer type, respectively, was 22.7% and 17.0% of 23.5 million.

The cancer survivors identified by type of cancer were, 1.0 million (4.4%), 1.6 million (6.9%), 0.6 million (2.6%), 3.5 million (15.3%), 2.9 million (12.3%), 2.7 million (11.7%), 1.1 million (4.6%), 1.0 million (4.5%), 0.2 million (0.8%), 1.9 million (8.2%), 9.9 million (42.8%), respectively, for head & neck, gastrointestinal, lung/bronchus, breast, gynecological, prostate, urogenital, hematological, bone, skin, and other/unspecified. The PCS scores stratified by types of cancer, respectively, were 42.4 (0.70), 38.5 (0.65), 34.1 (0.88), 43.2 (0.37), 43.4 (0.49), 42.9 (0.50), 40.1 (0.79), 40.7 (0.73), 38.0 (1.95), 44.4 (0.68),

45.4 (0.29); MCS scores, respectively, were 48.9 (0.55), 48.7 (0.56), 48.0 (0.86), 50.6 (0.37), 47.5 (0.40), 52.4 (0.33), 49.9 (0.80), 49.2 (0.70), 46.8 (1.79), 52.2 (0.51), 50.3 (0.23).

(g) Cancer status

As shown in table 15, based on cancer status, the pain medication use reported by cancer survivors currently diagnosed was 40.4 million (58.2%) and among previously diagnosed was 29.0 million (41.8%).

The narcotic analgesic combinations and opioids use among cancer survivors currently diagnosed, respectively, was 24.4%, and 16.5% of 40.4 million; among previously diagnosed cancer survivors, respectively, was 23.8%, and 17.4% of 29.0 million.

Around 68.0% cancer survivors were currently diagnosed and 32.0% were previously diagnosed with complete information on HRQoL measures. Stratified by cancer status, the PCS scores, respectively, were 44.5 (0.29), 43.5 (0.34); the MCS scores were, respectively, 50.5 (0.25), 49.7 (0.27).

(h) Years since first cancer diagnosis:

As shown in table 15, based on years since first cancer diagnosis the distribution of pain medication was 18.9 million (27.3%), 9.9 million (14.4%), 10.9 million (15.6%) and 20.3 million (29.2%), respectively, for >10, 6-10, 2-5, <2 years.

The distribution of narcotic analgesic combinations and opioids among cancer survivors with more than 10 years since first cancer diagnosis, respectively, was 22.2% and 18.0% of 18.9 million; among cancer survivors with 6-10 years since first cancer diagnosis, respectively, was 21.6% and 18.1% of 9.9 million; among cancer survivors 2-5 years since first cancer diagnosis, respectively, was 25.0% and 18.2% of 10.9 million; among cancer survivors < 2years since first cancer diagnosis, respectively, was 27.6% and 14.6% of 20.3 million.

Based on years since first cancer diagnosis, the cancer survivors identified were 5.2 million (22.4%), 2.9 million (12.6%), 3.5 million (15.0%) and 10.1 million (43.6%), respectively, for >10, 6-10, 2-5, <2 years. Stratified by years since first cancer diagnosis, the PCS scores, respectively, were 42.2 (0.36), 43.3 (0.38), 42.7 (0.43), 45.5 (0.28); the MCS scores were, respectively, 49.4 (0.30), 50.8 (0.41), 50.3 (0.38), 50.5 (0.22).

IV. Economic factors:

(a) Employment status:

Based on employment status, the pain medication use reported by cancer survivors currently employed was 24.1 million (34.8% of 69.4 million); among unemployed cancer survivors was 45.3 million (65.2%). Among employed individuals without cancer history, it was 134.0 million (47.0% 284.9 million) and unemployed individuals, it was 150.9 million (53.0%). As shown in table 17 & 18, when compared to individuals without cancer history, the utilization of pain medications was higher among unemployed cancer survivors.

The narcotic analgesic combinations and opioids use among cancer survivors currently employed, respectively, was 25.1%, and 13.1% of 24.1 million; among unemployed cancer survivors, respectively, was 23.7%, and 18.9% of 45.3 million. When compared to individuals without cancer history, the utilization of narcotic analgesic combinations was higher among unemployed cancer survivors and opioids use was higher across both categories of employment.

Around 48.4% cancer survivors identified were currently employed and 51.6% were unemployed. Individuals without cancer history, respectively, were 72.1%, 27.9%. Among the cancer survivors, stratified by employment status, the PCS scores were 49.1 (0.21), 39.0 (0.28), respectively; MCS scores were 51.0 (0.17), 49.5 (0.24), respectively. Among individuals without cancer history, stratified by employment status, the PCS scores were 52.4 (0.05), 43.8 (0.13), respectively; MCS scores were 51.8 (0.06), 49.5 (0.11), respectively.

(b) Family income as % of poverty line:

The distribution of pain prescriptions stratified by family income including poor, near poor, low, middle and high, respectively, was 11.3 million (16.4%), 5.0 million (7.2%), 11.8 million (17.0%), 19.6 million (28.3%), and 21.6 million (31.1%) among cancer survivors. Among individuals without cancer history, the distribution of pain prescriptions, respectively, was 58.9 million (20.6%), 16.9 million (5.9%), 49.1 million (17.2%), 83.1 million (29.2%) and 77.1 million (27.0%). As shown in table 17 & 18, when compared to individuals without cancer history, pain medications use was higher among cancer survivors with high family income.

The distribution of narcotic analgesic combinations and opioids among cancer survivors with poor family income, respectively, was 27.4% and 18.7% of 11.4 million; among cancer survivors with near poor family income, respectively, was 23.6% and 15.6% of 5.0 million; among cancer survivors with low family income, respectively, was 24.9% and 18.8% of 11.8 million; among cancer survivors with middle family income, respectively, was 23.8% and 16.0% of 19.6 million; among cancer survivors with high family income, respectively, was 22.6% and 15.9% of 21.6 million. When the percentages are compared to individual without cancer history the utilization of narcotic analgesic combinations was higher among cancer survivors with poor and low family income; opioids utilization was higher among cancer survivors across all categories of family income.

Based on family income categories including poor, near poor, low, middle and high, respectively, cancer survivors identified were 2.3 million (9.8%), 1.2 million (4.9%), 3.0 million (13.0%), 6.6 million (28.5%), and 10.2 million (43.8%). Individuals without cancer history, respectively, were 24.7 million (12.7%), 8.5 million (4.4%), 26.7 million (13.8%), 58.9 million (30.4%) and 74.8 million (38.6%). Among the cancer survivors, the PCS scores, respectively, were 38.9 (0.49), 37.8 (0.63), 40.5 (0.41), 43.7 (0.27), 46.9 (0.28); MCS scores, respectively, were 44.6 (0.48), 47.9 (0.65), 48.5 (0.42), 50.2 (0.26), 52.3 (0.21). Among individuals without cancer history, the PCS scores, respectively, were 46.9 (0.15), 46.7

(0.23), 48.3 (0.14), 50.3 (0.10), 51.8 (0.07); MCS scores, respectively, were 47.8 (0.13), 49.3 (0.19), 50.1 (0.11), 51.3 (0.08), 52.8 (0.07).

(c) Health insurance coverage:

The distribution of pain prescriptions stratified by health insurance coverage including any private, public only, uninsured, respectively, was 39.8 million (57.3%), 26.7 million (38.4%), 2.9 million (4.3%) among cancer survivors. Among individuals without cancer history, the distribution of pain prescriptions, respectively, was 157.6 million (55.3%), 100.5 million (35.3%) and 26.9 million (9.4%). As shown in table 17 & 18, when compared to individuals without cancer history, pain medications use was higher among cancer survivors insured through private or public only coverage.

The distribution of narcotic analgesic combinations and opioids among cancer survivors having private coverage, respectively, was 23.4% and 16.8% of 39.8 million; among cancer survivors having public only coverage, respectively, was 25.5% and 16.8% of 26.7 million; among cancer survivors having no coverage, respectively, was 23.4% and 18.7% of 2.9 million. When the percentages are compared to individual without cancer history, the utilization of narcotic analgesic combinations was higher among cancer survivors insured through public only coverage; opioids utilization was higher among cancer survivors across all categories of health insurance coverage.

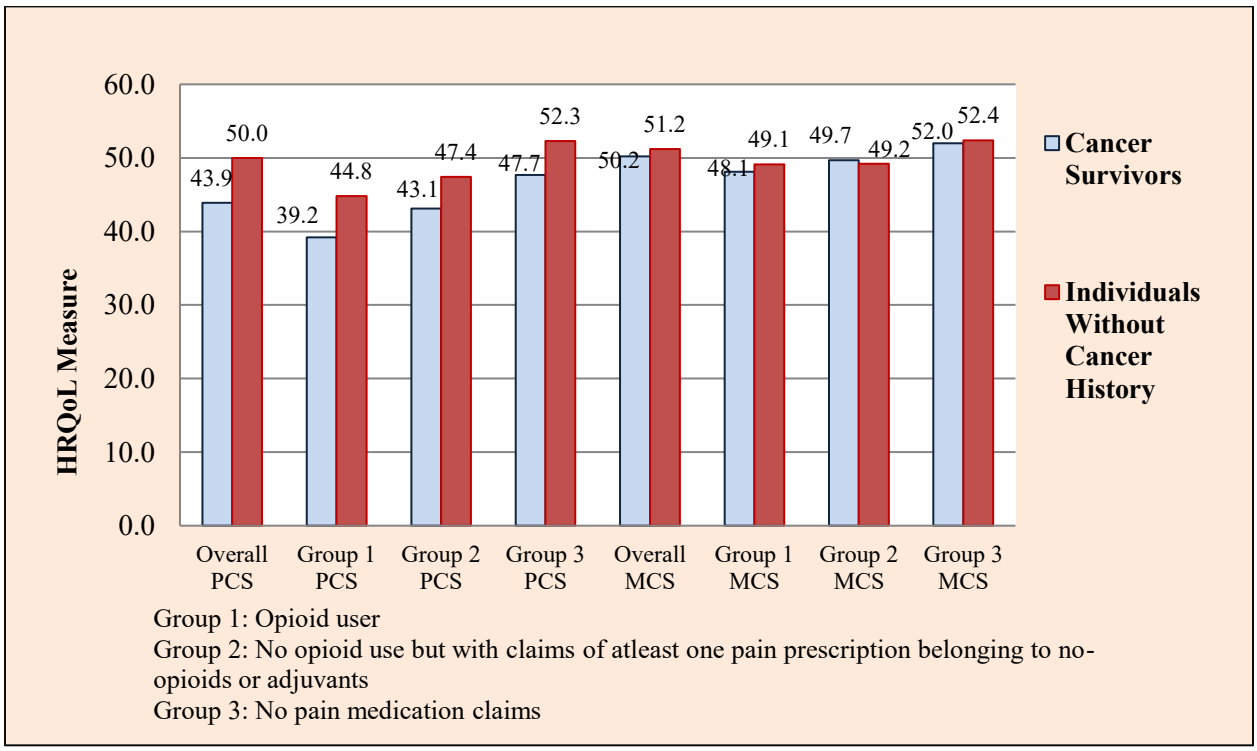
The cancer survivors identified were 68.2%, 26.5%, 5.3% of 23.2 million, respectively, for health insurance coverage including any private, public only and uninsured. Individuals without cancer history, respectively, were 67.4%, 16.3% and 16.3%, of 193.6 million. Among the cancer survivors, the PCS scores stratified by health insurance coverage were 46.1 (0.22), 38.1 (0.33), 44.6 (0.62), respectively; MCS scores were 51.3 (0.18), 48.4 (0.27), 46.3 (0.58), respectively. Among individuals without cancer history, stratified by health insurance coverage, PCS scores were 51.4 (0.06), 42.9 (0.15), 51.3 (0.11), respectively; MCS scores were, 52.1 (0.05), 48.4 (0.14), 50.4 (0.11), respectively.

4.1.3 Study 1c

Among 23.1 million cancer survivors identified over the six years of study period, 35.0% had at least one prescription claim for opioids, 18.4% reported no claim for opioids but had at least one prescription for pain medication and 46.6% had no prescription for a pain medication as shown in table 19. Among these three groups the PCS and MCS scores were 39.2 (0.31), 43.1 (0.42), 47.7 (0.23) and 48.1 (0.27), 49.7 (0.35), 52.0 (0.18), respectively as shown in figure 12.

As shown in table 20, among 193.5 million individuals without cancer history, 22.2% had at least one prescription claim for opioids, 13.7% had no claim for opioids but had at least one prescription for pain medication and 64.2% had no prescription for a pain medication; for these three groups the PCS and MCS scores were 44.8 (0.14), 47.4 (0.16), 52.3 (0.07) and 49.1 (0.11), 49.2 (0.12), 52.4 (0.05), respectively.

Figure 12: HRQoL Measures Among Cancer Survivors & Individuals Without Cancer History, Stratified by Opioid Exposure, MEPS 2008 - 2013



When compared to individuals without cancer history, the lowest PCS and MCS scores were reported by opioid users.

4.2 Results: Objective 2

4.2.1 Multicollinearity

Variance Inflation Factor:

Efforts were made to minimize multicollinearity that includes:

(i) Limiting the variable to categories of interest: variable BMI was reduced from categories obese, overweight, normal, underweight to binary categorical variable obese or not. Similarly, for education status, marital status, family income

(ii) Excluding the variable when two are almost identical: variable cancer status (currently/previously diagnosed) was excluded as it was defined very similar to years since cancer diagnosis.

A VIF was used to detect multicollinearity. It was observed that all the independent variables other than type of cancer had VIF value less than 4.0. The variables unspecified cancer, multi-cancer, breast cancer and gynecological cancer had VIF value $\geq$ 10.

Notably, the independent variables included for the regression are all categorical (qualitative) in nature. The characteristics include:

(a) Binary: n=36, female, education, panel, marital status, MSA, smoking status, obesity, head cancer, gastrointestinal cancer, lung cancer, breast cancer, gynecological cancer, prostate cancer, urogenital cancer, hematological cancer, bone cancer, skin cancer, unspecified cancer, multi-cancer, arthritis, back and neck pain, diabetes, headache, chest, connective, fracture, pelvic, multi-painful disorder, depression, anxiety, adjustment, bipolar, conduct, multi-mental disorder, substance abuse, employment

(b) Having 3 categories: n=1, income

(c) Having 4 categories: n=3, race, region, pain perception

(d) Having 5 categories: n=1, insurance status

(e) Having 6 categories: n=2, age groups, years since first cancer diagnosis

All the predictor in the model was retained because omitting unspecified cancer, multi-cancer, breast cancer and gynecological cancer may result in specification error. Moreover, the dataset consists of all qualitative variables and large sample size. Thereby, set of 43 predictor variables were incorporated in the model to predict the outcome.

4.2.2 Characteristics of Dependent Variable

Study 2a:

Dependent variable: Total number of pain prescriptions claims

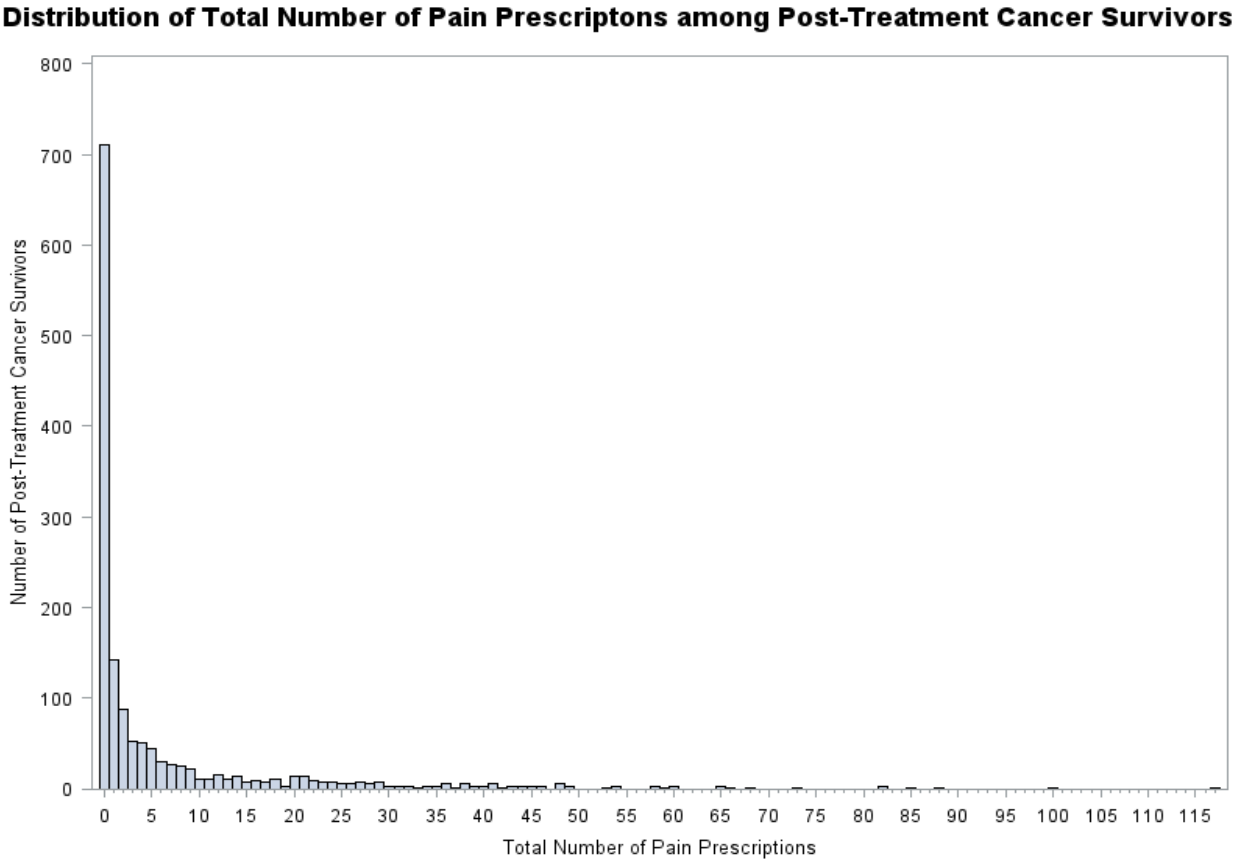
The total number of pain prescriptions was calculated based on individuals' claim of drugs. Maximum of 117 and minimum of zero claims for pain prescription were identified across 1,444 post-treatment cancer survivors. Around 49.0% (n=711) reported no claims of any pain medications. As shown in figure 13, from histogram of total number of pain prescription claims, a skewed right distribution was observed because of large number of individuals with no pain medication claims. Post-treatment cancer survivors with large number of pain prescriptions claims were less frequently observed.

The characteristics of dependent variable include:

- Non-negative integers with lowest possible value zero
- Non-normal distribution of count data
- Overdispersion, with variance (=146.8) greater than mean (=5.8)
- Excess zeros

Checking overdispersion and excess zeros						
	Sample size	**Minimum (n)**	**Maximum**	**Mean**	**Std. deviation**	**Variance**
Total Number of pain prescriptions	1,444	0 (711)	117.0	5.8	12.1	146.8
Total number of opioids prescriptions	1,444	0 (965)	73.0	2.4	6.8	45.7

Figure 13: Histogram For Total Number Of Pain Prescription Claims

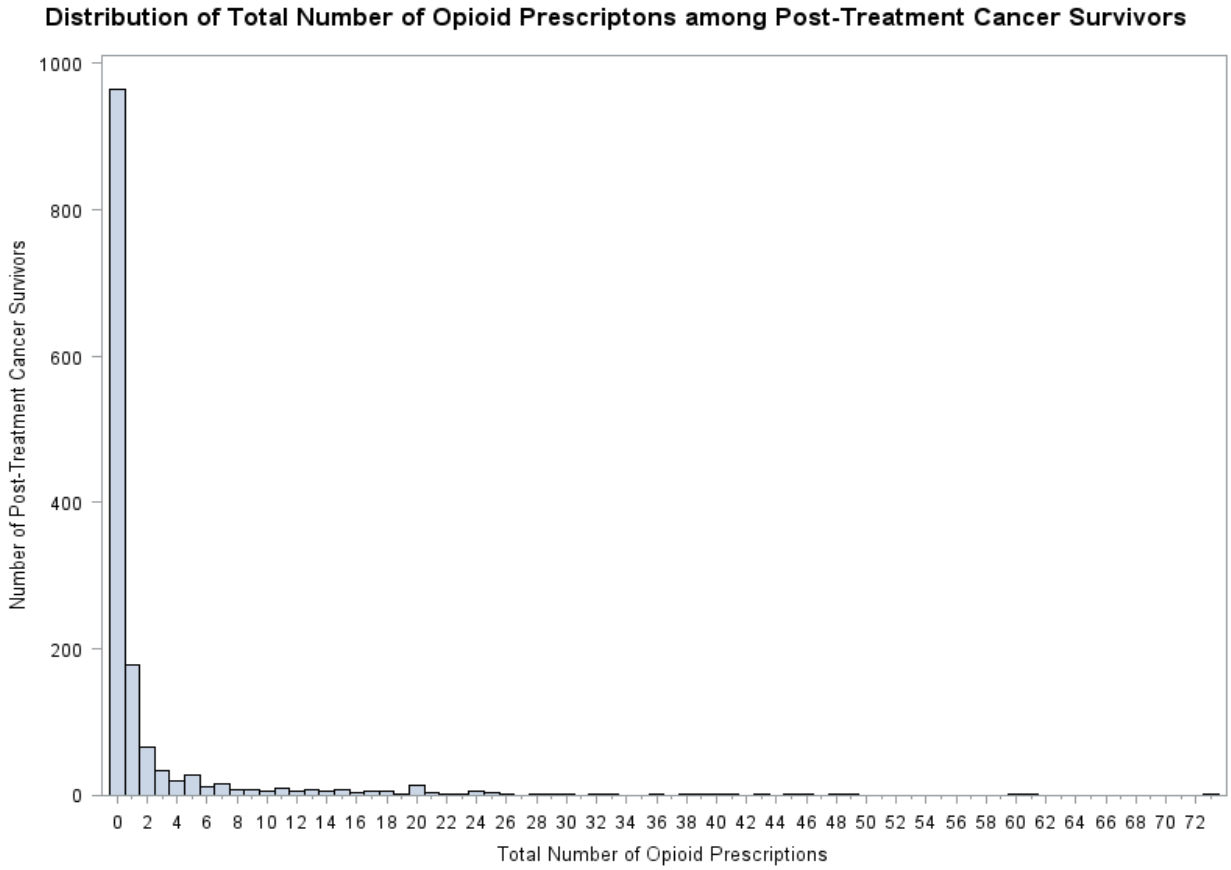


Study 2b:

Dependent variable: Total number of opioid prescription claims

The total number of opioid prescriptions was calculated based on individuals' claim of drugs belonging to narcotic analgesic combinations and opioids class. Maximum of 73 and minimum of zero claims for opioid prescription were identified across 1,444 post-treatment cancer survivors. Around 67.0% (n=965) reported no claims of opioid medications. As shown in figure 14, from histogram of total number of opioid prescription claims, a skewed right distribution was observed because of large number of individuals with no opioid prescription claims. Post-treatment cancer survivors with large number of opioid claims were less frequently observed.

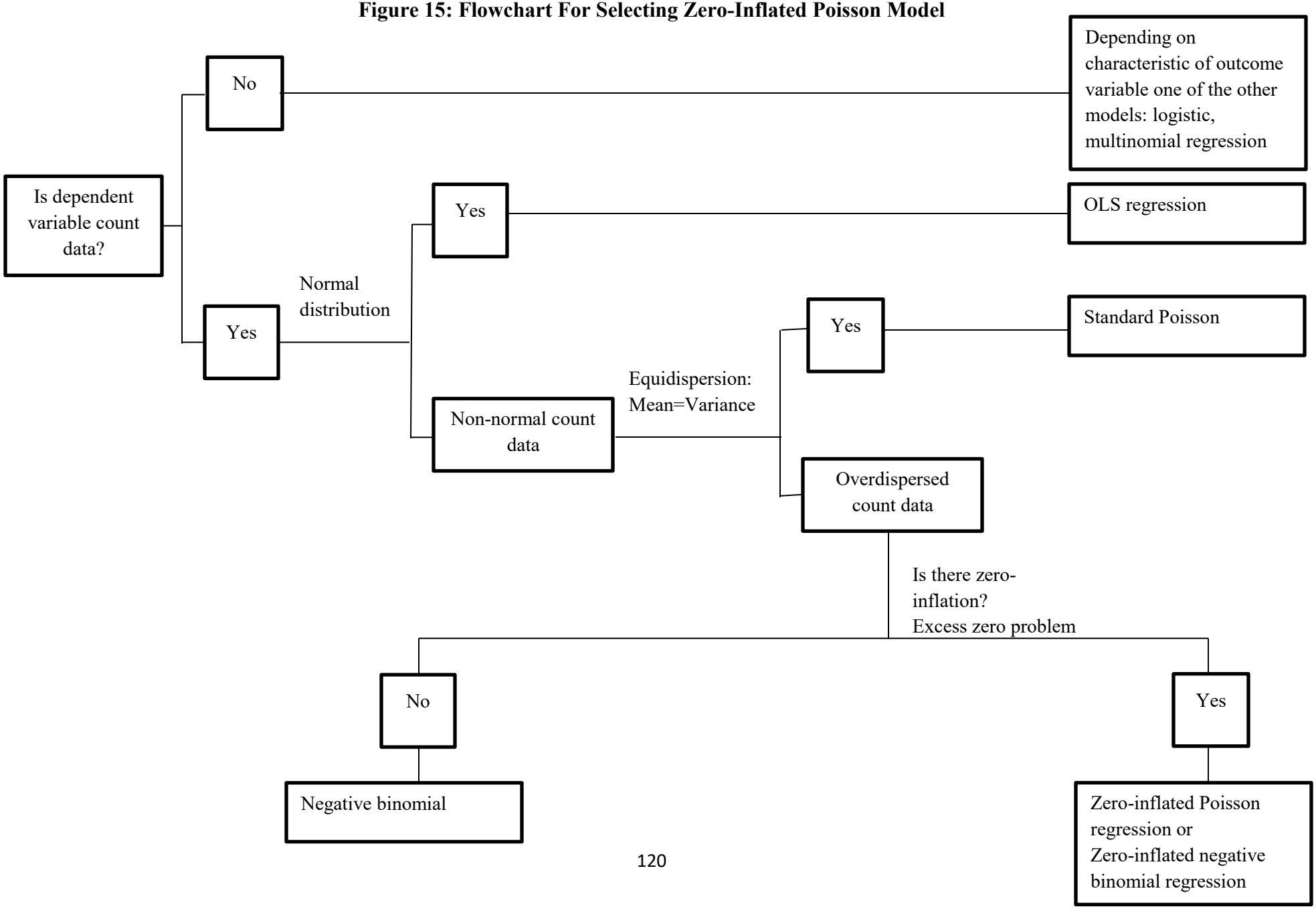
Figure 14: Histogram For Total Number Of Opioid Prescription Claims



The characteristics of dependent variable include:

- Non-negative integers with lowest possible value zero
- Non-normal distribution of count data
- Overdispersion, with variance (=45.7) greater than mean (=2.4)
- Excess zero

Figure 15: Flowchart For Selecting Zero-Inflated Poisson Model



4.2.3 Rationale for Using Zero-Inflated Poisson Model

Figure 15 depicts the flowchart for selecting a ZIP model for the dependent variable (Total number of pain prescriptions and Total number of opioid prescription):

1. For the count data that are normally distributed, the OLS regression can be used.
2. For highly non-normal count data Poisson regression is preferred. However, Poisson regression assumes equidispersion meaning the mean and variance are the equal.
3. For overdispersion, where variance is greater than mean, the negative binomial regression model can be used; however, it does not handle excess zero counts.
4. For this study, the presence of excess zeroes demands the use of zero-inflated models either zero-inflated Poisson or zero-inflated negative binomial.
5. Model comparison test:
   (a) The model fit tests: Such as goodness-of-fit, AIC and BIC, likelihood ratio for zero-inflated models using survey designs are yet to be developed in STATA limiting ability to select from Zero-inflated Poisson vs Zero-inflated negative binomial.
   (b) Vuong test: Numerous literature has used vuong test to compare different zero-inflated models or with non-inflated model. However, recently STATA removed the test since testing for zero inflation using the vuong test was inappropriate. The warning *"Vuong test is not appropriate for testing zero-inflation"* was generated asking to use forcevuong command.
   (c) Zero-inflated Poisson regression:
      (i) ZIP is used to model count data that has an excess of zero counts.
      (ii) Further, the theory suggests that excess zero are generated by two separate process.
      (iii) Unfortunately, SAS don't have provisions to run zip model for survey database.
      (iv) The diagnostic tests for comparing various types of regression model using survey database are still being developed in STATA.

6. The zeros (no claims of pain prescription) in the dataset were due to the two clinical situations arising either because patients are not in pain or they are not receiving pain prescriptions even with ongoing pain possibly due to patient-, physician-, system-related barriers. In context to this study, the zero-inflated Poisson regression was used to account for excess zeroes.
7. The zero-inflated Poisson regression generates estimates involving two separate models. Firstly, by fitting Poisson regression for non-zero outcomes (the count of pain prescriptions when prescribed); secondly, it accounts for additional zeroes by fitting logistic regression to predict the likelihood of not prescribing pain medications.

4.2.4 Model Fit Statistics

When overdispersion is observed due to excess zeroes, the assumption that mean and variance are equal is violated and thus the standard Poisson regression model is not appropriate. The zero-inflated Poisson model typically shows a better model fit than the standard Poisson regression, which can be confirmed by comparing the model indicated by post-estimation test for goodness of fit.

Whereas, model fit statistics are easily conducted for non-survey data, diagnostic tests for comparing various types of regression model using survey database are still being developed in STATA. The goodness of fit test to assess model fit for binary response models using survey design is now available in STATA; unfortunately, the goodness-of-fit tests for zero-inflated Poisson models using survey designs are yet to be developed.

The below are model fit statistics (for unweighted sample of 1,444 observations):

<u>Study 2a:</u>

(i) Goodness-of-fit test (for standard Poisson regression):

Whether standard Poisson model is better fit or not can be confirmed with the goodness-of-fit test. The command estat gof was used to obtain model goodness-of-fit test output. Both the likelihood ratio test

statistics (deviance) and Pearson chi-squared test statistics are reported. If the tests are significant, the model represents poor fit.

H_O: The total pain medications use is similar across post-treatment cancer survivors

H_A: The total pain medications use is not similar across post-treatment cancer survivors

Deviance goodness-of-fit = 11825.01
Prob > chi = 0.0000

Pearson goodness-of-fit = 16972.34
Prob > chi = 0.0000

From the output of deviance goodness-of-fit test, a significant p-value suggests that we can reject the null hypothesis at significance level of 0.05. The output from Pearson goodness-of-fit test suggests that the Poisson model is not a good choice. The p-value is 0.000 which is less than significance level of 0.05; the null hypothesis is rejected. Both the tests are statistically significant, and data do not fit model well due to overdispersion.

(ii) AIC and BIC:

The Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC) test statistics was used for model comparisons. Model is desirable that has minimum AIC and minimum BIC. The command estat ic was used in STATA to obtain results from both the test. It calculates two information criteria used to compare models. The output of the AIC and BIC test statistics is summarized below.

Dependent variable: TOTALPAIN					
Model	Log likelihood intercept only	Log likelihood full model	df	AIC	BIC
Poisson	-12264.66	-7236.047	62	14596.09	14923.15
Zero-Inflated Poisson Regression	-7319.375	-4999.244	124	10246.49	10900.61

The output consists of fit indices for the model including the log likelihood for the empty (intercept only) model, log likelihood of fitted model, degrees of freedom, AIC and BIC values. A zero-inflated Poisson

regression model is preferred because of lower AIC and BIC values compared to Poisson regression model.

Study 2b:

(i) Goodness-of-fit test (for standard Poisson regression):

H_O: The total opioid medications use is similar across post-treatment cancer survivors

H_A: The total opioid medications use is not similar across post-treatment cancer survivors

Deviance goodness-of-fit = 6758.503
Prob > chi = 0.0000

Pearson goodness-of-fit = 11512.42
Prob > chi = 0.0000

From the output of deviance goodness-of-fit test, a significant p-value suggests that we can reject the null hypothesis at significance level of 0.05. The output from Pearson goodness-of-fit test suggests that the Poisson model is not a good choice. The p-value is 0.000 which is less than significance level of 0.05; the null hypothesis is rejected. Both the tests are statistically significant, and data do not fit model well due to overdispersion.

(ii) AIC and BIC

Dependent variable: TOTALOPIOID					
Model	Log lik intercept only	Log lik full model	df	AIC	BIC
Poisson	-6899.635	-4125.523	62	8375.046	8702.107
Zero Inflated Poisson Regression	-3891.885	-2696.699	124	5641.397	6295.519

A zero-inflated Poisson regression model is preferred because of lower AIC and BIC values compared to standard Poisson regression model.

4.2.5 Regression Estimates: Study 2a

The weighted estimates were reported incorporating 33.2 million (n=1,444) post-treatment cancer survivors (Table 21). The zero-inflated Poisson model consists of two parts; the estimates were reported for both the Poisson and logit model. For interpreting the output, there's unique relationship between 2-sided 5% level of significance and 95% CI. Situations where 95% CI does not includes value of 0 for absolute measure of association, (e.g. mean difference) or 1 for relative measures of association (e.g. odds ratio), can be inferred as the association is statistically significant ($p \leq 0.05$).

I. Demographics

(a) Age:

From the Poisson model, among the post-treatment cancer survivors who were prescribed pain medications, belonging to age group 35-44 was associated with significant ($p \leq 0.05$) more expected counts of pain prescription by 105% [exp(0.716)=2.05 (1.39 - 3.01)] compared to age group 18-34, holding other variables constant. Similarly, belonging to age group 45-54, 55-64, 65-74 and 75-84 years, respectively, was associated with significant more expected counts of pain prescription by 122% [exp(0.800)=2.22 (1.55 - 3.18)], 116%[exp(0.770)=2.16 (1.46 - 3.20)], 106% [exp(0.722)=2.06 (1.35 - 3.13)], 75% [exp(0.559)=1.75 (1.02 - 3.01)].

From the logit model, among the post-treatment cancer survivors who were not prescribed pain medications, the odds of not receiving pain prescription was significantly ($p \leq 0.05$) higher among age group 35-44 by 285% [OR= 3.85 (1.61 - 9.22)] compared to age group 18-34 when other factors remain constant. Similarly, belonging to age group 45-54, 55-64, 65-74 and 75-84 years, respectively, was associated with significantly higher odds of not receiving pain prescription by 270% [OR= 3.70 (1.81 - 7.55)], 282%[OR= 3.82 (1.79 - 8.15)], 337% [OR= 4.37 (2.07 - 9.22)], 325% [OR= 4.25 (1.86 - 9.72)].

(b) Sex

From the Poisson model, among post-treatment cancer survivors who were prescribed pain medications, being a female was associated with more expected counts of pain prescription by 8% [exp(0.079)= 1.08 (0.86 - 1.37)]. However, it was not statistically significant.

From the logit model, non-significant association was obtained across pain medication use and gender.

(c) Race/Ethnicity:

From the Poisson model, among the post-treatment cancer survivors who were prescribed pain medications, compared to non-Hispanic White race group, belonging to non-Hispanic Black was associated with significant lower expected counts of pain prescription by 28% [exp(-0.326)=

0.72 (0.55 - 0.95)], holding other variables constant.

From the logit model, the odds of not receiving pain prescription was significantly higher among post-treatment cancer survivors belonging to other race group by 115% [OR= 2.15 (1.03 - 4.48)] compared to non-Hispanic Whites when other factors remain constant.

(d) Education:

From the Poisson model, among post-treatment cancer survivors who were prescribed pain medications, individuals with higher education was associated with less expected counts of pain prescription by 8% [exp(-0.084)= 0.92 (0.74 - 1.14)] compared to individuals with lower education. However, it was not statistically significant.

(e) Marital Status:

From the Poisson model, among post-treatment cancer survivors who were prescribed pain medications, being married was associated with more expected counts of pain prescription by 8% [exp(0.081)= 1.08 (0.90 - 1.30)] compared to not-married. However, the association was non-significant.

(f) Panel:

From the Poisson model, among post-treatment cancer survivors who were prescribed pain medications, belonging to panel 16 was associated with less expected counts of pain prescription by 7% [exp(-0.072)= 0.93 (0.79 - 1.10)] compared to individuals belonging to panel 15. However, this difference in utilization of pain medication was not significant.

II. Geographical

(a) Region:

From the Poisson model, among post-treatment cancer survivors who were prescribed pain medications, compared to Northeast, residing in Midwest, South and West was respectively associated with expected counts of pain prescription higher by 8% [exp(0.076)= 1.08 (0.80 - 1.46)], lower by 6% [exp(-0.058)= 0.94 (0.69 - 1.29)] and lower by 12% [exp(-0.124)= 0.88 (0.64 - 1.21)]. However, these associations were not significant. From logit model, non-significant association was obtained for region categories.

(b) MSA:

From the Poisson model, among post-treatment cancer survivors who were prescribed pain medications, residing in urban was associated with significantly less expected counts of pain prescription by 26% [exp(-0.307)= 0.74 (0.61 - 0.89)] compared to individuals residing in rural.

From the logit model, among the post-treatment cancer survivors who were not prescribed pain medications, the odds of not receiving pain prescription was higher among individuals residing in urban

by 21% [OR= 1.21 (0.82 - 1.80)] compared to individuals residing in rural and it was not statistically significant.

III. Clinical

(a) Smoking:

From the Poisson model, among post-treatment cancer survivors who were prescribed pain medications, individuals currently smoking was associated with significantly more expected counts of pain prescription by 63% [exp(0.488)= 1.63 (1.33 - 1.99)] compared to individuals currently not smoking.

(b) Pain perception:

From the Poisson model, among post-treatment cancer survivors who were prescribed pain medications, individuals currently experiencing high/severe pain and change in pain over time (from mild/moderate to high/severe and vice-versa) was associated with significantly more expected counts of pain prescription respectively by 89% [exp(0.637)= 1.89 (1.26 - 2.83)] and by 41% [exp(0.345)= 1.41 (1.03 - 1.99)] compared to individuals currently experiencing no pain.

From the logit model, the odds of not receiving pain prescription were significantly lower among individuals currently experiencing mild/moderate; high/severe and change in pain over time respectively by 45% [OR= 0.55 (0.35 - 0.86)]; by 82% [OR= 0.18 (0.09 - 0.34)] and by 40% [OR= 0.60 (0.37 - 0.96)] compared to individuals experiencing no pain.

(c) Obesity:

From the Poisson model, among post-treatment cancer survivors who were prescribed pain medications, being obese was associated with significant more expected counts of pain prescription by 25% [exp(0.224)= 1.25 (1.03 - 1.52)] compared to non-obese.

From the logit model, among the post-treatment cancer survivors who were not prescribed pain medications, the odds of not receiving pain prescription was lower among obese by 21% [OR= 0.79 (0.56 - 1.12)] compared to non-obese individuals and it was not statistically significant.

(d) Types of Cancer:

From the Poisson model, among post-treatment cancer survivors who were prescribed pain medications a non-significant association was obtained based on cancer site. For head & neck, gastrointestinal, lung/bronchus, breast, gynecological, prostate, urogenital, hematological, bone, skin, unspecified and multi-cancer, respectively, the estimates were exp(-0.253)= 0.78 (0.41 - 1.47), exp(-0.122)= 0.88 (0.43 - 1.81), exp(-0.130)= 0.88 (0.42 - 1.86), exp(-0.116)= 0.89 (0.45 - 1.75), exp(0.127)= 1.14 (0.57 - 2.27), exp(0.055)= 1.06 (0.52 - 2.13), exp(0.147)= 1.16 (0.55 - 2.44), exp(-0.609)= 0.54 (0.28 - 1.06), exp(0.357)= 1.43 (0.45 - 4.49), exp(-0.017)= 0.98 (0.46 - 2.08), exp(0.121)= 1.13 (0.60 - 2.13), exp(0.007)= 1.01 (0.49 - 2.06) compared to absence of disease. Similarly, non-significant association was obtained from logit model based on cancer site.

(e) Time since first cancer diagnosis:

From the Poisson model, a non-significant association was obtained based on time since first cancer diagnosis. For individuals with 1-5, 6-10, 11-15, 16-20, >20 years, respectively, the estimates were exp(0.203)= 1.23 (0.95 - 1.59), exp(0.247)= 1.28 (0.97 - 1.69), exp(0.161)= 1.17 (0.89 - 1.55), exp(-0.064)= 0.94 (0.60 - 1.47), exp(0.167)= 1.18 (0.91 - 1.54) compared to less than a year of cancer diagnosis. Similarly, non-significant association was obtained from logit model.

(f) Types of painful conditions:

From the Poisson model, among post-treatment cancer survivors who were prescribed pain medications, individuals with arthritis was associated with significantly more expected counts of pain prescription by 43% [exp(0.360)= 1.43 (1.13 - 1.82)] compared to individuals without arthritis.

From the logit model, the odds of not receiving pain prescription were significantly lower among post-treatment cancer survivors with arthritis, back and neck pain, connective tissue disorder, pelvic pain, respectively by 65% [OR= 0.35 (0.23 - 0.53)]; by 54% [OR= 0.46 (0.28 - 0.74)]; by 51% [OR= 0.49 (0.29 - 0.80)]; by 54% [OR= 0.46 (0.25 - 0.83)] compared to individuals without respective painful conditions.

(g) Mental conditions:

From the Poisson model, among post-treatment cancer survivors who were prescribed pain medications, individuals with bipolar was associated with significantly more expected counts of pain prescription by 46% [exp(0.376)= 1.46 (1.18 - 1.79)] compared to individuals without bipolar disorder. Individuals with adjustment disorder was associated with significantly less expected counts of pain prescription by 55% [exp(-0.798)= 0.45 (0.23 - 0.88)] compared to individuals without adjustment disorder.

From the logit model, the odds of not receiving pain prescription were significantly lower among post-treatment cancer survivors with anxiety, bipolar respectively by 53% [OR= 0.47 (0.28 - 0.79)]; by 70% [OR= 0.30 (0.18 - 0.50)] compared to individuals without respective mental conditions.

(h) History of drug/substance abuse:

From the Poisson model, among post-treatment cancer survivors who were prescribed pain medications, individuals with substance abuse was associated with more expected counts of pain prescription by 32% [exp(0.274)= 1.32 (0.80 - 2.17)] compared to individuals without history of drug abuse. However, the association was non-significant.

From the logit model, the odds of not receiving pain prescription was lower by 34% [OR= 0.66 (0.27 - 1.65)] among post-treatment cancer survivors with drug abuse history compared to individuals with no history of drug abuse. However, the association was non-significant.

IV. Economic factors

(a) Income

From the Poisson model, among post-treatment cancer survivors who were prescribed pain medications, individuals with higher family income was associated with significant more expected counts of pain prescription by 22% [exp(0.196)= 1.22 (1.00 - 1.49)] compared to individuals with lower family income. Also, individuals with change in family income was associated with significant more expected counts of pain prescription by 50% [exp(0.404)= 1.50 (1.19 - 1.88)] compared to individuals with lower family income.

(b) Employment status

From the Poisson model, among post-treatment cancer survivors who were prescribed pain medications, individuals currently employed was associated with significant less expected counts of pain prescription by 35% [exp(-0.424)= 0.65 (0.53 - 0.81)] compared to unemployed individuals.

(c) Insurance status

From the Poisson model, among post-treatment cancer survivors who were prescribed pain medications, compared to uninsured, individuals those are insured privately, Medicaid only and all Medicare was associated with expected counts of pain prescription, respectively, more by 12%[exp(0.110)= 1.12 (0.81 - 1.54)], less by 12% [exp(-0.132)= 0.88 (0.57 - 1.35)], more by 11%[exp(0.104)= 1.11 (0.82 - 1.49)]; however, these association were not significant. Among individuals with change in insurance was associated with significant more expected counts of pain prescription by 67% [exp(0.510)= 1.67 (1.12 - 2.48)] compared to uninsured. From the logit model, non-significant association was obtained across insurance categories.

4.2.6 Regression Estimates: Study 2b

The weighted estimates were reported from both the model incop incorporating 33.2 million (n=1,444) post-treatment cancer survivors (Table 21). The estimates were generated for both the Poisson and logit model with dependent variable as total number of opioid prescription claims. Based on demographic, geographic, clinical and economic factors the estimates obtained were as follows:

I. Demographics

(a) Age:

From the Poisson model, among the post-treatment cancer survivors who were prescribed opioid medications, compared to age group 18-34, belonging to age group 35-44, 45-54, 55-64, 65-74 and 75-84 years, respectively, was associated with expected counts of opioid prescription more by 21% [exp(0.194)= 1.21 (0.66 - 2.22)], more by 25%[exp(0.221)= 1.25 (0.70 - 2.23)], more by 1% [exp(0.011)= 1.01 (0.52 - 1.96)], more by 3% [exp(0.030)= 1.03 (0.51 - 2.07)], less by 14% [exp(-0.150)= 0.86 (0.38 - 1.97)]. However, the association was not significant.

From the logit model, among the post-treatment cancer survivors who were not prescribed opioid medications, compared to age group 18-34, the odds of not receiving opioid prescription was significantly higher among age group 75-84, 65-74, 55-64 and 35-4, respectively, by 222% [OR= 3.22 (1.41 - 7.35)] 173% [OR= 2.73 (1.32 - 5.64)], 198%[OR= 2.98 (1.48 - 6.01)] and 143% [OR= 2.43 (1.15 - 5.16)].

(b) Sex

From both the regression model, a non-significant association was obtained across gender categories and opioid medication use.

(c) Race/Ethnicity:

From the logit model, the odds of not receiving opioid prescription was significantly higher among post-treatment cancer survivors belonging to other race group by 114% [OR= 2.14 (1.03 - 4.43)] compared to non-Hispanic Whites.

(d) Education:

From the Poisson model, among post-treatment cancer survivors who were prescribed opioid medications, individuals with higher education was associated with significant less expected counts of opioid prescription by 48% [exp(-0.645)= 0.52 (0.36 - 0.77)] compared to individuals with lower education.

(e) Marital Status:

From the Poisson model, among post-treatment cancer survivors who were prescribed opioid medications, being married was associated with more expected counts of opioid prescription by 24% [exp(0.214)= 1.24 (0.95 - 1.61)] compared to individuals who are not-married. However, the association was non-significant.

(f) Panel:

From both the regression model, a non-significant association was obtained across panel categories.

II. Geographical

(a) Region:

From the logit model, the odds of not receiving opioid prescription was significantly lower among post-treatment cancer residing in Midwest by 48% [OR= 0.52 (0.28 - 0.99)] compared to those residing in Northeast.

(b) MSA:

From both the regression model, a non-significant association was obtained across MSA categories and opioid medication use.

III. Clinical

(a) Smoking:

From the Poisson model, among post-treatment cancer survivors who were prescribed opioid medications, individuals currently smoking was associated with significantly more expected counts of opioid prescription by 72% [exp(0.545)= 1.72 (1.32 - 2.24)] compared to individuals currently not smoking.

(b) Pain perception:

From the Poisson model, among post-treatment cancer survivors who were prescribed opioid medications, individuals currently experiencing mild/moderate, high/severe and change in pain over time (from mild/moderate to high/severe and vice-versa) was associated with significantly more expected counts of opioid prescription, respectively, by 88% [exp(0.629)= 1.88 (1.16 - 3.02)], by 249% [exp(1.251)= 3.49 (2.09 - 5.84)], by 64% [exp(0.493)= 1.64 (1.08 - 2.49)] compared to individuals currently experiencing no pain.

From the logit model, the odds of not receiving opioid prescription was significantly lower among post-treatment cancer survivors currently experiencing mild/moderate; high/severe pain respectively by 43% [OR= 0.57 (0.37 - 0.88)]; by 80% [OR= 0.20 (0.10 - 0.39)] compared to individuals experiencing no pain.

(c) Obesity:

From the Poisson model, among post-treatment cancer survivors who were prescribed opioid medications, being obese was associated with more expected counts of opioid prescription by 3%

[exp(0.025)= 1.03 (0.74 - 1.42)] compared to non-obese individuals. However, the association was not significant.

From the logit model, among the post-treatment cancer survivors who were not prescribed opioid medications, the odds of not receiving opioid prescription was lower among obese by 12% [OR= 0.88 (0.61 - 1.28)] compared to non-obese individuals and it was not statistically significant.

(d) Types of Cancer:

From the Poisson model, among post-treatment cancer survivors who were prescribed opioid medications a non-significant association was obtained based on cancer site. For head & neck, gastrointestinal, lung/bronchus, breast, gynecological, prostate, urogenital, hematological, bone, skin, unspecified and multi-cancer, respectively, the estimates were exp(-0.727)= 0.48 (0.17 - 1.38), exp(-0.407)= 0.67 (0.21 - 2.12), exp(0.413)= 1.51 (0.43 - 5.26), exp(-0.608)= 0.54 (0.15 - 1.95), exp(-0.299)= 0.74 (0.24 - 2.33), exp(-0.062)= 0.94 (0.31 - 2.90), exp(-0.279)= 0.76 (0.21 - 2.70), exp(-0.665)= 0.51 (0.14 - 1.83), exp(0.937)= 2.55 (0.55 - 11.84), exp(-0.372)= 0.69 (0.20 - 2.41), exp(0.078)= 1.08 (0.37 - 3.20), exp(0.345)= 1.41 (0.43 - 4.59) compared to absence of disease. Similarly, non-significant association was obtained from logit model based on cancer site.

(e) Time since first cancer diagnosis:

From the Poisson model, among post-treatment cancer survivors who were prescribed opioid medications, individuals with 1-5 years since first cancer diagnosis was associated with significantly more expected counts of opioid prescription by 51% [exp(0.412)= 1.51 (1.06 - 2.15)] compared to individuals with less than a year of cancer diagnosis.

From the logit model, the odds of not receiving opioid prescription was significantly higher among post-treatment cancer survivors with 1-5 years and 11-15 years since first cancer diagnosis, respectively by

129% [OR= 2.29 (1.34 - 3.90)] and by 127% [OR= 2.27 (1.09 - 4.70)] compared to individuals with less than a year of cancer diagnosis.

(f) Types of painful conditions:

From the Poisson model, among post-treatment cancer survivors who were prescribed opioid medications, individuals with arthritis and multi-painful conditions was associated with significantly more expected counts of opioid prescription, respectively by 93% [exp(0.658)= 1.93 (1.33 - 2.80)] and by 69% [exp(0.525)= 1.69 (1.12 - 2.55)] compared to individuals without respective painful conditions.

From the logit model, the odds of not receiving opioid prescription were significantly lower among post-treatment cancer survivors with back and neck pain, connective tissue disorder, fracture and pelvic pain, respectively by 52% [OR= 0.48 (0.31 - 0.76)]; by 39% [OR= 0.61 (0.38 - 0.96)]; by 75% [OR= 0.25 (0.10 - 0.58)] and by 42% [OR= 0.58 (0.33 – 0.98)] compared to individuals without respective painful conditions.

(g) Mental conditions:

From the logit model, the odds of not receiving opioid prescription were significantly higher among post-treatment cancer survivors with adjustment disorder and multi-mental condition, respectively by 241% [OR= 3.41 (1.35 - 8.57)] and by 264% [OR= 3.64 (1.51 - 8.76)] compared to individuals without respective mental conditions. The odds of not receiving opioid prescription was significantly lower among post-treatment cancer survivors with bipolar by 68% [OR= 0.32 (0.17 - 0.58)] compared to individuals without bipolar condition.

(h) History of drug/substance abuse:

From the Poisson model, among post-treatment cancer survivors who were prescribed opioid medications, individuals with substance abuse was associated with more expected counts of opioid

prescription by 13% [exp(0.126)= 1.13 (0.54 - 2.40)] compared to individuals without history of drug abuse. However, the association was non-significant. Similarly, non-significant association was obtained from logit model based on history of substance abuse.

IV. Economic factors

(a) Income

From the Poisson model, among post-treatment cancer survivors who were prescribed opioid medications, individuals with higher family income was associated with significant more expected counts of opioid prescription by 52% [exp(0.416)= 1.52 (1.09 - 2.11)] compared to individuals with lower family income. Also, individuals with change in family income was associated with significant more expected counts of opioid prescription by 85% [exp(0.617)= 1.85 (1.37 - 2.51)] compared to individuals with lower family income.

(b) Employment status

From the Poisson model, among post-treatment cancer survivors who were prescribed opioid medications, individuals currently employed was associated with significant less expected counts of opioid prescription by 31% [exp(-0.374)= 0.69 (0.51 - 0.92)] compared to unemployed individuals.

(c) Insurance status

From the Poisson model, among post-treatment cancer survivors who were prescribed opioid medications, compared to uninsured, individuals those are insured privately, Medicaid only and all Medicare was associated with expected counts of opioid prescription, respectively, more by 5%[exp(0.046)= 1.05 (0.67 - 1.63)], less by 16% [exp(-0.174)= 0.84 (0.46 - 1.53)], less by 11% [exp(-0.119)= 0.89 (0.61 - 1.30)]; however, these association were not significant. Among individuals with change in insurance status was associated with significant more expected counts of opioid prescription by 112% [exp(0.749)= 2.12 (1.41 - 3.16)] compared to uninsured.

4.3 Results: Objective 3

4.3.1 Study 3a

I. Frequency distribution of SF-12 productivity measures among post-treatment cancer survivors by pain medication use

The number and percent of post-treatment cancer survivors across different categories of SF-12 productivity measure and pain medication use are summarized in table 23. Total of 1.444 post-treatment cancer survivors were identified from the objective 2 who filled out SF-12 questionnaire and the output in terms of frequency distribution of workers' productivity (none of the time, little/some of the time, most of the time, work limitation changes over time) and pain medication use (none, acute, moderate, and chronic) obtained was:

(a) During past 4 weeks, as result of physical health, limited in kind of work or other activities?

Around 54.0 % of post-treatment cancer survivors experienced little (23.5%)/no work (30.6%) limitation; whereas, 14% respondents reported most of the time. Significant difference existed across various categories of productivity measures and pain medication use. Among those who experienced no work limitation, 73.0% (n=323) respondents were non-users of pain medications and those who experienced work limitation most of the time, 42.8% (n=86) respondents were chronic users of pain medications.

(b) During past 4 weeks, as result of mental problems, did work or other activities less carefully than usual?

Around 62.0 % of post-treatment cancer survivors experienced little (20.6%)/no work (41.5%) limitation; whereas, 5.1% respondents reported most of the time. Significant difference existed across various categories of productivity measures and pain medication use. Among those who experienced no work limitation, 64.5% (n=387) respondents were non-users of pain medications and those who experienced work limitation most of the time, 43.2% (n=32) respondents were chronic users of pain medications.

(c) During past 4 weeks, as result of physical problems, accomplished less than would like?

Around 54.0 % of post-treatment cancer survivors experienced little (27.6%)/no work (26.8%) limitation; whereas, 13.0% respondents reported most of the time. Significant difference existed across various categories of productivity measures and pain medication use. Among those who experienced no work limitation, 71.8 % (n=278) respondents were non-users of pain medications and those who experienced work limitation most of the time, 44.4% (n=83) respondents were chronic users of pain medications.

(d) During past 4 weeks, as result of mental problems, accomplished less than would like?

Around 62.0 % of post-treatment cancer survivors experienced little (21.0%)/no work (41.1%) limitation; whereas, 6.5% respondents reported most of the time. Significant difference existed across various categories of productivity measures and pain medication use. Among those who experienced no work limitation, 61.4% (n=364) respondents were non-users of pain medications and those who experienced work limitation most of the time, 47.9% (n=45) respondents were chronic users of pain medications.

II. Frequency distribution of SF-12 productivity measures among post-treatment cancer survivors by opioid use

The number and percent of post-treatment cancer survivors across different categories of SF-12 productivity measure and opioid use are summarized in table 24. Total of 1.444 post-treatment cancer survivors were identified who filled out SF-12 questionnaire and the output in terms of frequency distribution of workers' productivity (none of the time, little/some of the time, most of the time, work limitation changes over time) and opioid use (none, acute, moderate, and chronic) obtained was:

(a) During past 4 weeks, as result of physical health, limited in kind of work or other activities?

Around 54.0 % of post-treatment cancer survivors experienced little (23.5%)/no work (30.6%) limitation; whereas, 14.0% respondents reported most of the time. Significant difference existed across various categories of productivity measures and opioid use. Among those who experienced no work limitation,

83.7% (n=370) respondents were non-users of opioids and those who experienced work limitation most of the time, 42.8% (n=86) respondents were non-users and 22.4% (n=45) were chronic users of opioids.

(b) During past 4 weeks, as result of mental problems, did work or other activities less carefully than usual?

Around 62.0 % of post-treatment cancer survivors experienced little (20.6%)/no work (41.5%) limitation; whereas, 5.1% respondents reported most of the time. Significant difference existed across various categories of productivity measures and opioid use. Among those who experienced no work limitation, 77.3% (n=464) respondents were non-users of opioids and those who experienced work limitation most of the time, 44.6% (n=33) respondents were non-users and 27.0% (n=20) were chronic users of opioids.

(c) During past 4 weeks, as result of physical problems, accomplished less than would like?

Around 54.0 % of post-treatment cancer survivors experienced little (27.6%)/no work (26.8%) limitation; whereas, 13.0% respondents reported most of the time. Significant difference existed across various categories of productivity measures and opioid use. Among those who experienced no work limitation, 83.0 % (n=321) respondents were non-users of opioids and those who experienced work limitation most of the time, 40.6% (n=76) respondents were non-users and 24.1% (n=45) were chronic users of opioids.

(d) During past 4 weeks, as result of mental problems, accomplished less than would like?

Around 62.0 % of post-treatment cancer survivors experienced little (21.0%)/no work (41.1%) limitation; whereas, 6.5% respondents reported most of the time. Significant difference existed across various categories of productivity measures and opioid use. Among those who experienced no work limitation, 75.4% (n=447) respondents were non-users of opioids and those who experienced work limitation most of the time, 39.4% (n=37) respondents were non-users and 28.7% (n=27) were chronic users of opioids.

4.3.2 Study 3b

I. Frequency distribution of CSAQ productivity measures among post-treatment cancer survivors by pain medication use

The number and percent of post-treatment cancer survivors across different categories of CSAQ productivity measure and pain medication use are summarized in table 25. The output in terms of frequency distribution of workers' productivity (yes/no) and pain medication use (none, acute, moderate, and chronic) obtained was:

(a) CSAQ, Q9: At any time from first cancer diagnosis until now, employed for pay at a job or business?

Around 63.0% (n=464) of post-treatment cancer survivors were employed for pay at job or business at any time since cancer diagnosis. Among those who were employed, 51.5% (n=239) were non-users and 15.5% (n=72) were chronic users of pain medication. However, the association was not significant.

(b) CSAQ, Q10: Work-related changes?

At any time since first cancer diagnosis, 50.0% (n=230) of post-treatment cancer survivors made work-related changes in hours, duties or employment status. Among those who made work-related changes 49.5% (n=114) were non-users and 14.4% (n=33) were chronic users of pain medication. However, the association was not significant.

(c) CSAQ, Q14: Extended time off from work?

Seventy percent (n=142) of post-treatment cancer survivors took extended time off from work including vacation, sick time, disability leave. Among those who took extended paid time off, 52.8% (n=75) were non-users and 11.3% (n=16) were chronic users of pain medication. However, the association was not significant.

(d) CSAQ, Q18: Unpaid time off from work?

Nearly 46.2% (n=92) of post-treatment cancer survivors took unpaid time off from work among which 46.7% (n=43) were non-users and 19.6% (n=18) were chronic users of pain medication. However, the association was not significant.

(e) CSAQ, Q26: Change in work schedule from full-time to part-time?

Around 80.0% (n=157) of post-treatment cancer survivors did not made changes in work schedule from full-time to part-time. Significant difference existed across various categories of productivity measure and pain medication use. Among those who made changes in work schedule 37.5% (n=15) were non-users and 10.0% (n=4) were chronic users of pain medication; among those who did not made changes in work schedule 53.5 % (n=84) were non-users and 14.7% (n=23) were chronic users of pain medications.

(f) CSAQ, Q32: Change to less demanding job?

Around 90.0% (n=179) of post-treatment cancer survivors did not change to less demanding job. A non-significant association was obtained across various categories of productivity measure and pain medication use.

(g) CSAQ, Q38: Retire earlier than planned?

Because of the cancer, its treatment, or the lasting effects of that treatment, 12.0% (n=54) retired earlier than planned. Among 88.0% (n=396) who did not took early retirement, 53.0% (n=210) were non-users and 15.6% (n=62) were chronic users of pain medications. However, the association was not significant.

(h) CSAQ, Q40: Malignancy interfered with ability to perform physical tasks required at job?

Significant difference existed across various categories of productivity measure and pain medication use. Nearly 75.0% (n=331) of post-treatment cancer survivors reported cancer, its treatment, or the lasting effects of that treatment did not interfered with ability to perform any physical tasks at job. Among these individuals 54.7% (n=181) were non-users and 16.3% (n=54) were chronic users of pain medication.

(i) CSAQ, Q41: Malignancy interfered with ability to perform mental tasks required at job?

Nearly 84.2% (n=379) of post-treatment cancer survivors reported cancer, its treatment, or the lasting effects of that treatment did not interfered with ability to perform any mental tasks at job. Among these individuals 52.5% (n=199) were non-users and 15.3% (n=58) were chronic users of pain medication. However, the association was not significant.

(j) CSAQ, Q42: Feel less productive at work?

Nearly 75.0% (n=336) of post-treatment cancer survivors reported cancer, its treatment, or the lasting effects of that treatment did not interfere with productivity at work. Among these individuals 53.6% (n=180) were non-users and 16.4% (n=55) were chronic users of pain medication. However, the association was not significant.

II. Frequency distribution of CSAQ productivity measures among post-treatment cancer survivors by opioid medication use

The number and percent of post-treatment cancer survivors across different categories of CSAQ productivity measure and opioid use are summarized in table 26. The output in terms of frequency distribution of workers' productivity (yes/no) and opioid medication use (none, acute, moderate, and chronic) obtained was:

(a) CSAQ, Q9: At any time from first cancer diagnosis until now, employed for pay at a job or business?

Around 63.0% (n=464) of post-treatment cancer survivors were employed for pay at job or business at any time since cancer diagnosis. Among those who were employed, 71.5% (n=332) were non-users and 5.0% (n=23) were chronic users of opioid medication. However, the association was not significant.

(b) CSAQ, Q10: Work-related changes?

At any time since first cancer diagnosis, 50.0% (n=230) of post-treatment cancer survivors made work-related changes in hours, duties or employment status. Among those who made these changes 71.7% (n=165) were non-users and 4.8% (n=11) were chronic users of opioid medication. However, the association was not significant.

(c) CSAQ, Q14: Extended time off from work?

Seventy percent (n=142) of post-treatment cancer survivors took extended time off from work including vacation, sick time, disability leave. Among those who took extended paid time off, 70.4% (n=100) were non-users and 5.6% (n=8) were chronic users of opioid medication. However, the association was not significant.

(d) CSAQ, Q18: Unpaid time off from work?

Nearly 46.2% (n=92) of post-treatment cancer survivors took unpaid time off from work among which 72.8% (n=67) were non-users and 6.5% (n=6) were chronic users of opioid medication. However, the association was not significant.

(e) CSAQ, Q26: Change in work schedule from full-time to part-time?

Around 80.0% (n=157) of post-treatment cancer survivors did not made changes in work schedule from full-time to part-time. A non-significant association was obtained across various categories of productivity measure and opioid medication use.

(f) CSAQ, Q32: Change to less demanding job?

Around 90.0% (n=179) of post-treatment cancer survivors did not change to less demanding job; among which 71.5% (n=128) were non-users and 4.5% (n=8) were chronic users of opioid medication. However, the association was not significant.

(g) CSAQ, Q38: Retire earlier than planned?

Because of the cancer, its treatment, or the lasting effects of that treatment, 12.0% (n=54) retired earlier than planned. Among 88.0% (n=396) who did not took early retirement, 71.7% (n=284) were non-users and 4.6% (n=18) were chronic users of opioid medications. However, the association was not significant.

(h) CSAQ, Q40: Malignancy interfered with ability to perform physical tasks required at job?

Nearly 75.0% (n=331) of post-treatment cancer survivors reported cancer, its treatment, or the lasting effects of that treatment did not interfered with ability to perform any physical tasks at job. Among these individuals 73.1% (n=242) were non-users and 4.8% (n=16) were chronic users of opioid medication. However, the association was not significant.

(i) CSAQ, Q41: Malignancy interfered with ability to perform mental tasks required at job?

Nearly 84.2% (n=379) of post-treatment cancer survivors reported cancer, its treatment, or the lasting effects of that treatment did not interfered with ability to perform any mental tasks at job. Among these individuals 71.5% (n=271) were non-users and 5.3% (n=20) were chronic users of opioid medication. However, the association was not significant.

(j) CSAQ, Q42: Feel less productive at work?

Nearly 75.0% (n=336) of post-treatment cancer survivors reported cancer, its treatment, or the lasting effects of that treatment did not interfere with productivity at work. Significant differences existed across various categories of productivity measure and opioid medication use. Among those 25.0% (n=113) who were less productive at work, 68.1% (n=77) were non-users of opioid medication; whereas, only a small proportion of respondents were chronic users (n=6, 5.4%). Among those who were productive at work, 73.2% (n=246) were non-users and only a small proportion of respondents were chronic users (n=17, 5.1%) of opioid medications.

Table 9: Trends In The Utilization, Cost, Payer Cost Share Of Pain Medication & HRQoL Among Cancer Survivors In The United States: MEPS 2008-2013

Variable	2008	2009	2010	2011	2012	2013	Pooled value	P- value
All pain medications								
Number of Prescriptions	60,337,930	63,921,183	70,459,547	76,202,304	70,983,895	74,357,694	69,377,092	
[a]Total Cost	$3,526,170,929	$4,172,461,779	$5,266,319,629	$5,354,120,936	$5,858,672,737	$5,562,460,125	$4,956,701,023	
Patient Cost Share	23.3%	23.4%	19.6%	22.7%	16.8%	17.0%	20.5%	
Non-opioids								
Number of Prescriptions	14,405,507 (23.9%)	14,727,948 (23.1%)	15,561,521 (22.1%)	17,559,654 (23.0%)	17,760,588 (25.0%)	19,030,913 (25.6%)	16,507,688 (23.8%)	*P<0.0001
[a]Total Cost (column %)	$638,918,411 (18.1%)	$724,290,027 (17.4%)	$771,581,042 (14.7%)	$728,236,872 (13.6%)	$705,348,705 (12.1%)	$1,022,932,969 (18.4%)	$765,218,004 (15.4%)	
Patient Cost Share	28.7%	22.0%	24.6%	33.1%	25.1%	21.9%	25.9%	
Narcotic analgesic combinations								
Number of Prescriptions	16,498,067 (27.3%)	15,459,300 (24.2%)	18,626,908 (26.4%)	17,367,750 (22.8%)	16,094,558 (22.7%)	16,597,602 (22.3%)	16,774,031 (24.2%)	*P<0.0001
[a]Total Cost (column %)	$390,212,826 (11.1%)	$397,890,175 (9.53%)	$440,495,174 (8.36%)	$442,015,293 (8.26%)	$756,313,416 (12.9%)	$482,162,299 (8.66%)	$484,848,197 (9.78%)	
Patient Cost Share	31.0%	38.2%	34.9%	36.5%	19.6%	37.6%	32.9%	
Opioids								
Number of Prescriptions	8,871,217 (14.7%)	11,320,402 (17.7%)	11,319,999 (16.1%)	15,290,470 (20.1%)	11,810,690 (16.6%)	11,614,612 (15.6%)	11,704,565 (16.8%)	*P<0.0001
[a]Total Cost (column %)	$811,497,948 (23.0%)	$1,033,619,627 (24.8%)	$1,565,885,163 (29.7%)	$2,143,362,186 (40.3%)	$1,708,384,386 (29.2%)	$755,905,153 (13.6%)	$1,336,442,411 (26.9%)	
Patient Cost Share	19.2%	20.8%	9.73%	14.0%	9.17%	15.7%	14.8%	
Adjuvant analgesics (for neuropathic pain)								
Number of Prescriptions	20,563,139 (34.1%)	22,413,533 (35.0%)	24,951,119 (35.4%)	25,984,431 (34.1%)	25,318,059 (35.7%)	27,114,567 (36.5%)	24,390,808 (35.2%)	*P<0.0001
[a]Total Cost (column %)	$1,685,541,744 (47.8%)	$2,016,661,950 (48.3%)	$2,488,358,251 (47.3%)	$2,040,506,585 (38.1%)	$2,688,626,230 (45.9%)	$3,301,459,704 (59.3%)	$2,370,192,411 (47.8%)	
Patient Cost Share	21.4%	22.3%	21.6%	24.9%	18.6%	12.8%	20.3%	
Cancer survivors (persons/year)								
Number, unweighted	1,951	2,226	2,008	2,173	2,262	2,138	2,126	
Number, weighted	23,432,809	24,072,895	23,638,906	25,192,189	25,093,319	24,760,993	24,365,185	
(%) Taking Pain Medication, weighted	40.8%	41.1%	42.4%	42.0%	41.6%	43.9%	42.0%	
HRQoL								
Number, unweighted	1,814	2,067	1,859	1,989	2,105	1,946	1,963	
Number, weighted	22,214,628	23,015,186	22,656,109	23,828,846	24,035,848	23,273,775	23,170,732	
Mental Health Score (SE)	50.2 (0.28)	50.1 (0.30)	50.4 (0.32)	50.1 (0.26)	49.9 (0.27)	50.7 (0.32)	50.2 (0.16)	[e]P<0.0001

Physical Health Score (SE)	44.0 (0.35)	43.8 (0.36)	43.8 (0.40)	44.3 (0.37)	43.6 (0.38)	44.2 (0.38)	43.9 (0.20)	€P<0.0001

~ Column % in parenthesis
~ Pooled value represents average estimates over the 6-year study period
~ SE = Standard Error
[a] All the costs are reported in actual years
* p-value is of chisquare test comparing the differences in the utilization of pain medications by different class across cancer survivors and individuals without cancer history
€ p-value is a of two sample t- test, comparing the weighted mean score across cancer survivors and individuals without cancer history

Table 10: Trends In The Utilization, Cost, Payer Cost Share Of Pain Medication & HRQoL Among Individuals Without Cancer History In The United States: MEPS 2008-2013

Variable	2008	2009	2010	2011	2012	2013	Pooled Value
All pain medications							
Number of Prescriptions	260,170,742	274,023,713	285,317,810	297,604,714	297,711,397	295,094,531	284,987,151
[a]Total Cost	$14,979,285,373	$15,653,152,049	$17,127,678,002	$16,238,475,599	$16,652,916,029	$17,758,952,518	$16,401,743,262
Patient Cost Share	25.5%	22.9%	21.3%	23.7%	22.6%	18.5%	22.4%
Non-opioids							
Number of Prescriptions	76,582,121 (29.4%)	75,597,928 (27.6%)	77,263,841 (27.1%)	81,741,104 (27.5%)	79,716,665 (26.7%)	83,805,080 (28.4%)	79,117,790 (27.8%)
[a]Total Cost (column %)	$3,145,685,772 (21.0%)	$2,736,248,614 (17.5%)	$2,584,705,770 (15.1%)	$2,831,343,271 (17.4%)	$2,574,029,658 (15.5%)	$2,827,200,522 (15.9%)	$2,783,202,268 (17.0%)
Patient Cost Share	27.5%	25.0%	26.3%	28.4%	28.0%	24.4%	26.6%
Narcotic analgesic combinations							
Number of Prescriptions	69,893,570 (26.9%)	69,666,981 (25.4%)	77,184,386 (27.1%)	68,432,534 (23.0%)	67,138,720 (22.6%)	67,365,351 (22.8%)	69,946,924 (24.5%)
[a]Total Cost (column %)	$1,798,896,838 (12.0%)	$1,601,642,479 (10.2%)	$2,182,578,202 (12.7%)	$2,220,610,726 (13.7%)	$2,501,537,430 (15.0%)	$2,881,892,486 (16.2%)	$2,197,859,694 (13.4%)
Patient Cost Share	39.2%	39.8%	33.9%	27.7%	27.2%	21.6%	31.6%
Opioids							
Number of Prescriptions	30,740,533 (11.8%)	32,736,863 (11.9%)	34,971,623 (12.2%)	44,753,859 (15.0%)	44,327,048 (14.9%)	39,599,338 (13.4%)	37,854,877 (13.3%)
Total Cost	$2,940,102,846 (19.6%)	$2,770,273,067 (17.7%)	$2,742,910,415 (16.0%)	$3,996,024,729 (24.6%)	$3,274,671,609 (19.7%)	$2,502,553,857 (14.1%)	$3,037,756,087 (18.5%)
Patient Cost Share	20.2%	16.5%	16.4%	16.2%	15.8%	21.0%	17.7%
Adjuvant analgesics (for neuropathic pain)							

Number of Prescriptions	82,954,518 (31.9%)	96,021,941 (35.1%)	95,897,960 (33.6%)	102,677,216 (34.5%)	106,528,964 (35.8%)	104,324,761 (35.4%)	98,067,560 (34.4%)
[a]Total Cost (column %)	$7,094,599,917 (47.4%)	$8,544,987,889 (54.6%)	$9,617,483,616 (56.2%)	$7,190,496,873 (44.3%)	$8,302,677,332 (49.8%)	$9,547,305,653 (53.8%)	$8,382,925,213 (51.1%)
Patient Cost Share	23.4%	21.3%	18.5%	24.7%	22.2%	15.2%	20.9%
Individuals without cancer history (persons/year)							
Number, unweighted	21,165	23,722	21,369	22,979	25,488	24,124	23,141
Number, weighted	203,906,845	205,111,953	207,477,305	209,329,107	211,960,168	214,386,192	208,695,262
(%) Taking Pain Medication, weighted	22.7%	22.9%	22.9%	22.7%	21.7%	23.7%	22.8%
HRQoL							
Number, unweighted	18,495	20,822	18,742	20,237	22,747	20,828	20,312
Number, weighted	189,627,314	190,745,727	192,046,883	193,802,402	199,007,320	196,053,415	193,547,177
Mental Health Score (SE)	51.0 (0.10)	51.0 (0.09)	51.2 (0.11)	51.0 (0.09)	51.2 (0.09)	51.8 (0.10)	51.2 (0.05)
Physical Health Score (SE)	50.2 (0.11)	50.1 (0.11)	50.1 (0.12)	49.9 (0.11)	49.7 (0.11)	49.9 (0.12)	50.0 (0.07)

~ Column % in parenthesis
~ Pooled value represents average estimates over the 6-year study period
~ SE=Standard Error
[a] All the costs are reported in actual years
* p-value is of chisquare test comparing the differences in the utilization of pain medications by different class across cancer survivors and individuals without cancer history
[€] p-value is a of two sample t- test, comparing the weighted mean score across cancer survivors and individuals without cancer history

Table 11: Utilization Of Pain Medication and HRQoL For Cancer Survivors Over The 6-Year period January 2008-December 2013 Stratified By Demographic Variables

Characteristics		Pain medications					HRQoL		
		All Pain medications (Column %)	Non-opioids (Row %)	Narcotic analgesics combinations (Row %)	Opioids (Row %)	Adjuvant analgesics (Row %)	n Weighted (Column %)	MCS (SE)	PCS (SE)
All Cancer Survivors		69,377,092	16,507,688 (23.8%)	16,774,031 (24.2%)	11,704,565 (16.9%)	24,390,808 (35.2%)	23,170,732	50.2 (0.16)	43.9 (0.20)
Age (years)	≤ 55	26,610,304 (38.4%)	5,612,755 (21.1%)	7,517,134 (28.2%)	4,459,831 (16.8%)	9,020,584 (33.9%)	8,217,786 (35.5%)	48.3 (0.24)	48.0 (0.31)
	56 - 65	19,178,320 (27.6%)	4,368,095 (22.8%)	4,337,183 (22.6%)	3,226,375 (16.8%)	7,246,667 (37.8%)	5,326,130 (23.0%)	50.2 (0.34)	44.2 (0.41)
	66 - 75	13,826,868 (19.9%)	3,756,747 (27.2%)	2,882,171 (20.8%)	2,290,880 (16.6%)	4,897,070 (35.4%)	5,042,714 (21.8%)	52.2 (0.29)	42.9 (0.33)
	≥ 76	9,761,600 (14.1%)	2,770,091 (28.4%)	2,037,543 (20.9%)	1,727,479 (17.7%)	3,226,487 (33.1%)	4,584,102 (19.8%)	51.5 (0.30)	37.4 (0.37)
Sex	Men	21,867,893 (31.5%)	6,067,481 (27.7)	5,486,702 (25.1%)	4,040,669 (18.5%)	6,273,041 (28.7%)	8,919,986 (38.5%)	51.3 (0.25)	43.5 (0.32)
	Women	47,509,199 (68.5%)	10,440,207 (22.0%)	11,287,329 (23.8%)	7,663,896 (16.1%)	18,117,767 (38.1%)	14,250,746 (61.5%)	49.6 (0.19)	44.2 (0.25)
Race/ Ethnicity	White, non-Hispanic	56,903,433 (82.0%)	12,687,437 (22.3%)	13,641,873 (24.0%)	9,530,834 (16.7%)	21,043,289 (37.0%)	19,201,520 (82.9%)	50.5 (0.18)	44.1 (0.23)
	Blacks, non-Hispanic	5,573,463 (8.0%)	1,770,864 (31.8%)	1,570,060 (28.2%)	870,935 (15.6%)	1,361,604 (24.4%)	1,835,290 (7.9%)	48.9 (0.33)	41.6 (0.45)
	Hispanic	4,293,002 (6.2%)	1,453,081 (33.8%)	979,363 (22.8%)	762,612 (17.8%)	1,097,946 (25.6%)	1,346,984 (5.8%)	47.6 (0.47)	44.4 (0.44)
	Other/multiple, non-Hispanic	2,607,194 (3.8%)	596,306 (22.9%)	582,735 (22.4%)	540,184 (20.7%)	887,969 (34.1%)	786,938 (3.4%)	49.7 (0.65)	43.9 (0.71)
Education	< High school	9,781,635 (14.1%)	2,353,594 (24.1%)	2,854,937 (29.2%)	1,802,736 (18.4%)	2,770,368 (28.3%)	2,529,178 (10.9%)	47.5 (0.40)	38.2 (0.41)
	High school graduate	30,470,453 (43.9%)	7,146,338 (23.5%)	7,889,476 (25.9%)	5,495,329 (18.0%)	9,939,310 (32.6%)	9,158,646 (39.5%)	49.7 (0.25)	42.4 (0.27)
	Some college or more	17,246,537 (24.9%)	4,351,184 (25.2%)	3,461,490 (20.1%)	2,487,107 (14.4%)	6,946,756 (40.3%)	9,425,325 (40.7%)	51.6 (0.21)	47.1 (0.24)
	Other*	11,878,467 (17.1%)	2,656,572 (22.4%)	2,568,128 (21.6%)	1,919,393 (16.2%)	4,734,374 (39.9%)	2,057,583 (8.9%)	49.7 (0.45)	42.8 (0.49)
Marital status	Married	37,702,560 (54.3%)	8,949,510 (23.7%)	8,599,339 (22.8%)	6,253,421 (16.6%)	13,900,290 (36.9%)	13,627,340 (58.8%)	51.3 (0.19)	44.9 (0.26)
	Widowed/Divorced/Separated	24,962,595 (36.0%)	5,977,695 (23.9%)	6,366,190 (25.5%)	4,344,554 (17.4%)	8,274,156 (33.1%)	7,035,269 (30.4%)	49.1 (0.28)	40.8 (0.33)
	Never Married	6,711,937 (9.7%)	1,580,483 (23.5%)	1,808,502 (26.9%)	1,106,590 (16.5%)	2,216,362 (33.0%)	2,508,123 (10.8%)	47.6 (0.45)	47.1 (0.54)

*Other includes value that are not ascertained, inapplicable, respondent don't know or refused
- Percentage or SE mentioned in parenthesis

Table 12: Utilization Of Pain Medication and HRQoL For Individuals Without Cancer History Over The 6-Year period January 2008- December 2013 Stratified By Demographic Variables

Characteristics		Pain medications					HRQoL		
		All Pain medications (Column %)	Non-opioids (Row %)	Narcotic analgesics combinations (Row %)	Opioids (Row %)	Adjuvant analgesics (Row %)	n Weighted (Column %)	MCS (SE)	PCS (SE)
Individuals without cancer history		284,987,151	79,117,790 (27.8%)	69,946,924 (24.5%)	37,854,877 (13.3%)	98,067,560 (34.4%)	193,547,177	51.2 (0.05)	50.0 (0.07)
Age (years)	≤ 55	161,048,763 (56.5%)	38,877,566 (24.1%)	43,175,204 (26.8%)	22,060,669 (13.7%)	56,935,324 (35.4%)	138,490,349 (71.6%)	50.8 (0.06)	52.1 (0.06)
	56 - 65	63,088,786 (22.1%)	19,482,632 (30.9%)	14,055,401 (22.3%)	8,286,788 (13.1%)	21,263,965 (33.7%)	28,617,282 (14.8%)	51.4 (0.12)	46.8 (0.16)
	66 - 75	36,991,043 (13.0%)	12,307,189 (33.3%)	7,603,480 (20.6%)	4,658,754 (12.6%)	12,421,620 (33.6%)	15,285,973 (7.9%)	53.1 (0.16)	44.2 (0.20)
	≥ 76	23,858,559 (8.4%)	8,450,403 (35.4%)	5,112,839 (21.4%)	2,848,666 (11.9%)	7,446,651 (31.2%)	11,153,573 (5.8%)	51.7 (0.22)	39.2 (0.22)
Sex	Men	108,381,377 (38.0%)	31,192,064 (28.8%)	29,032,347 (26.8%)	15,926,115 (14.7%)	32,230,851 (29.7%)	94,912,769 (49.0%)	52.0 (0.06)	50.7 (0.07)
	Women	176,605,774 (62.0%)	47,925,726 (27.1%)	40,914,577 (23.2%)	21,928,762 (12.4%)	65,836,709 (37.3%)	98,634,408 (51.0%)	50.4 (0.07)	49.3 (0.09)
Race/ Ethnicity	White, non-Hispanic	209,306,982 (73.4%)	50,095,635 (23.9%)	51,495,671 (24.6%)	29,170,749 (13.9%)	78,544,927 (37.5%)	126,874,880 (65.6%)	51.1 (0.07)	49.9 (0.08)
	Blacks, non-Hispanic	31,292,616 (11.0%)	11,329,948 (36.2%)	9,004,299 (28.8%)	3,465,058 (11.1%)	7,493,311 (23.9%)	22,851,428 (11.8%)	51.4 (0.11)	48.9 (0.14)
	Hispanic	30,246,650 (10.6%)	12,610,140 (41.7%)	6,494,802 (21.5%)	3,079,837 (10.2%)	8,061,871 (26.7%)	29,663,920 (15.3%)	50.9 (0.11)	51.0 (0.13)
	Other/multiple, non-Hispanic	14,140,903 (5.0%)	5,082,067 (35.9%)	2,952,152 (20.9%)	2,139,233 (15.1%)	3,967,451 (28.1%)	14,156,949 (7.3%)	51.6 (0.16)	50.6 (0.16)
Education	< High school	43,739,655 (15.3%)	14,813,300 (33.9%)	11,670,022 (26.7%)	5,393,667 (12.3%)	11,862,667 (27.1%)	27,251,394 (14.1%)	49.9 (0.12)	47.6 (0.17)
	High school graduate	122,927,699 (43.1%)	31,875,093 (25.9%)	32,562,094 (26.5%)	16,283,415 (13.2%)	42,207,097 (34.3%)	78,079,943 (40.3%)	51.0 (0.07)	49.4 (0.08)
	Some college or more	68,114,146 (23.9%)	18,546,829 (27.2%)	14,555,778 (21.4%)	8,881,837 (13.0%)	26,129,702 (38.4%)	70,346,030 (36.3%)	52.0 (0.07)	51.8 (0.08)
	Other*	50,205,651 (17.6%)	13,882,568 (27.7%)	11,159,030 (22.2%)	7,295,959 (14.5%)	17,868,094 (35.6%)	17,869,811 (9.2%)	51.1 (0.12)	49.3 (0.16)
Marital status	Married	144,886,946 (50.8%)	40,125,800 (27.7%)	35,807,083 (24.7%)	18,786,072 (13.0%)	50,167,991 (34.6%)	102,067,520 (52.7%)	52.1 (0.06)	50.0 (0.07)
	Widowed/Divorced/Separated	94,343,886 (33.1%)	26,598,821 (28.2%)	22,482,789 (23.8%)	13,116,369 (13.9%)	32,145,907 (34.1%)	37,184,531(19.2%)	49.4 (0.11)	45.9 (0.16)
	Never Married	45,756,319 (16.1%)	12,393,169 (27.1%)	11,657,052 (25.5%)	5,952,436 (13.0%)	15,753,662 (34.4%)	54,295,126 (28.1%)	50.8 (0.09)	52.8 (0.08)

*Other includes value that are not ascertained, inapplicable, respondent don't know or refused
- Percentage or SE mentioned in parenthesis

Table 13: Utilization Of Pain Medication and HRQoL For Cancer Survivors Over The 6-Year period January 2008-December 2013 Stratified By Geographic Variables

Characteristics		Pain medications					HRQoL		
		All Pain medications (Column %)	Non-opioids (Row %)	Narcotic analgesics combinations (Row %)	Opioids (Row %)	Adjuvant analgesics (Row %)	n Weighted (Column %)	MCS (SE)	PCS (SE)
All Cancer Survivors		69,377,092	16,507,688 (23.8%)	16,774,031 (24.2%)	11,704,565 (16.9%)	24,390,808 (35.2%)	23,170,732	50.2 (0.16)	43.9 (0.20)
Geographic region	Northeast	10,893,942 (15.7%)	3,566,044 (32.7%)	2,068,372 (19.0%)	1,302,695 (12.0%)	3,956,831 (36.3%)	4,289,842 (18.5%)	50.7 (0.41)	44.9 (0.60)
	Midwest	17,175,903 (24.8%)	3,924,042 (22.8%)	4,058,095 (23.6%)	3,233,567 (18.8%)	5,960,199 (34.7%)	5,425,808 (23.4%)	50.5 (0.38)	43.7 (0.42)
	South	27,262,665 (39.3%)	5,944,418 (21.8%)	7,434,549 (27.3%)	4,437,294 (16.3%)	9,446,404 (34.6%)	8,618,732 (37.2%)	49.9 (0.24)	43.1 (0.31)
	West	14,044,582 (20.2%)	3,073,184 (21.9%)	3,213,015 (22.9%)	2,731,009 (19.4%)	5,027,374 (35.8%)	4,836,350 (20.9%)	49.9 (0.30)	44.6 (0.34)
Metropolitan statistical area+	Yes	52,014,940 (75.0%)	12,626,390 (24.3%)	12,387,696 (23.8%)	8,967,824 (17.2%)	18,033,030 (34.7%)	15,975,262 (68.9%)	50.2 (0.19)	44.3 (0.24)
	No	14,301,633 (20.6%)	3,034,948 (21.2%)	3,604,541 (25.2%)	2,290,163 (16.0%)	5,371,981 (37.6%)	3,316,508 (14.3%)	49.7 (0.42)	41.9 (0.51)
	Other*	3,060,519 (4.4%)	846,350 (27.7%)	781,794 (25.5%)	446,578 (14.6%)	985,797 (32.2%)	3,878,962 (16.7%)	50.7 (0.32)	44.1 (0.37)

*Other includes value that are not ascertained, inapplicable, respondent don't know or refused
+ Variable MSA was not available for year 2013

Table 14: Utilization Of Pain Medication and HRQoL For Individuals Without Cancer History Over The 6-Year period January 2008- December 2013 Stratified By Geographic Variables

Characteristics		Pain medications					HRQoL		
		All Pain medications (Column %)	Non-opioids (Row %)	Narcotic analgesics combinations (Row %)	Opioids (Row %)	Adjuvant analgesics (Row %)	n Weighted (Column %)	MCS (SE)	PCS (SE)
Individuals without cancer history		284,987,151	79,117,790 (27.8%)	69,946,924 (24.5%)	37,854,877 (13.3%)	98,067,560 (34.4%)	193,547,177	51.2 (0.05)	50.0 (0.07)
Geographic region	Northeast	44,643,543 (15.7%)	13,282,637 (29.8%)	9,396,745 (21.0%)	5,903,497 (13.2%)	16,060,664 (36.0%)	34,721,797 (17.9%)	51.4 (0.15)	50.4 (0.16)
	Midwest	67,581,641 (23.7%)	18,107,988 (26.8%)	16,710,174 (24.7%)	8,174,991 (12.1%)	24,588,488 (36.4%)	41,876,198 (21.6%)	51.1 (0.11)	50.1 (0.17)
	South	110,904,804 (38.9%)	29,446,345 (26.6%)	28,943,692 (26.1%)	15,567,249 (14.0%)	36,947,518 (33.3%)	71,913,075 (37.2%)	51.3 (0.09)	49.5 (0.11)
	West	61,857,163 (21.7%)	18,280,820 (29.6%)	14,896,313 (24.1%)	8,209,140 (13.3%)	20,470,890 (33.1%)	45,036,108 (23.3%)	50.9 (0.11)	50.4 (0.14)
Metropolitan statistical area+	Yes	213,593,372 (74.9%)	59,543,149 (27.9%)	52,314,174 (24.5%)	28,145,269 (13.2%)	73,590,780 (34.5%)	135,907,060 (70.2%)	51.1 (0.06)	50.3 (0.07)
	No	57,630,228 (20.2%)	15,435,907 (26.8%)	14,170,579 (24.6%)	8,010,834 (13.9%)	20,012,908 (34.7%)	24,964,547 (12.9%)	50.8 (0.15)	48.3 (0.21)
	Other*	13,763,551 (4.8%)	4,138,734 (30.1%)	3,462,171 (25.2%)	1,698,774 (12.3%)	4,463,872 (32.4%)	32,675,569 (16.9%)	51.8 (0.09)	50.0 (0.11)

*Other includes value that are not ascertained, inapplicable, respondent don't know or refused
+ Variable MSA was not available for year 2013

Table 15: Utilization Of Pain Medication and HRQoL For Cancer Survivors Over The 6-Year period January 2008-December 2013 Stratified By Clinical Variables

Characteristics		Pain medications					HRQoL		
		All Pain medications (Column %)	Non-opioids (Row %)	Narcotic analgesics combinations (Row %)	Opioids (Row %)	Adjuvant analgesics (Row %)	n Weighted (Column %)	MCS (SE)	PCS (SE)
All Cancer Survivors		69,377,092	16,507,688 (23.8%)	16,774,031 (24.2%)	11,704,565 (16.9%)	24,390,808 (35.2%)	23,170,732	50.2 (0.16)	43.9 (0.20)
Smoking status	Yes	18,202,274 (26.2%)	3,452,191 (19.0%)	5,379,311 (29.6%)	3,442,344 (18.8%)	5,928,428 (32.6%)	3,538,924 (15.3%)	45.5 (0.43)	41.6 (0.46)
	No	47,806,447 (68.9%)	12,230,156 (25.6%)	10,567,010 (22.1%)	7,608,178 (15.9%)	17,401,103 (36.4%)	19,272,815 (83.2%)	51.2 (0.16)	44.4 (0.21)
	Other*	3,368,371 (4.9%)	825,341 (24.5%)	827,710 (24.6%)	654,043 (19.4%)	1,061,277 (31.5%)	358,993 (1.5%)	47.7 (0.87)	40.2 (1.13)
BMI, kg/m^2	Obese, ≥ 30.0	29,759,902 (42.9%)	7,563,675 (25.4%)	7,448,791 (25.0%)	4,098,333 (13.8%)	10,649,103 (35.8%)	7,051,416 (30.4%)	49.7 (0.26)	40.7 (0.31)
	Overweight, 25.0 – 29.9	20,433,661 (29.5%)	4,941,587 (24.2%)	4,667,615 (22.8%)	3,391,497 (16.6%)	7,432,962 (36.4%)	7,748,890 (33.4%)	51.0 (0.27)	45.2 (0.32)
	Normal, 18.5 – 24.9	15,446,185 (22.3%)	3,518,384 (22.8%)	3,837,401 (24.8%)	3,118,987 (20.2%)	4,971,413 (32.2%)	7,309,237 (31.5%)	50.3 (0.24)	46.4 (0.30)
	Underweight, < 18.5	1,310,501 (1.9%)	70,075 (5.3%)	403,765 (30.8%)	461,094 (35.2%)	375,567 (28.7%)	316,066 (1.4%)	48.7 (0.97)	41.6 (1.34)
	Other*	2,426,843 (3.5%)	413,967 (17.0%)	416,459 (17.2%)	634,654 (26.2%)	961,763 (39.6%)	745,123 (3.2%)	47.8 (0.66)	38.3 (0.86)
Pain perception- During past 4 weeks, pain interfered with normal work outside the home and housework?	Extremely/ quite a bit	32,851,696 (47.4%)	6,106,293 (18.6%)	9,079,140 (27.6%)	7,311,416 (22.3%)	10,354,847 (31.5%)	4,356,543 (18.8%)	43.5 (0.39)	26.5 (0.21)
	Moderately	12,539,758 (18.1%)	2,872,438 (22.9%)	2,694,410 (21.5%)	2,052,609 (16.4%)	4,920,301 (39.2%)	3,487,349 (15.1%)	48.9 (0.36)	37.4 (0.25)
	A little bit	12,751,449 (18.4%)	3,955,846 (31.0%)	2,501,279 (19.6%)	978,532 (7.7%)	5,315,792 (41.7%)	6,623,374 (28.6%)	51.2 (0.25)	46.2 (0.18)
	No pain	8,604,721 (12.4%)	2,873,399 (33.4%)	1,795,631 (20.8%)	874,194 (10.2%)	3,061,497 (35.6%)	8,638,038 (37.3%)	53.4 (0.15)	53.7 (0.14)
	Other*	2,629,468	699,712	703,571	487,814	738,371	65,429	48.4 (2.23)	37.0 (3.11)

			(3.8%)	(26.6%)	(26.8%)	(18.6%)	(28.0%)	(0.3%)		
Chronic conditions	Arthritis		48,016,518 (69.2%)	12,032,640 (25.1%)	11,546,466 (24.1%)	9,099,064 (18.9%)	15,338,348 (31.9%)	9,670,756 (41.7%)	48.8 (0.27)	38.4 (0.28)
	Asthma		12,505,753 (18.0%)	2,546,990 (20.4%)	2,841,715 (22.7%)	2,288,658 (18.3%)	4,828,390 (38.6%)	2,040,760 (8.8%)	46.7 (0.44)	36.2 (0.59)
	Chronic Bronchitis		13,266,105 (19.1%)	2,918,671 (22.0%)	3,187,489 (24.1%)	2,431,618 (18.3%)	4,728,327 (35.6%)	2,640,443 (11.4%)	47.5 (0.47)	35.6 (0.50)
	Diabetes		16,291,998 (23.5%)	3,945,145 (24.2%)	3,333,297 (20.5%)	2,982,113 (18.3%)	6,031,442 (37.0%)	3,938,284 (17.0%)	49.2 (0.38)	37.1 (0.39)
	Heart disease		12,867,612 (18.5%)	3,234,510 (25.1%)	2,847,887 (22.1%)	2,734,360 (21.2%)	4,050,855 (31.5%)	3,386,844 (14.6%)	49.4 (0.41)	35.2 (0.46)
	Hypertension		38,738,628 (55.8%)	10,176,525 (26.3%)	8,989,083 (23.2%)	6,310,347 (16.3%)	13,262,673 (34.2%)	10,997,232 (47.5%)	50.1 (0.23)	39.9 (0.28)
	Stroke		602,339 (0.9%)	74,449 (12.4%)	135,217 (22.4%)	6,229 (1.0%)	386,444 (64.2%)	137,853 (0.6%)	51.0 (1.58)	35.5 (2.43)
	High cholesterol		34,119,798 (49.2%)	8,587,275 (25.2%)	7,717,468 (22.6%)	5,377,946 (15.8%)	12,437,109 (36.5%)	9,566,847 (41.3%)	50.3 (0.25)	40.8 (0.30)
Number of other known MEPS priority conditions, excluding cancer		3+	34,292,789 (49.4%)	8,660,377 (25.3%)	7,790,839 (22.7%)	6,091,151 (17.8%)	11,750,422 (34.3%)	7,486,428 (32.3%)	49.2 (0.28)	36.7 (0.30)
		2	15,651,410 (22.6%)	3,677,496 (23.5%)	3,668,097 (23.4%)	2,797,528 (17.9%)	5,508,289 (35.2%)	4,675,276 (20.2%)	50.4 (0.34)	43.0 (0.34)
		1	11,251,471 (16.2%)	2,718,367 (24.2%)	2,865,219 (25.5%)	1,753,606 (15.6%)	3,914,280 (34.7%)	5,006,966 (21.6%)	50.5 (0.28)	46.7 (0.30)
		0	8,181,423 (11.8%)	1,451,449 (17.8%)	2,449,876 (29.9%)	1,062,280 (13.0%)	3,217,818 (39.3%)	6,002,062 (25.9%)	51.2 (0.24)	51.2 (0.23)
Type of cancer+	Head/Neck		3,815,304 (5.5%)	732,356 (19.2%)	867,858 (22.7%)	466,368 (12.2%)	1,748,722 (45.8%)	1,023,784 (4.4%)	48.9 (0.55)	42.4 (0.70)
	Gastrointestinal		4,620,820 (6.7%)	1,103,686 (23.9%)	1,237,653 (26.8%)	949,370 (20.5%)	1,330,111 (28.8%)	1,599,193 (6.9%)	48.7 (0.56)	38.5 (0.65)
	Lung/bronchus		2,242,270 (3.2%)	319,202 (14.2%)	680,551 (30.4%)	557,021 (24.8%)	685,496 (30.6%)	601,549 (2.6%)	48.0 (0.86)	34.1 (0.88)
	Breast		10,802,966 (15.6%)	3,123,333 (28.9%)	2,174,157 (20.1%)	1,621,031 (15.0%)	3,884,446 (36.0%)	3,535,696 (15.3%)	50.6 (0.37)	43.2 (0.37)
	Gynecological		10,278,047	2,014,627	2,756,441	1,856,676	3,650,302	2,850,267	47.5 (0.40)	43.4 (0.49)

		(14.8%)	(19.6%)	(26.8%)	(18.1%)	(35.5%)	(12.3%)		
	Prostate	4,970,147 (7.2%)	1,824,363 (36.7%)	1,112,393 (22.4%)	775,119 (15.6%)	1,258,273 (25.3%)	2,708,550 (11.7%)	52.4 (0.33)	42.9 (0.50)
	Urogenital	4,348,883 (6.3%)	773,197 (17.8%)	1,209,850 (27.8%)	1,074,213 (24.7%)	1,291,623 (29.7%)	1,066,457 (4.6%)	49.9 (0.80)	40.1 (0.79)
	Hematological	3,241,765 (4.7%)	724,060 (22.3%)	751,056 (23.2%)	848,591 (26.2%)	918,057 (28.3%)	1,040,326 (4.5%)	49.2 (0.70)	40.7 (0.73)
	Bone	848,471 (1.2%)	190,813 (22.5%)	193,236 (22.8%)	299,141 (35.3%)	165,281 (19.5%)	195,095 (0.8%)	46.8 (1.79)	38.0 (1.95)
	Skin	4,405,944 (6.4%)	1,049,562 (23.8%)	1,159,620 (26.3%)	387,553 (8.8%)	1,809,209 (41.1%)	1,906,152 (8.2%)	52.2 (0.51)	44.4 (0.68)
	Others and Unspecified	23,540,190 (33.9%)	5,171,832 (22.0%)	5,343,184 (22.7%)	3,997,532 (17.0%)	9,027,641 (38.3%)	9,914,780 (42.8%)	50.3 (0.23)	45.4 (0.29)
Cancer status	Currently diagnosed	40,412,151 (58.2%)	10,027,715 (24.8%)	9,871,643 (24.4%)	6,670,680 (16.5%)	13,842,113 (34.3%)	15,735,657 (67.9%)	50.5 (0.25)	44.5 (0.29)
	Previously diagnosed	28,964,941 (41.8%)	6,479,973 (22.4%)	6,902,388 (23.8%)	5,033,885 (17.4%)	10,548,695 (36.4%)	7,435,075 (32.1%)	49.7 (0.27)	43.5 (0.34)
Years since first cancer diagnosis	> 10	18,906,809 (27.3%)	4,075,283 (21.6%)	4,196,048 (22.2%)	3,405,602 (18.0%)	7,229,876 (38.2%)	5,189,041 (22.4%)	49.4 (0.30)	42.2 (0.36)
	6 - 10	9,973,842 (14.4%)	2,211,327 (22.2%)	2,156,198 (21.6%)	1,808,961 (18.1%)	3,797,356 (38.1%)	2,909,143 (12.6%)	50.8 (0.41)	43.3 (0.38)
	2 - 5	10,848,280 (15.6%)	3,131,809 (28.9%)	2,710,204 (25.0%)	1,974,467 (18.2%)	3,031,800 (27.9%)	3,479,715 (15.0%)	50.3 (0.38)	42.7 (0.43)
	< 2	20,286,476 (29.2%)	4,830,030 (23.8%)	5,599,036 (27.6%)	2,959,940 (14.6%)	6,897,470 (34.0%)	10,096,009 (43.6%)	50.5 (0.22)	45.5 (0.28)
	Other*	9,361,685 (13.5%)	2,259,239 (24.1%)	2,112,545 (22.6%)	1,555,595 (16.6%)	3,434,306 (36.7%)	1,496,823 (6.5%)	49.9 (0.47)	43.2 (0.68)

*Other includes value that are not ascertained, inapplicable, respondent don't know or refused
+ Types of cancer includes individuals currently diagnosed and/or diagnosed in past

Table 16: Utilization Of Pain Medication and HRQoL For Individuals Without Cancer History Over The 6-Year period January 2008- December 2013 Stratified By Clinical Variables

Characteristics		Pain medications					HRQoL		
		All Pain medications (Column %)	Non-opioids (Row %)	Narcotic analgesics combinations (Row %)	Opioids (Row %)	Adjuvant analgesics (Row %)	n Weighted (Column %)	MCS (SE)	PCS (SE)
Individuals without cancer history		284,987,151	79,117,790 (27.8%)	69,946,924 (24.5%)	37,854,877 (13.3%)	98,067,560 (34.4%)	193,547,177	51.2 (0.05)	50.0 (0.07)
Smoking status	Yes	75,496,009 (26.5%)	16,233,165 (21.5%)	20,815,589 (27.6%)	13,013,218 (17.2%)	25,434,037 (33.7%)	35,545,023 (18.4%)	48.4 (0.11)	48.4 (0.14)
	No	196,581,984 (69.0%)	59,521,492 (30.3%)	45,492,759 (23.1%)	23,147,237 (11.8%)	68,420,496 (34.8%)	155,565,014 (80.4%)	51.9 (0.05)	50.4 (0.07)
	Other*	12,909,158 (4.5%)	3,363,133 (26.1%)	3,638,576 (28.2%)	1,694,422 (13.1%)	4,213,027 (32.6%)	2,437,139 (1.3%)	49.7 (0.32)	47.5 (0.37)
BMI, kg/m^2	Obese, ≥ 30.0	121,624,090 (42.7%)	35,716,573 (29.4%)	29,358,689 (24.1%)	15,422,358 (12.7%)	41,126,470 (33.8%)	56,521,924 (29.2%)	50.4 (0.08)	47.0 (0.10)
	Overweight, 25.0 – 29.9	87,381,465 (30.7%)	24,472,939 (28.0%)	21,301,876 (24.4%)	11,175,588 (12.8%)	30,431,062 (34.8%)	65,093,216 (33.6%)	51.7 (0.07)	50.6 (0.08)
	Normal, 18.5 – 24.9	65,533,034 (23.0%)	16,364,940 (25.0%)	16,725,306 (25.5%)	9,787,675 (14.9%)	22,655,113 (34.6%)	64,334,184 (33.2%)	51.5 (0.07)	52.2 (0.09)
	Underweight, < 18.5	4,543,008 (1.6%)	960,591 (21.1%)	1,028,905 (22.6%)	811,153 (17.9%)	1,742,359 (38.4%)	3,196,231 (1.7%)	49.6 (0.35)	49.4 (0.39)
	Other*	5,905,554 (2.1%)	1,602,747 (27.1%)	1,532,148 (25.9%)	658,103 (11.1%)	2,112,556 (35.8%)	4,401,622 (2.3%)	50.5 (0.27)	47.7 (0.36)
Pain perception- During past 4 weeks, pain interfered with normal work outside the home and housework?	Extremely/ quite a bit	117,691,819 (41.3%)	27,896,365 (23.7%)	32,383,498 (27.5%)	22,412,455 (19.1%)	34,999,501 (29.7%)	19,857,464 (10.3%)	43.8 (0.17)	30.0 (0.13)
	Moderately	45,893,320 (16.1%)	13,858,244 (30.2%)	11,216,162 (24.4%)	5,514,202 (12.1%)	15,304,712 (33.3%)	18,648,466 (9.6%)	48.1 (0.14)	40.6 (0.11)
	A little bit	56,423,399 (19.8%)	18,695,096 (33.1%)	11,675,356 (20.7%)	4,612,963 (8.2%)	21,439,984 (38.0%)	46,470,062 (24.0%)	50.4 (0.09)	49.0 (0.06)
	No pain	53,924,587 (18.9%)	15,661,242 (29.0%)	11,630,577 (21.6%)	3,844,659 (7.1%)	22,788,109 (42.3%)	108,125,380 (55.9%)	53.4 (0.05)	55.7 (0.04)

	Other*		11,054,026 (3.9%)	3,006,843 (27.2%)	3,041,331 (27.5%)	1,470,598 (13.3%)	3,535,254 (32.0%)	445,805 (0.2%)	47.4 (0.79)	46.9 (0.80)
Chronic conditions	Arthritis		179,642,444 (63.0%)	54,152,236 (30.1%)	43,518,873 (24.3%)	28,233,098 (15.7%)	53,738,238 (29.9%)	45,402,734 (23.5%)	48.9 (0.11)	42.1 (0.14)
	Asthma		37,262,023 (13.1%)	10,103,409 (27.1%)	8,979,179 (24.1%)	5,146,867 (13.8%)	13,032,569 (35.0%)	11,306,389 (5.8%)	48.2 (0.20)	43.8 (0.27)
	Chronic Bronchitis		37,604,785 (13.2%)	8,864,426 (23.6%)	10,352,225 (27.5%)	5,624,524 (15.0%)	12,763,610 (33.9%)	10,772,784 (5.6%)	47.8 (0.23)	41.9 (0.29)
	Diabetes		61,100,149 (21.4%)	18,211,664 (29.8%)	13,192,642 (21.6%)	7,345,648 (12.0%)	22,350,196 (36.6%)	17,931,078 (9.3%)	49.4 (0.18)	41.2 (0.19)
	Heart disease		38,880,504 (13.6%)	12,117,544 (31.1%)	8,909,618 (22.9%)	5,466,265 (14.1%)	12,387,078 (31.9%)	10,407,267 (5.4%)	48.7 (0.24)	37.6 (0.27)
	Hypertension		139,758,874 (49.0%)	42,593,190 (30.5%)	31,838,320 (22.8%)	18,759,649 (13.4%)	46,567,716 (33.3%)	47,931,188 (24.8%)	50.3 (0.10)	43.4 (0.14)
	Stroke		1,398,475 (0.5%)	309,668 (22.1%)	245,156 (17.5%)	159,697 (11.5%)	683,955 (48.9%)	332,058 (0.2%)	49.5 (0.86)	40.3 (1.02)
	High cholesterol		113,745,050 (39.9%)	34,066,388 (29.9%)	24,479,737 (21.5%)	13,970,117 (12.4%)	41,228,808 (36.2%)	39,405,334 (20.4%)	50.5 (0.11)	44.1 (0.15)
Number of other known MEPS priority conditions, excluding cancer		3+	113,066,675 (39.7%)	34,459,779 (30.5%)	26,338,416 (23.3%)	15,201,064 (13.4%)	37,067,416 (32.8%)	26,732,384 (13.8%)	48.8 (0.15)	39.1 (0.16)
		2	55,570,629 (19.5%)	16,231,099 (29.2%)	12,204,049 (22.0%)	8,294,942 (14.9%)	18,840,539 (33.9%)	22,887,977 (11.8%)	50.7 (0.13)	45.7 (0.16)
		1	64,535,749 (22.6%)	17,246,598 (26.7%)	16,271,242 (25.2%)	9,158,367 (14.2%)	21,859,542 (33.9%)	40,717,153 (21.0%)	50.6 (0.10)	49.5 (0.11)
		0	51,814,098 (18.2%)	11,180,314 (21.6%)	15,133,217 (29.2%)	5,200,504 (10.0%)	20,300,063 (39.2%)	103,209,663 (53.2%)	52.1 (0.06)	54.0 (0.04)
*Other includes value that are not ascertained, inapplicable, respondent don't know or refused										

Table 17: Utilization Of Pain Medication and HRQoL For Cancer Survivors Over The 6-Year period January 2008-December 2013 Stratified By Economic Variables

Characteristics		Pain medications					HRQoL		
		All Pain medications (Column %)	Non-opioids (Row %)	Narcotic analgesics combinations (Row %)	Opioids (Row %)	Adjuvant analgesics (Row %)	n Weighted (Column %)	MCS (SE)	PCS (SE)
All Cancer Survivors		69,377,092	16,507,688 (23.8%)	16,774,031 (24.2%)	11,704,565 (16.9%)	24,390,808 (35.2%)	23,170,732	50.2 (0.16)	43.9 (0.20)
Employment status	Yes	24,111,191 (34.8%)	6,419,086 (26.6%)	6,050,322 (25.1%)	3,163,862 (13.1%)	8,477,921 (35.2%)	11,203,620 (48.4%)	51.0 (0.17)	49.1 (0.21)
	No	45,265,901 (65.2%)	10,088,602 (22.3%)	10,723,709 (23.7%)	8,540,703 (18.9%)	15,912,887 (35.1%)	11,962,590 (51.6%)	49.5 (0.24)	39.0 (0.28)
Family income as percent of poverty line	Poor	11,354,204 (16.4%)	2,836,460 (25.0%)	3,107,609 (27.4%)	2,124,835 (18.7%)	3,285,300 (28.9%)	2,280,873 (9.8%)	44.6 (0.48)	38.9 (0.49)
	Near poor	5,003,796 (7.2%)	1,315,604 (26.4%)	1,182,656 (23.6%)	782,625 (15.6%)	1,722,911 (34.4%)	1,145,589 (4.9%)	47.9 (0.65)	37.8 (0.63)
	Low	11,820,953 (17.0%)	2,579,455 (21.8%)	2,940,766 (24.9%)	2,223,005 (18.8%)	4,077,727 (34.5%)	3,001,971 (13.0%)	48.5 (0.42)	40.5 (0.41)
	Middle	19,618,720 (28.3%)	4,227,211 (21.5%)	4,671,665 (23.8%)	3,145,608 (16.0%)	7,574,235 (38.6%)	6,597,748 (28.5%)	50.2 (0.26)	43.7 (0.27)
	High	21,579,420 (31.1%)	5,548,959 (25.7%)	4,871,334 (22.6%)	3,428,492 (15.9%)	7,730,635 (35.8%)	10,144,550 (43.8%)	52.3 (0.21)	46.9 (0.28)
Health insurance coverage	Any private	39,764,217 (57.3%)	9,313,225 (23.4%)	9,296,046 (23.4%)	6,683,113 (16.8%)	14,471,833 (36.4%)	15,802,449 (68.2%)	51.3 (0.18)	46.1 (0.22)
	Public only	26,647,890 (38.4%)	6,509,045 (24.4%)	6,783,993 (25.5%)	4,467,225 (16.8%)	8,887,627 (33.4%)	6,137,961 (26.5%)	48.4 (0.27)	38.1 (0.33)
	Uninsured	2,964,985 (4.3%)	685,418 (23.1%)	693,992 (23.4%)	554,227 (18.7%)	1,031,348 (34.8%)	1,230,322 (5.3%)	46.3 (0.58)	44.6 (0.62)
*Other includes value that are not ascertained, inapplicable, respondent don't know or refused									

Table 18: Utilization Of Pain Medication and HRQoL For Individuals Without Cancer History Over The 6-Year period January 2008- December 2013 Stratified By Economic Variables

Characteristics		Pain medications					HRQoL		
		All Pain medications (Column %)	Non-opioids (Row %)	Narcotic analgesics combinations (Row %)	Opioids (Row %)	Adjuvant analgesics (Row %)	n Weighted (Column %)	MCS (SE)	PCS (SE)
Individual without cancer history		284,987,151	79,117,790 (27.8%)	69,946,924 (24.5%)	37,854,877 (13.3%)	98,067,560 (34.4%)	193,547,177	51.2 (0.05)	50.0 (0.07)
Employment status	Yes	133,989,059 (47.0%)	37,873,414 (28.3%)	34,815,900 (26.0%)	14,510,807 (10.8%)	46,788,938 (34.9%)	139,562,477 (72.1%)	51.8 (0.06)	52.4 (0.05)
	No	150,976,554 (53.0%)	41,240,430 (27.3%)	35,125,718 (23.3%)	23,331,784 (15.5%)	51,278,622 (34.0%)	53,927,155 (27.9%)	49.5 (0.11)	43.8 (0.13)
	Other*	21,538 (0.01%)	3,946 (18.4%)	5,306 (24.6%)	12,286 (57.0%)	-	57,544 (0.01%)	54.6 (1.71)	50.3 (3.16)
Family income as percent of poverty line	Poor	58,846,302 (20.6%)	16,260,429 (27.6%)	14,957,395 (25.4%)	8,694,985 (14.8%)	18,933,493 (32.2%)	24,676,169 (12.7%)	47.8 (0.13)	46.9 (0.15)
	Near poor	16,947,216 (5.9%)	5,306,110 (31.3%)	4,322,054 (25.5%)	2,090,652 (12.3%)	5,228,401 (30.9%)	8,479,518 (4.4%)	49.3 (0.19)	46.7 (0.23)
	Low	49,061,151 (17.2%)	13,568,477 (27.7%)	11,962,278 (24.4%)	7,483,911 (15.3%)	16,046,485 (32.7%)	26,660,347 (13.8%)	50.1 (0.11)	48.3 (0.14)
	Middle	83,083,422 (29.2%)	22,422,394 (27.0%)	19,936,952 (24.0%)	10,961,070 (13.2%)	29,763,007 (35.8%)	58,933,191 (30.4%)	51.3 (0.08)	50.3 (0.10)
	High	77,049,061 (27.0%)	21,560,381 (28.0%)	18,768,246 (24.4%)	8,624,259 (11.2%)	28,096,175 (36.5%)	74,797,952 (38.6%)	52.8 (0.07)	51.8 (0.07)
Health insurance coverage	Any private	157,603,112 (55.3%)	41,855,276 (26.6%)	39,078,791 (24.8%)	20,049,666 (12.7%)	56,619,379 (35.9%)	130,360,536 (67.4%)	52.1 (0.05)	51.4 (0.06)
	Public only	100,534,764 (35.3%)	30,011,030 (29.9%)	23,352,332 (23.2%)	13,941,692 (13.9%)	33,229,710 (33.1%)	31,564,214 (16.3%)	48.4 (0.14)	42.9 (0.15)
	Uninsured	26,849,275 (9.4%)	7,251,484 (27.0%)	7,515,801 (28.0%)	3,863,519 (14.4%)	8,218,471 (30.6%)	31,622,427 (16.3%)	50.4 (0.11)	51.3 (0.11)
*Other includes value that are not ascertained, inapplicable, respondent don't know or refused									

Table 19: HRQoL Among Cancer Survivors Over The 6-Year Period January 2008- December 2013 Stratified By Different Class Of Pain Medications

Different class and combination of pain medication	HRQoL		
	Weighted (Column %)	MCS (SE)	PCS (SE)
All Cancer survivors	23,170,732	50.2 (0.16)	43.9 (0.20)
I. Based on Opioid exposer			
(a) Individuals who have any opioid use	8,105,777 (35.0%)	48.1 (0.27)	39.2 (0.31)
(b) Individuals with NO opioid use but atleast one prescription claim for pain medication	4,257,115 (18.4%)	49.7 (0.35)	43.1 (0.42)
(c) Individuals without pain medication	10,807,840 (46.6%)	52.0 (0.18)	47.7 (0.23)
II. All the combinations possible			
(a) Non-opioids only	2,379,235 (10.3%)	51.6 (0.42)	44.1(0.51)
(b) Narcotic analgesic combination only	2,651,967 (11.4%)	50.6 (0.41)	43.6 (0.42)
(c) Opioids only	600,182 (2.6%)	51.2 (0.87)	37.9 (1.08)
(d) Adjuvant analgesics only	1,368,151 (5.9%)	47.5 (0.67)	42.9 (0.69)
(e) Non-opioids and Opioids	405,594 (1.8%)	49.9 (1.04)	38.2 (1.54)
(f) Non-opioids and Narcotic analgesic combination	1,346,623 (5.8%)	49.8 (0.56)	42.0 (0.73)
(g) Non-opioids and Adjuvant analgesics	509,729 (2.2%)	47.0 (0.92)	38.8 (1.13)
(h) Opioids and Narcotic analgesic combination	448,013 (1.9%)	47.9 (1.12)	36.6 (1.16)
(i) Opioids and Adjuvant analgesics	287,395 (1.2%)	45.0 (1.22)	34.1 (1.54)
(j) Narcotic analgesic combination and Adjuvant analgesics	714,875 (3.1%)	46.0 (0.86)	38.3 (1.02)
(k) Non-opioids and Opioids and Narcotic analgesic combination	346,067 (1.5%)	45.9 (1.30)	35.6 (1.16)
(l) Non-opioids and Opioids and Adjuvant analgesics	154,005 (0.7%)	43.1 (1.79)	31.4 (1.59)
(m) Non-opioids and Narcotic analgesic combination and Adjuvant analgesics	476,825 (2.1%)	43.4 (1.18)	33.6 (1.12)
(n) Opioids and Narcotic analgesic combination and Adjuvant analgesics	339,857 (1.5%)	41.4 (1.52)	31.1 (1.30)
(o) All pain medication	334,374 (1.4%)	40.8 (1.51)	31.8 (1.33)
(p) No pain medication	10,807,840 (46.6%)	52.0 (0.18)	47.7 (0.23)

Table 20: HRQoL Among Individuals Without Cancer History Over The 6-Year Period January 2008- December 2013 Stratified By Different Class Of Pain Medications

Different class and combination of pain medication	HRQoL		
	Weighted (Column %)	MCS (SE)	PCS (SE)
All individuals without cancer history	193,547,177	51.2 (0.05)	50.0 (0.07)
I. Based on Opioid exposer			
(d) Individuals who have any opioid use	42,898,458 (22.2%)	49.1 (0.11)	44.8 (0.14)
(e) Individuals with NO opioid use but atleast one prescription claim for pain medication	26,458,805 (13.7%)	49.2 (0.12)	47.4 (0.16)
(f) Individuals without pain medication	124,189,914 (64.2%)	52.4 (0.05)	52.3 (0.07)
II. All the combinations possible			
(a) Non-opioids only00	16,430,780 (8.5%)	51.4 (0.13)	47.9 (0.16)
(b) Narcotic analgesic combination only	17,566,793 (9.1%)	50.7 (0.14)	48.8 (0.18)
(c) Opioids only	2,879,679 (1.5%)	50.9 (0.37)	44.8 (0.46)
(d) Adjuvant analgesics only	7,561,379 (3.9%)	45.5 (0.28)	48.0 (0.31)
(e) Non-opioids and Opioids	1,854,752 (1.0%)	49.7 (0.44)	42.7 (0.64)
(f) Non-opioids and Narcotic analgesic combination	8,308,437 (4.3%)	50.3 (0.19)	46.2 (0.25)
(g) Non-opioids and Adjuvant analgesics	2,466,646 (1.3%)	46.0 (0.43)	42.4 (0.58)
(h) Opioids and Narcotic analgesic combination	1,727,846 (0.9%)	47.8 (0.62)	40.6 (0.64)
(i) Opioids and Adjuvant analgesics	885,972 (0.5%)	43.5 (0.92)	37.6 (0.91)
(j) Narcotic analgesic combination and Adjuvant analgesics	2,755,844 (1.4%)	44.9 (0.51)	42.1 (0.58)
(k) Non-opioids and Opioids and Narcotic analgesic combination	1,523,638 (0.8%)	49.1 (0.51)	39.4 (0.77)
(l) Non-opioids and Opioids and Adjuvant analgesics	868,271 (0.4%)	44.8 (0.68)	37.2 (0.88)
(m) Non-opioids and Narcotic analgesic combination and Adjuvant analgesics	2,183,936 (1.1%)	44.5 (0.59)	38.5 (0.65)
(n) Opioids and Narcotic analgesic combination and Adjuvant analgesics	988,551 (0.5%)	43.3 (0.76)	34.2 (0.79)
(o) All pain medication	1,354,738 (0.7%)	43.3 (0.61)	33.6 (0.81)
(p) No pain medication	124,189,914 (64.2%)	52.4 (0.05)	52.3 (0.07)

Table 21: Regression Results Of Total Pain Prescription Stratified By Demographics, Geographical, Clinical & Economic Variables Among Post-Treatment Cancer Survivors

Zero-inflated Poisson Model for Total Pain Prescription								
Variable			Poisson			Logit		
			β Coefficient	exp^ β (95% CI)	p-value	β Coefficient	exp^ β (95% CI)	p-value
Demographics								
1.	Age	Age 35-44 vs Age 18-34	0.716	2.05 (1.39 - 3.01)	0.00*	1.347	3.85 (1.61 - 9.22)	0.00*
		Age 45-54 vs Age 18-34	0.800	2.22 (1.55 - 3.18)	0.00*	1.308	3.70 (1.81 - 7.55)	0.00*
		Age 55-64 vs Age 18-34	0.770	2.16 (1.46 - 3.20)	0.00*	1.339	3.82 (1.79 - 8.15)	0.00*
		Age 65-74 vs Age 18-34	0.722	2.06 (1.35 - 3.13)	0.00*	1.474	4.37 (2.07 - 9.22)	0.00*
		Age 75-84 vs Age 18-34	0.559	1.75 (1.02 - 3.01)	0.04*	1.447	4.25 (1.86 - 9.72)	0.00*
2.	Sex	Female vs Male	0.079	1.08 (0.86 - 1.37)	0.51	0.156	1.17 (0.75 - 1.82)	0.49
3.	Race/ Ethnicity	Black, non-Hispanic vs White, non-Hispanic	-0.326	0.72 (0.55 - 0.95)	0.02*	-0.279	0.76 (0.48 - 1.19)	0.23
		Hispanic vs White, non-Hispanic	0.236	1.27 (0.94 - 1.71)	0.12	-0.208	0.81 (0.51 - 1.30)	0.38
		Other race vs White, non-Hispanic	-0.022	0.98 (0.66 - 1.45)	0.91	0.764	2.15 (1.03 - 4.48)	0.04*
4.	Education	More Education vs Less Education	-0.084	0.92 (0.74 - 1.14)	0.45	0.082	1.09 (0.78 - 1.51)	0.63
5.	Marital Status	Married vs Not-married	0.081	1.08 (0.90 - 1.30)	0.39	-0.144	0.87 (0.59 - 1.26)	0.45
6.	Panel	Panel 16 vs Panel 15	-0.072	0.93 (0.79 - 1.10)	0.39	0.095	1.10 (0.80 - 1.52)	0.56
Geographical								
7.	Region	Midwest vs Northeast	0.076	1.08 (0.80 - 1.46)	0.62	-0.454	0.64 (0.36 - 1.11)	0.11
		South vs Northeast	-0.058	0.94 (0.69 - 1.29)	0.72	-0.216	0.81 (0.49 - 1.33)	0.39
		West vs Northeast	-0.124	0.88 (0.64 - 1.21)	0.44	-0.191	0.83 (0.48 - 1.42)	0.49
8.	Urban Status	Urban vs Rural	-0.307	0.74 (0.61 - 0.89)	0.00*	0.192	1.21 (0.82 - 1.80)	0.34
Clinical								
9.	Smoke	Smoker vs Nonsmoker	0.488	1.63 (1.33 - 1.99)	0.00*	0.083	1.09 (0.69 - 1.70)	0.72
10.	Pain	Mild/Moderate vs Nopain	0.339	1.40 (0.95 - 2.07)	0.09	-0.605	0.55 (0.35 - 0.86)	0.01*

	Perception	High/Severe vs Nopain	0.637	1.89 (1.26 - 2.83)	0.00*	-1.733	0.18 (0.09 - 0.34)	0.00*
		Pain change vs Nopain	0.345	1.41 (1.03 - 1.99)	0.05*	-0.510	0.60 (0.37 - 0.96)	0.04*
11.	Obesity	Obese vs Non-obese	0.224	1.25 (1.03 - 1.52)	0.02*	-0.231	0.79 (0.56 - 1.12)	0.18
12.	Head/Neck	Present vs Absent	-0.253	0.78 (0.41 - 1.47)	0.44	-0.349	0.71 (0.21 - 2.33)	0.57
13.	GI	Present vs Absent	-0.122	0.88 (0.43 - 1.81)	0.74	-0.296	0.74 (0.19 - 2.93)	0.67
14.	Lung	Present vs Absent	-0.130	0.88 (0.42 - 1.86)	0.73	-0.357	0.70 (0.18 - 2.76)	0.61
15.	Breast	Present vs Absent	-0.116	0.89 (0.45 - 1.75)	0.74	-0.175	0.84 (0.24 - 2.89)	0.78
16.	Gynecology	Present vs Absent	0.127	1.14 (0.57 - 2.27)	0.72	0.339	1.40 (0.43 - 4.60)	0.58
17.	Prostate	Present vs Absent	0.055	1.06 (0.52 - 2.13)	0.88	0.048	1.05 (0.33 - 3.34)	0.94
18.	Urogenital	Present vs Absent	0.147	1.16 (0.55 - 2.44)	0.70	-0.242	0.78 (0.21 - 2.98)	0.72
19.	Hematology	Present vs Absent	-0.609	0.54 (0.28 - 1.06)	0.08	-0.815	0.44 (0.10 - 1.89)	0.27
20.	Bone	Present vs Absent	0.357	1.43 (0.45 - 4.49)	0.54	0.426	1.53 (0.23 - 10.25)	0.66
21.	Skin	Present vs Absent	-0.017	0.98 (0.46 - 2.08)	0.97	-0.433	0.65 (0.17 - 2.42)	0.52
22.	Unspecified	Present vs Absent	0.121	1.13 (0.60 - 2.13)	0.71	0.175	1.19 (0.37 - 3.80)	0.77
23.	Multi-Cancer	Present vs Absent	0.007	1.01 (0.49 - 2.06)	0.99	-0.102	0.90 (0.24 - 3.38)	0.88
24.	Years since first cancer diagnosis	1-5 vs <1 years	0.203	1.23 (0.95 - 1.59)	0.12	0.147	1.16 (0.70 - 1.93)	0.57
		6-10 vs <1 years	0.247	1.28 (0.97 - 1.69)	0.08	-0.250	0.78 (0.44 - 1.37)	0.38
		11-15 vs <1 years	0.161	1.17 (0.89 - 1.55)	0.25	-0.025	0.97 (0.52 - 1.83)	0.94
		16-20 vs <1 years	-0.064	0.94 (0.60 - 1.47)	0.78	-0.213	0.81 (0.40 - 1.65)	0.56
		>20 vs <1 years	0.167	1.18 (0.91 - 1.54)	0.21	0.007	1.01 (0.55 - 1.86)	0.98
25.	Arthritis	Present vs Absent	0.360	1.43 (1.13 - 1.82)	0.00*	-1.045	0.35 (0.23 - 0.53)	0.00*
26.	Back & Neck pain	Present vs Absent	-0.066	0.94 (0.76 - 1.16)	0.55	-0.785	0.46 (0.28 - 0.74)	0.00*
27.	Chest pain	Present vs Absent	-0.212	0.81 (0.57 - 1.15)	0.24	-0.308	0.73 (0.35 - 1.53)	0.41
28.	Connective tissue	Present vs Absent	-0.013	0.99 (0.82 - 1.19)	0.89	-0.722	0.49 (0.29 - 0.80)	0.01*
29.	Diabetes	Present vs Absent	0.045	1.05 (0.84 - 1.31)	0.69	-0.247	0.78 (0.48 - 1.27)	0.32
30.	Fracture	Present vs Absent	-0.176	0.84 (0.60 - 1.17)	0.30	-0.792	0.45 (0.16 - 1.29)	0.14
31.	Headaches	Present vs Absent	0.029	1.03 (0.81 - 1.31)	0.82	-0.725	0.48 (0.22 - 1.05)	0.07
32.	Pelvic	Present vs Absent	-0.025	0.98 (0.76 - 1.24)	0.84	-0.786	0.46 (0.25 - 0.83)	0.01*
33.	Multi-pain	Present vs Absent	0.287	1.33 (0.98 - 1.81)	0.07	0.080	1.08 (0.57 - 2.05)	0.80

34.	Major depressive disorder	Present vs Absent	0.065	1.07 (0.62 - 1.82)	0.81	0.120	1.13 (0.24 - 5.30)	0.88
35.	Adjustment disorder	Present vs Absent	-0.798	0.45 (0.23 - 0.88)	0.02*	1.377	3.96 (0.57 - 27.67)	0.16
36.	Anxiety	Present vs Absent	0.070	1.07 (0.82 - 1.40)	0.60	-0.755	0.47 (0.28 - 0.79)	0.01*
37.	Bipolar	Present vs Absent	0.376	1.46 (1.18 - 1.79)	0.00*	-1.220	0.30 (0.18 - 0.50)	0.00*
38.	Conduct	Present vs Absent	-0.083	0.92 (0.46 - 1.86)	0.82	-1.510	0.22 (0.00 - 21.45)	0.52
39.	Multi-Mental disorder	Present vs Absent	0.107	1.11 (0.79 - 1.57)	0.54	0.311	1.36 (0.47 - 3.96)	0.57
40.	Substance abuse	Present vs Absent	0.274	1.32 (0.80 - 2.17)	0.28	-0.413	0.66 (0.27 - 1.65)	0.37
Economic								
41.	Income	Higher vs Lower Income	0.196	1.22 (1.03 - 1.49)	0.05*	0.115	1.12 (0.73 - 1.72)	0.59
		Income change vs Lower Income	0.404	1.50 (1.19 - 1.88)	0.00*	0.166	1.18 (0.74 - 1.88)	0.48
42.	Employment Status	Employed vs Unemployed	-0.424	0.65 (0.53 - 0.81)	0.00*	-0.128	0.88 (0.57 - 1.36)	0.56
43.	Insurance	Private Only vs Uninsured	0.110	1.12 (0.81 - 1.54)	0.50	-0.163	0.85 (0.51 - 1.40)	0.52
		Medicaid Only (OR Other Public Only) vs Uninsured	-0.132	0.88 (0.57 - 1.35)	0.55	-0.329	0.72 (0.34 - 1.51)	0.38
		All Medicare (Medicare Only, Medicare + Medicaid, Medicare + Private) vs Uninsured	0.104	1.11 (0.82 - 1.49)	0.49	0.039	1.04 (0.63 - 1.71)	0.88
		Change Insurance vs Uninsured	0.510	1.67 (1.12 - 2.48)	0.01*	-0.235	0.79 (0.39 - 1.60)	0.51

*= $p<0.005$; **β** = raw coefficient; **exp^β** is the factor change in expected count of pain prescription for unit increase in independent variable.
The Poisson model represents factor change in expected count for pain prescription those not always 0. The logit model represents factor change in pain prescription for odds of always 0.

Table 22: Regression Results Of Total Opioid Prescription Stratified By Demographics, Geographical, Clinical & Economic Variables Among Post-Treatment Cancer Survivors

Zero-inflated Poisson Model for Total Opioid Prescription								
Variable			Poisson			Logit		
			β Coefficient	exp^β (95% CI)	p-value	β Coefficient	exp^β (95% CI)	p-value
Demographics								
1.	Age	Age 35-44 vs Age 18-34	0.194	1.21 (0.66 - 2.22)	0.53	0.890	2.43 (1.15 - 5.16)	0.02*
		Age 45-54 vs Age 18-34	0.221	1.25 (0.70 - 2.23)	0.46	0.525	1.69 (0.76 - 3.77)	0.20
		Age 55-64 vs Age 18-34	0.011	1.01 (0.52 - 1.96)	0.98	1.093	2.98 (1.48 - 6.01)	0.00*
		Age 65-74 vs Age 18-34	0.030	1.03 (0.51 - 2.07)	0.93	1.005	2.73 (1.32 - 5.64)	0.01*
		Age 75-84 vs Age 18-34	-0.150	0.86 (0.38 - 1.97)	0.72	1.169	3.22 (1.41 - 7.35)	0.01*
2.	Sex	Female vs Male	-0.083	0.92 (0.67 - 1.27)	0.61	0.134	1.14 (0.72 - 1.81)	0.57
3.	Race/ Ethnicity	Black, non-Hispanic vs White, non-Hispanic	-0.114	0.89 (0.62 - 1.28)	0.54	-0.253	0.78 (0.46 - 1.30)	0.33
		Hispanic vs White, non-Hispanic	0.128	1.14 (0.71 - 1.81)	0.59	-0.059	0.94 (0.54 - 1.65)	0.84
		Other race vs White, non-Hispanic	-0.150	0.86 (0.55 - 1.34)	0.51	0.761	2.14 (1.03 - 4.43)	0.04*
4.	Education	More Education vs Less Education	-0.645	0.52 (0.36 - 0.77)	0.00*	-0.264	0.77 (0.49 - 1.20)	0.24
5.	Marital Status	Married vs Not-married	0.214	1.24 (0.95 - 1.61)	0.11	-0.138	0.87 (0.58 - 1.30)	0.50
6.	Panel	Panel 16 vs Panel 15	-0.059	0.94 (0.75 - 1.19)	0.61	0.009	1.01 (0.72 - 1.42)	0.96
Geographical								
7.	Region	Midwest vs Northeast	0.278	1.32 (0.80 - 2.18)	0.28	-0.652	0.52 (0.28 - 0.99)	0.05*
		South vs Northeast	0.178	1.20 (0.70 - 2.04)	0.51	-0.453	0.64 (0.37 - 1.09)	0.10
		West vs Northeast	0.025	1.03 (0.62 - 1.71)	0.92	-0.472	0.62 (0.35 - 1.12)	0.11
8.	Urban Status	Urban vs Rural	0.041	1.04 (0.76 - 1.43)	0.80	0.003	1.00 (0.60 - 1.69)	0.99
Clinical								
9.	Smoke	Smoker vs Nonsmoker	0.545	1.72 (1.32 - 2.24)	0.00*	-0.277	0.76 (0.50 - 1.15)	0.19
10.	Pain	Mild/Moderate vs Nopain	0.629	1.88 (1.16 - 3.02)	0.01*	-0.565	0.57 (0.37 - 0.88)	0.01*

	Perception	High/Severe vs Nopain	1.251	3.49 (2.09 - 5.84)	0.00*	-1.607	0.20 (0.10 - 0.39)	0.00*
		Pain change vs Nopain	0.493	1.64 (1.08 - 2.49)	0.02*	-0.367	0.69 (0.43 - 1.11)	0.13
11.	Obesity	Obese vs Non-obese	0.025	1.03 (0.74 - 1.42)	0.88	-0.125	0.88 (0.61 - 1.28)	0.51
12.	Head/Neck	Present vs Absent	-0.727	0.48 (0.17 - 1.38)	0.17	-0.391	0.68 (0.18 - 2.47)	0.55
13.	GI	Present vs Absent	-0.407	0.67 (0.21 - 2.12)	0.49	0.055	1.06 (0.26 - 4.26)	0.94
14.	Lung	Present vs Absent	0.413	1.51 (0.43 - 5.26)	0.52	0.230	1.26 (0.31 - 5.14)	0.75
15.	Breast	Present vs Absent	-0.608	0.54 (0.15 - 1.95)	0.35	-0.091	0.91 (0.25 - 3.35)	0.89
16.	Gynecology	Present vs Absent	-0.299	0.74 (0.24 - 2.33)	0.61	0.192	1.21 (0.37 - 4.02)	0.75
17.	Prostate	Present vs Absent	-0.062	0.94 (0.31 - 2.90)	0.91	0.041	1.04 (0.31 - 3.52)	0.95
18.	Urogenital	Present vs Absent	-0.279	0.76 (0.21 - 2.70)	0.67	-0.820	0.44 (0.11 - 1.70)	0.23
19.	Hematology	Present vs Absent	-0.665	0.51 (0.14 - 1.83)	0.30	-0.372	0.69 (0.17 - 2.87)	0.61
20.	Bone	Present vs Absent	0.937	2.55 (0.55 - 11.84)	0.23	0.255	1.29 (0.19 - 8.56)	0.79
21.	Skin	Present vs Absent	-0.372	0.69 (0.20 - 2.41)	0.56	-0.743	0.48 (0.14 - 1.64)	0.24
22.	Unspecified	Present vs Absent	0.078	1.08 (0.37 - 3.20)	0.89	0.719	2.05 (0.62 - 6.76)	0.24
23.	Multi-Cancer	Present vs Absent	0.345	1.41 (0.43 - 4.59)	0.57	-0.468	0.63 (0.16 - 2.48)	0.50
24.	Years since first cancer diagnosis	1-5 vs <1 years	0.412	1.51 (1.06 - 2.15)	0.02*	0.827	2.29 (1.34 - 3.90)	0.00*
		6-10 vs <1 years	0.300	1.35 (0.90 - 2.03)	0.15	0.589	1.80 (0.91 - 3.56)	0.09
		11-15 vs <1 years	0.254	1.29 (0.88 - 1.89)	0.20	0.818	2.27 (1.09 - 4.70)	0.03*
		16-20 vs <1 years	0.519	1.68 (0.98 - 2.87)	0.06	0.556	1.74 (0.69 - 4.40)	0.24
		>20 vs <1 years	0.203	1.23 (0.86 - 1.74)	0.26	0.537	1.71 (0.76 - 3.86)	0.19
25.	Arthritis	Present vs Absent	0.658	1.93 (1.33 - 2.80)	0.00*	-0.456	0.63 (0.39 - 1.03)	0.07
26.	Back & Neck Pain	Present vs Absent	-0.190	0.83 (0.63 - 1.09)	0.17	-0.732	0.48 (0.31 - 0.76)	0.00*
27.	Chest pain	Present vs Absent	-0.488	0.61 (0.36 - 1.05)	0.07	-0.157	0.85 (0.40 - 1.83)	0.69
28.	Connective tissue	Present vs Absent	-0.105	0.90 (0.71 - 1.13)	0.37	-0.502	0.61 (0.38 - 0.96)	0.03*
29.	Diabetes	Present vs Absent	-0.151	0.86 (0.62 - 1.18)	0.35	-0.150	0.86 (0.55 - 1.34)	0.51
30.	Fracture	Present vs Absent	-0.553	0.58 (0.41 - 0.80)	0.00*	-1.404	0.25 (0.10 - 0.58)	0.00*
31.	Headaches	Present vs Absent	-0.023	0.98 (0.74 - 1.29)	0.87	-0.408	0.67 (0.33 - 1.33)	0.25
32.	Pelvic	Present vs Absent	-0.118	0.89 (0.62 - 1.28)	0.52	-0.550	0.58 (0.33 – 0.98)	0.05*
33.	Multi-pain	Present vs Absent	0.525	1.69 (1.12 - 2.55)	0.01*	-0.104	0.90 (0.50 - 1.62)	0.73
34.	Major depressive disorder	Present vs Absent	-0.366	0.69 (0.19 - 2.49)	0.57	1.198	3.31 (0.79 - 13.84)	0.10

35.	Adjustment disorder	Present vs Absent	0.911	2.49 (0.67 - 9.19)	0.17	1.226	3.41 (1.35 - 8.57)	0.01*
36.	Anxiety	Present vs Absent	0.092	1.10 (0.74 - 1.63)	0.65	-0.482	0.62 (0.35 - 1.08)	0.09
37.	Bipolar	Present vs Absent	-0.204	0.82 (0.58 - 1.15)	0.24	-1.154	0.32 (0.17 - 0.58)	0.00*
38.	Conduct	Present vs Absent	-0.070	0.93 (0.34 - 2.57)	0.89	0.436	1.55 (0.24 - 9.84)	0.64
39.	Multi-Mental disorder	Present vs Absent	0.258	1.29 (0.67 - 2.51)	0.44	1.291	3.64 (1.51 - 8.76)	0.00*
40.	Substance abuse	Present vs Absent	0.126	1.13 (0.54 - 2.40)	0.74	0.868	2.38 (0.65 - 8.80)	0.19
Economic								
41.	Income	Higher vs Lower Income	0.416	1.52 (1.09 - 2.11)	0.01*	0.551	1.73 (1.04 - 2.88)	0.03*
		Income change vs Lower Income	0.617	1.85 (1.37 - 2.51)	0.00*	0.459	1.58 (0.97 - 2.58)	0.07
42.	Employment Status	Employed vs Unemployed	-0.374	0.69 (0.51 - 0.92)	0.01*	-0.316	0.73 (0.45 - 1.18)	0.20
43.	Insurance	Private Only vs Uninsured	0.046	1.05 (0.67 - 1.63)	0.84	0.120	1.13 (0.63 - 2.02)	0.68
		Medicaid Only (OR Other Public Only) vs Uninsured	-0.174	0.84 (0.46 - 1.53)	0.57	0.208	1.23 (0.53 - 2.84)	0.62
		All Medicare (Medicare Only, Medicare + Medicaid, Medicare + Private) vs Uninsured	-0.119	0.89 (0.61 - 1.30)	0.54	0.122	1.13 (0.62 - 2.05)	0.69
		Change Insurance vs Uninsured	0.749	2.12 (1.41 - 3.16)	0.00*	-0.213	0.81 (0.40 - 1.65)	0.56

*= $p<0.005$; **β** = raw coefficient; **exp^β** is the factor change in expected count of pain prescription for unit increase in independent variable.
The Poisson model represents factor change in expected count for pain prescription those not always 0. The logit model represents factor change in pain prescription for odds of always 0.

Table 23: Frequency Distribution of SF-12 Productivity Measures Among Post-Treatment Cancer Survivors By Pain Medication Use

SF-12Productivity Measures		Total (N) = 1,444 (Column %)	Pain Medication Use				*p-value
			None n (row %)	Acute n (row %)	Moderate n (row %)	Chronic n (row %)	
During past 4 weeks, as result of physical health, limited in kind of work or other activities?	None of the time	442 (30.6%)	323 (73.0%)	60 (13.6%)	44 (10.0%)	15 (3.4%)	0.001 (1,444)
	Little/some of the time	339 (23.5%)	154 (42.9%)	50 (14.3%)	66 (20.6%)	69 (22.3%)	
	Work limitation changes over time	462 (31.9%)	187 (40.5%)	88 (19.1%)	104 (22.5%)	83 (17.9%)	
	Most/All of the time	201 (14.0%)	47 (23.4%)	19 (9.4%)	49 (24.4%)	86 (42.8%)	
During past 4 weeks, as result of mental problems, did work or other activities less carefully than usual?	None of the time	600 (41.5%)	387 (64.5%)	84 (14.0%)	85 (14.2%)	44 (7.3%)	0.001 (1,444)
	Little/some of the time	297 (20.6%)	111 (37.4%)	56 (18.9%)	60 (20.2%)	70 (23.6%)	
	Work limitation changes over time	473 (32.8%)	194 (41.0%)	72 (15.2%)	100 (21.1%)	107 (22.6%)	
	Most/All of the time	74 (5.1%)	19 (25.7%)	5 (6.8%)	18 (24.3%)	32 (43.2%)	
During past 4 weeks, as result of physical problems, accomplished less than would like?	None of the time	387 (26.8%)	278 (71.8%)	51 (13.2%)	39 (10.1%)	19 (4.9%)	0.001 (1,444)
	Little/some of the time	399 (27.6%)	178 (44.6%)	66 (16.5%)	77 (19.3%)	78 (19.6%)	
	Work limitation changes over time	471 (32.6%)	215 (45.7%)	85 (18.0%)	98 (20.8%)	73 (15.5%)	
	Most/All of the time	187 (13.0%)	40 (21.4%)	15 (8.0%)	49 (26.2%)	83 (44.4%)	
During past 4 weeks, as result of mental problems, accomplished less than would like?	None of the time	593 (41.1%)	364 (61.4%)	91 (15.4%)	89 (15.0%)	49 (8.3%)	0.001 (1,444)
	Little/some of the time	303 (21.0%)	116 (38.3%)	53 (17.5%)	58 (19.1%)	76 (25.1%)	
	Work limitation changes over time	454 (31.4%)	214 (47.2%)	66 (14.5%)	91 (20.0%)	83 (18.3%)	
	Most/All of the time	94 (6.5%)	17 (18.1%)	7 (7.5%)	25 (26.6%)	45 (47.9%)	

* = p-value is a chisquare test for the row comparison

Pain medication use: (i) No users: individuals with no claim of pain prescription (ii) Acute users: individuals with claim of at least one pain prescription on one round only. (iii) Moderate: individuals with claim of pain prescription on 2-3 rounds (iv) Chronic users: individuals with claim of pain prescription on atleast 4 rounds

Table 24: Frequency Distribution of SF-12 Productivity Measures Among Post-Treatment Cancer Survivors By Opioid Use

SF-12Productivity Measures		Total (N) = 1,444 (Column %)	Opioid Use				*p-value
			None n (row %)	Acute n (row %)	Moderate n (row %)	Chronic n (row %)	
During past 4 weeks, as result of physical health, limited in kind of work or other activities?	None of the time	442 (30.6%)	370 (83.7%)	52 (11.8%)	17 (3.9%)	3 (0.7%)	0.001 (1,444)
	Little/some of the time	339 (23.5%)	226 (66.7%)	55 (16.2%)	35 (10.3%)	23 (6.8%)	
	Work limitation changes over time	462 (31.9%)	283 (61.3%)	89 (19.3%)	59 (12.8%)	31 (6.7%)	
	Most/All of the time	201 (14.0%)	86 (42.8%)	31 (15.4%)	39 (19.4%)	45 (22.4%)	
During past 4 weeks, as result of mental problems, did work or other activities less carefully than usual?	None of the time	600 (41.5%)	464 (77.3%)	81 (13.5%)	41 (6.83%)	14 (2.3%)	0.001 (1,444)
	Little/some of the time	297 (20.6%)	185 (62.3%)	50 (16.8%)	39 (13.1%)	23 (7.7%)	
	Work limitation changes over time	473 (32.8%)	283 (59.8%)	88 (18.6%)	57 (12.1%)	45 (9.5%)	
	Most/All of the time	74 (5.1%)	33 (44.6%)	8 (10.8%)	13 (17.6%)	20 (27.0%)	
During past 4 weeks, as result of physical problems, accomplished less than would like?	None of the time	387 (26.8%)	321 (83.0%)	48 (12.4%)	14 (3.6%)	4 (1.0%)	0.001 (1,444)
	Little/some of the time	399 (27.6%)	260 (65.2%)	71 (17.8%)	42 (10.5%)	26 (6.5%)	
	Work limitation changes over time	471 (32.6%)	308 (65.4%)	79 (16.8%)	57 (12.1%)	27 (5.7%)	
	Most/All of the time	187 (13.0%)	76 (40.6%)	29 (15.5%)	37 (19.8%)	45 (24.1%)	
During past 4 weeks, as result of mental problems, accomplished less than would like?	None of the time	593 (41.1%)	447 (75.4%)	88 (14.8%)	42 (7.1%)	16 (2.7%)	0.001 (1,444)
	Little/some of the time	303 (21.0%)	189 (62.4%)	46 (15.2%)	34 (11.2%)	34 (11.2%)	
	Work limitation changes over time	454 (31.4%)	292 (64.3%)	76 (16.7%)	61 (13.4%)	25 (5.5%)	
	Most/All of the time	94 (6.5%)	37 (39.4%)	17 (18.1%)	13 (13.8%)	27 (28.7%)	

* = p-value is a chisquare test for the row comparison

Opioid use: (i) No users: individuals with no claim of opioids prescription (ii) Acute: individuals with claim of opioids on one round only (iii) Moderate: individuals with claim of opioids on 2-3 rounds (iv) Chronic: individuals with claim of opioids on atleast 4 rounds

Table 25: Frequency Distribution of CSAQ Productivity Measures Among Post-Treatment Cancer Survivors By Pain Medication Use

CSAQ Productivity Measures		Total n (column%)	Pain Medication Use				p-value
			None n (row %)	Acute n (row %)	Moderate n (row %)	Chronic n (row %)	
CSAQ, Q9: At any time from first cancer diagnosis until now, employed for pay at a job or business?	Yes	464 (63.0%)	239 (51.5%)	80 (17.2%)	73 (15.7%)	72 (15.5%)	0.12 (736)
	No	272 (37.0%)	126 (46.3%)	31 (11.4%)	51 (18.7%)	64 (23.5%)	
CSAQ, Q10: Work-related changes?	Yes	230 (50.0%)	114 (49.5%)	43 (18.7%)	40 (17.4%)	33 (14.4%)	0.17 (459)
	No	229 (50.0%)	123 (53.7%)	37 (16.2%)	31 (13.5%)	38 (16.6%)	
CSAQ, Q14: Extended time off from work?	Yes	142 (70.0%)	75 (52.8%)	25 (17.6%)	26 (18.3%)	16 (11.3%)	0.09 (203)
	No	61 (30.0%)	29 (47.5%)	15 (24.6%)	8 (13.1%)	9 (14.8%)	
CSAQ, Q18: Unpaid time off from work?	Yes	92 (46.2%)	43 (46.7%)	18 (19.6%)	13 (14.1%)	18 (19.6%)	0.09 (199)
	No	107 (53.8%)	57 (53.2%)	21 (19.6%)	19 (17.8%)	10 (9.4%)	
CSAQ, Q26: Change in work schedule from full-time to part-time?	Yes	40 (20.3%)	15 (37.5%)	11 (27.5%)	10 (25.0%)	4 (10.0%)	0.002 (197)
	No	157 (79.7%)	84 (53.5%)	28 (17.8%)	22 (14.0%)	23 (14.7%)	
CSAQ, Q32: Change to less demanding job?	Yes	19 (9.6%)	12 (63.2%)	3 (15.8%)	2 (10.5%)	2 (10.5%)	0.84 (198)[£]
	No	179 (90.4%)	88 (49.2%)	35 (19.6%)	30 (16.8%)	26 (14.5%)	
CSAQ, Q38: Retire earlier than planned?	Yes	54 (12.0%)	23 (42.6%)	11 (20.4%)	11 (20.4%)	9 (16.7%)	0.23 (450)

	No	396 (88.0%)		210 (53.0%)	62 (15.7%)	62 (15.7%)	62 (15.6%)	
CSAQ, Q40: Malignancy interfered with ability to perform physical tasks required at job?	Yes	112 (25.3%)		46 (41.1%)	28 (25.0%)	21 (18.8%)	17 (15.2%)	0.003 (443)
	No	331 (74.7%)		181 (54.7%)	46 (13.9%)	50 (15.1%)	54 (16.3%)	
CSAQ, Q41: Malignancy interfered with ability to perform mental tasks required at job?	Yes	71 (15.8%)		32 (45.1%)	15 (21.1%)	11 (15.5%)	13 (18.3%)	0.72 (450)
	No	379 (84.2%)		199 (52.5%)	62 (16.4%)	60 (15.8%)	58 (15.3%)	
CSAQ, Q42: Feel less productive at work?	Yes	113 (25.2%)		51 (45.1%)	26 (23.0%)	21 (18.6%)	15 (13.3%)	0.14 (449)
	No	336 (74.8%)		180 (53.6%)	51 (15.2%)	50 (14.9%)	55 (16.4%)	

p-value is a chisquare test for the row comparison
[£]= p- value is a Fishers exact test for the row comparison

Pain medication use: (i) No users: individuals with no claim of pain prescription (ii) Acute users: individuals with claim of at least one pain prescription on one round only. (iii) Moderate: individuals with claim of pain prescription on 2-3 rounds (iv) Chronic users: individuals with claim of pain prescription on atleast 4 rounds

Table 26: Frequency Distribution of CSAQ Productivity Measures Among Post-Treatment Cancer Survivors By Opioid Use

CSAQ Productivity Measures		Total n (column%)	Opioid Use				p-value
			None n (row %)	Acute n (row %)	Moderate n (row %)	Chronic n (row %)	
CSAQ, Q9: At any time from first cancer diagnosis until now, employed for pay at a job or business?	Yes	464 (63.0%)	332 (71.5%)	69 (14.9%)	40 (8.6%)	23 (5.0%)	0.83 (736)
	No	272 (37.0%)	178 (65.5 %)	39 (14.3%)	31 (11.4%)	24 (8.8%)	
CSAQ, Q10: Work-related changes?	Yes	230 (50.0%)	165 (71.7%)	36 (15.7%)	18 (7.8%)	11 (4.8%)	0.35 (459)
	No	229 (50.0%)	166 (72.5%)	32 (14.0%)	20 (8.7%)	11 (4.8%)	
CSAQ, Q14: Extended time off from work?	Yes	142 (70.0%)	100 (70.4%)	23 (16.2%)	11 (7.8%)	8 (5.6%)	0.54 (203) [£]
	No	61 (30.0%)	48 (78.7%)	9 (14.7%)	3 (4.9%)	1 (1.6%)	
CSAQ, Q18: Unpaid time off from work?	Yes	92 (46.2%)	67 (72.8%)	13 (14.1%)	6 (6.5%)	6 (6.5%)	0.54 (199) [£]
	No	107 (53.8%)	76 (71.0%)	18 (16.8%)	10 (9.4%)	3 (2.8%)	
CSAQ, Q26: Change in work schedule from full-time to part-time?	Yes	40 (20.3%)	28 (70.0%)	7 (17.5%)	5 (12.5%)	0 (0.0%)	0.36 (197) [£]
	No	157 (79.7%)	114 (72.6%)	24 (15.3%)	11 (7.0%)	8 (5.1%)	
CSAQ, Q32: Change to less demanding job?	Yes	19 (9.6%)	16 (84.1%)	1 (5.3%)	1 (5.3%)	1 (5.3%)	0.64 (198) [£]
	No	179 (90.4%)	128 (71.5%)	29 (16.2%)	14 (7.8%)	8 (4.5%)	
CSAQ, Q38: Retire earlier than planned?	Yes	54 (12.0%)	39 (72.2%)	5 (9.3%)	5 (9.3%)	5 (9.3%)	0.68 (450)

	No	396 (88.0%)		284 (71.7%)	60 (15.2%)	34 (8.6%)	18 (4.6%)	
CSAQ, Q40: Malignancy interfered with ability to perform physical tasks required at job?	Yes	112 (25.3%)		77 (68.7%)	20 (17.9%)	8 (7.1%)	7 (6.3%)	0.24 (443)
	No	331 (74.7%)		242 (73.1%)	43 (13.0%)	30 (9.1%)	16 (4.8%)	
CSAQ, Q41: Malignancy interfered with ability to perform mental tasks required at job?	Yes	71 (15.8%)		53 (74.7%)	9 (12.7%)	6 (8.5%)	3 (4.1%)	0.47 (450)
	No	379 (84.2%)		271 (71.5%)	56 (14.8%)	32 (8.4%)	20 (5.3%)	
CSAQ, Q42: Feel less productive at work?	Yes	113 (25.2%)		77 (68.1%)	19 (16.8%)	11 (9.7%)	6 (5.4%)	0.05 (449)
	No	336 (74.8%)		246 (73.2%)	46 (13.7%)	27 (8.0%)	17 (5.1%)	

p-value is a chisquare test for the row comparison
[£]= p- value is a Fishers exact test for the row comparison

Opioid use: (i) No users: individuals with no claim of opioids prescription (ii) Acute: individuals with claim of opioids on one round only (iii) Moderate: individuals with claim of opioids on 2-3 rounds (iv) Chronic: individuals with claim of opioids on atleast 4 rounds

CHAPTER FIVE:- DISCUSSION

Objective 1:

The number of people with cancer is growing. The number of cancer survivors we identified was higher compared to other previous studies.[76,84] Whereas, other studies used the cancer question, "whether they ever been told by healthcare professional or doctor that they had cancer or malignancy of any kind?" we identified cancer survivors using a combination of both a cancer question and CCCs=011-047, excluding individuals solely diagnosed with non-epithelial cancer of skin (CCC=023 or CASKINNM) or unknown skin cancer (CASKINDK). Pain related to condition or treatment is common and experienced by many across the lifespan. If managed as per WHO guidelines, nearly 80-90% of cancer pain can be controlled by pharmacological agents.[66] The majority of published studies focused on epidemiology of cancer pain, utilization of pain medications among cancer survivors have received scanty attention from researchers.[11,36,44,53,55] This study is the first retrospective study to report utilization of pain medication, total expenditures and payer cost share among US civilian non-institutionalized population.

I. Trends in utilization, expenditure and spending of pain medications from 2008 - 2013

The results from the study showed both number and the percent of cancer survivors taking pain medications increased over time. For year 2013, around 44.0% of 24.8 million cancer survivors took pain medications compared to 40.8% of 23.4 million cancer survivors in year 2008.

This study documented substantial changes in the utilization of pain medications in the US from 2008 to 2013, notably increase in opioids, and adjuvant class of analgesics. The trend in utilization for narcotic analgesic combinations remained steady. Among the cancer survivors, the opioid utilization peaked in year 2011 and then decreased each year through 2013. However, throughout the study period, prescribing opioid among cancer survivors remained significantly high compared to individuals without cancer history. This utilization trend was consistent with the opioid prescribing trends published by CDC that

analyzed QuintilesIMS retail prescription data in US from 2006 to 2015.[85] According to report, in US from 2006 to 2010, annual prescribing rates (number of opioids prescription/US census population each year) increased from 72.4 to 81.2 prescriptions/100 persons and then began to decrease in 2011.

Prescribing opioids requires patient careful risk assessment as drugs belonging to these classes are associated with abuse, addiction and/or diversion to the illicit drug marketplace. In US, opioids and narcotic analgesic combinations are designated as "controlled substances" and are regulated with restrictions on whether and how the medication can be prescribed. Over the past decade, there was remarkable increase in the rate of opioid prescribing, average opioid prescription size and the amount distributed in US.[86] During same period of time, CDC reported prescription opioid-related overdose death increased four-fold from 1999 to 2010 and hospital admissions related to drug abuse treatment increased parallel to number of opioids prescribed.[85] In April 2011, the White House Office of National Drug Control Policy announced an epidemic of prescription drug abuse, stating:

"*Prescription drug misuse and abuse is a major public health and public safety crisis. As a nation, we must take urgent action to ensure the appropriate balance between the benefits of these medications and the risks they pose*."[70]

The overall cost (not adjusted for inflation) for pain medications increased from $3.5 billion in 2008 to $5.6 billion in 2013. Among different class of pain medications, the cost of prescriptions for adjuvant analgesics, non-opioids increased over time. The cost of opioid prescriptions increased from $811.5 million in 2008 to $2.1 billion in 2011, followed by decline to $755.9 million in 2013. Similar trend was observed for narcotic analgesic combinations class of pain medication. This may be due to decrease in opioids prescribing by healthcare providers across US because of epidemic of prescription drug abuse. The spending in terms of patient share decreased except for narcotic analgesic combinations where the patient cost share increased.

II. Utilization, expenditure and spending of pain medications among cancer survivors compared to individuals without cancer history

Published research has shown high prevalence of pain and guidelines exists recommending analgesic ladder to manage pain among cancer patients. In a study conducted by Van-de Beuken *et al,* a self-report questionnaire was administered among cancer patients; less than 30% of patients used pain medications according to WHO 3-step pain ladder.[11] In an EPIC survey study by Breivik *et al*., 77% of adult cancer patients were receiving prescription only analgesics with 41% reported taking strong opioids either alone or in combination with other.[55] Our study documented nearly 42.0% of cancer survivors and 22.8% of individuals without cancer history reported claims of at least one pain medication. When compared to the general population, a significant higher percent of cancer survivors took pain medications. Notably, the utilization of opioids and adjuvant class was significantly higher among cancer survivors compared to individuals without cancer history.

The economic burden of cancer is substantial and in future is expected to increase significantly because of growing population, aging and improvements in survival. Patients and their families' pay expenses of tens of thousands of dollars for direct medical costs associated with cancer-related hospitalizations, surgery and treatment; typically measured by insurance payments and patient out-of-pocket costs. This study documented total expenditure and payment share associated with pharmacological treatment to manage cancer pain in US. Over the six years of study period, the total expenditure of pain prescriptions among cancer survivors was $5.0 billion. The total expenditure associated with opioids prescription was higher among cancer survivors (26.9% of $5.0 billion) compared to individuals without cancer history (18.5% of $16.4 billion). Compared to individuals without cancer history, overall the spending in terms of patient share was lower among cancer survivors. This may be due to higher number of elderly cancer survivors compared to individuals without cancer history. Among elderly, the expenses are covered by Medicare

Part D and/or private insurance. Since 2006, Medicare has become major payer for the prescription drugs. In addition, the adult cancer survivors might be returning to work to maintain employer sponsored health insurance coverage. Job loss would result in losing health insurance thereby increasing financial burden on self/family and restricting access to optimal care. The out-of pocket costs among cancer survivors was 20.5% of $5.0 billion and among individual without cancer history was 22.4% of $16.4 billion. Among the cancer survivors, for different class of pain medication, the spending was lower for non-opioids, opioids, adjuvants class of drugs.

III. Among cancer survivors: Distribution of treatments across different socio-demographics, geographical, clinical and economic factors

a. Demographic factors

Based on demographic factors, cancer survivors with age group, Age 56-65, Age 66-75, Age $\geq$ 76 was associated with higher use of total pain medications compared to individuals without cancer history. The use of opioids medication was higher across all age group categories. Previous studies have shown high pain prevalence rate and poor cancer pain management among elderly patients.[87] The elderly cancer survivors with daily pain were more likely to receive no analgesia (OR=1.40, 1.13 – 1.73).[60] There exist gender disparities not only when it comes to pain- perception, coping, reporting but also pain-related behaviors such as use of social welfare and health care services. Evidence exist that women seek health care services for pain at a higher rate than men.[88] When compared to individuals without cancer history, the utilization of pain medications, narcotic analgesic combinations and opioids was higher among female cancer survivors. Racial based discrepancies exist when it comes to management of cancer pain. It has been well documented that African Americans, Hispanics, and Asians receives less effective analgesics even tough pain severity levels are comparable.[89] This study found that when compared to individuals without cancer history, total pain medications use was lower among cancer survivors belonging to non-Hispanic Blacks, Hispanic, non-Hispanic Other/Multiple race group. However, the opioids use was higher among cancer survivors across all race groups. Conflicting results exist; theory suggests that education

level was identified as a barrier among minorities for whom English was not a native language; as a result pain was undertreated because of poor communication.[90] Thus, lower education level was associated with lower utilization of analgesics. On the contrary, theory also suggests that individuals with lower education have more concerns about cancer pain management.[91] It was shown that among US adults, lower education level was associated with higher opioid use.[92] Findings from our study showed that when compared to individuals without cancer history, total pain medications use was higher among cancer survivors with high school graduates and some college or more. The utilization of opioids was higher among cancer survivors across all education categories. The literature suggests that spouse of cancer patients were more concerned about cancer pain[93]; hence, the assumption is married individuals will seek out adequate care because of social and family responsibilities resulting in higher utilization of pain medications. Our findings also suggest that compared to individuals without cancer history, total pain medications use was higher among married cancer survivors. However, the utilization of opioids was higher among cancer survivors across all categories of marital status.

b. Geographic factors

Pain medications utilization among cancer survivors by geographical variation has received little attention. Published studies suggest that geographic differences in prescribing exist. In a study conducted by Olsen *et al*., the prescribing trend of opioids in US by primary care physicians from 1992 to 2001 was described.[94] This study reported compared to patients residing in west, those in northeast (OR=0.60 [95% CI 0.51 – 0.69]) or midwest (OR = 0.75 [95% CI 0.66 – 0.85]) had significantly lower odds of visit where opioid was prescribed.[94] In another study it was reported that counties disproportionately located in appalachia, southern and western had highest prescribing rates for opioids.[95] However, these studies reported opioid prescribing trends including patients with injuries, surgeries, painful conditions that requires analgesic including cancer. Findings from our study showed that pain medication was higher among cancer survivors residing in midwest and south compared to individuals without cancer history. The utilization of narcotic analgesic combinations was higher among cancer survivors residing in south;

opioids utilization was higher among cancer survivors residing in midwest, south and west. Based on MSA, the utilization of pain medications in urban and rural were nearly similar across both study groups. However, for individual class of drugs, when compared to individuals without cancer history, the utilization of narcotic analgesic combinations was higher among cancer survivors residing in rural and opioids use was higher across both categories of MSA.

c. Clinical factors:

It was documented that cancer survivors currently smoking experiences more pain.[96] Based on smoking status, our study found that the utilization of pain medications were nearly similar across both study groups. However, for individual class of drugs, when compared to individuals without cancer history, the utilization of narcotic analgesic combinations was higher among cancer survivors currently smoking and opioids use was higher across both categories of smoking status. Studies have reported that obese individuals were more likely to experience pain.[97] Our study found that the utilization of pain medications among obese were nearly similar across both study groups. However, for individual class of drugs, the utilization of narcotic analgesic combinations was higher among obese cancer survivors; opioids utilization was higher among cancer survivors across all BMI categories. Among the cancer survivors experiencing extreme and moderate pain, the utilization of total pain medications and opioid class was higher compared to individuals without cancer history. Chronic conditions are defined as the diseased state that are persistent; expected to last at least $\geq$ 12 months causes limitations in self-care, independent living, social interactions and/or in the need for ongoing medical intervention.[98,99] The chronic condition requires aggressively approach to treat and has been used in epidemiological studies as an indicator of higher medical expenditure and resource utilization. Looking at individuals with different comorbidities, the pain medication use was higher among cancer survivors with arthritis, asthma, chronic bronchitis, diabetes, heart disease, hypertension, stroke and high cholesterol compared to general population presenting same comorbidities. When both the study groups are compared for narcotic analgesic combinations utilization, it was higher among cancer survivors with hypertension, stroke and high

cholesterol; opioids utilization was higher among cancer survivors with arthritis, asthma, chronic bronchitis, diabetes, heart disease, hypertension, and high cholesterol. Moreover, the pain medications use was higher among cancer survivors with presence of 2 or at least 3 chronic conditions. When the percentage utilization for individual class is compared to individual without cancer history, the narcotic analgesic combinations claims was higher among cancer survivors with no comorbidities, presence of 1 or 2 chronic conditions; opioids utilization was higher across all categories of chronic conditions among cancer survivors. Studies have shown that patient with cancer of visceral organs and bone have the highest prevalence of pain.[27] Findings from our study showed that from total pain medications use among lung and bone cancer survivors, more than half of the pain prescription claims constitutes of opioids and narcotic analgesic combinations class. Many cancer survivors experience pain during or after cancer treatment and early stage of diagnosis; the findings from our study showed that the pain medication use reported by cancer survivors currently diagnosed was 40.4 million (58.2%) and among previously diagnosed was 29.0 million (41.8%). Similarly, among those with <2 years since first cancer diagnosis, the pain medication use reported was 20.3 million (29.2%).

d. Economic factors:

Pharmacological treatment to manage cancer pain is costly particularly for prescriptions of narcotic analgesic combinations and opioids class of drugs. Having a diagnosis of cancer may limit employment opportunities, which in turn may affect insurance status. Cancer survivors may continue work after treatment; however, many cannot because of the pain and long-term effect due to illness. In a systematic review conducted by Mehnert *et al*., 63.5% (range 24% - 94%) of cancer survivors returned to work after treatment.[67] Cancer survivors who do not continue work either stay at home, are unemployed or retire earlier than planned. Thus, unemployment, low income and lack of insurance are economic barriers to healthcare access and prevent many patients from getting optimal medical care. When these economic factors were checked for distribution of pain medication, the findings from our study showed that compared to individuals without cancer history, the utilization of pain medications was higher among

unemployed cancer survivors. The utilization of narcotic analgesic combinations was higher among unemployed cancer survivors and opioids use was higher across both categories of employment. Based on family income, pain medications use was higher among cancer survivors with high family income. The utilization of narcotic analgesic combinations was higher among cancer survivors with poor and low family income; opioids utilization was higher among cancer survivors across all categories of family income. Based on insurance coverage, pain medications use was higher among cancer survivors insured through private or public only coverage compared to individual without cancer history. The utilization of narcotic analgesic combinations was higher among cancer survivors insured through public only coverage; opioids utilization was higher among cancer survivors across all categories of health insurance coverage.

IV. HRQoL among cancer survivors compared to individuals without cancer history

The Quality of Life is multidimensional concept that incorporates individual physical, mental, social and spiritual well-being. Pain is strong contributor that negatively affects cancer patient's functional status and quality of life. According to data from NHIS, nearly 25% cancer survivors reported decreased in QOL due to physical and 10.0% due to mental problems.[72] Our findings were consistent with other published studies where the PCS scores were lower among cancer survivors and MCS scores were not notably different from general population.[72,100] Our study documented cancer survivors had PCS and MCS scores 43.9(SE=0.20) and 50.2(SE=0.16) compared to individuals without cancer history, 50.0(SE=0.07) and 51.2(SE=0.05) respectively; these differences across both study group was significant.

The physical well-being score, as measured by SF-12, represents the degree to which symptoms and side effects such as pain, affects general health and ability to perform daily and/or work related physical activities. Similarly, mental well-being refers to ability of patient to cope up with disease, control fear, anxiety and perform daily and/or work related mental activities like memory and concentration. The

overall PCS scores were significantly lower among cancer survivors and MCS scores were not notably different from general population.

Based on socio-demographic factors, the MCS scores were lower among cancer survivors with age ≤ 55, non-Hispanic Blacks, Hispanics and those who are widowed/divorced or separated; whereas, PCS scores were lower for all socio-demographics factors across all categories compared to individuals without cancer history. Based on geographical factors, the mean score for MCS scores obtained for both, region and MSA was nearly ≥ 50 representing better mental health well-being. However, the PCS scores were lower for geographic factors across all categories compared to individuals without cancer history indicating poorer physical functioning. Based on clinical factors, poor mental HRQoL scores were reported among cancer survivors smoking, underweight, currently experiencing extreme pain and having asthma. Whereas, the poor physical HRQoL scores were reported across all categories of smoking status, BMI, pain perception, number and type of comorbidities compared to individuals without cancer history. Individuals with bone and gynecological cancer reported lower MCS scores and those with gastrointestinal, lung, hematological and bone reported lower PCS scores. Notably, the poor physical functioning was reported across all categories of type of cancer, cancer status, and years since first cancer diagnosis compared to individuals without cancer history. Increased financial burden because of the cancer and its treatment is the strongest independent factor resulting in poor HRQoL.[101] Based on the economic factors, the MCS scores were lower among cancer survivors with poor, near poor or low family income and among those who were uninsured. However, the PCS scores were lower for economic factors across all categories compared to individuals without cancer history indicating poorer physical functioning.

The lower HRQoL scores indicate cancer survivors are in pain and need to be screened appropriately for their physical and psychological concern. Identifying who in the cancer survivor's population is at risk of poor health status is important first step in direction to develop appropriate target interventions with potential to improve cancer survivorship and reduce cancer burden.

V. HRQoL among cancer survivors stratified by opioid exposure

Despite continuing research and extensive data on HRQoL among cancer survivors, we do not yet have an estimate on mental and physical health scores compared to population norms stratified by pain medication use. Three groups were categorized among cancer survivors and individuals without cancer history to compare HRQoL scores: (1) individuals with opioid exposure (opioids, narcotic analgesic combinations), (b) no opioid use but at least one prescription for pain medication (adjuvant analgesics and non-opioids such as NSAIDs, salicylates, non-narcotic analgesics combinations) and (c) without pain medication. A high percentage of cancer survivors (35.0%) were identified taking opioids for the pain due to disease or for treatment compared to individuals without cancer history (22.2%).

As hypothesized, this study documents prevalence of poor HRQoL scores among cancer survivors stratified by opioid exposure compared to individuals without cancer history. The lowest PCS and MCS scores were reported by cancer survivors using opioids. The lower HRQoL scores indicate cancer survivors are in pain and need to be screened appropriately for their physical and psychological concern. However, this study does not establish the casual relationship between the two events; if opioid use resulted in poor HRQol scores or because of lower PCS and MCS scores higher percent of cancer survivors use opioids.

Objective 2:

The impact of cancer and its treatment on general health, HRQoL and functional status is substantial, leading to questions about the most appropriate care for follow-up of post-treatment cancer survivors. With increasing survivorship, they encounter variety of physical, mental and emotional concerns in post-treatment phase of life. Pain is one of the most common physical concerns reported by post-treatment cancer survivors.[102] In study conducted by Barbera *et al*, among 45,118 ambulatory cancer survivors nearly half reported pain on first assessment around four years post-diagnosis.[103] No previous study exists that investigated pain medication or opioid use among post-treatment cancer survivors. The high

prevalence of pain and gaps in knowledge demands continued research to improve symptom management. The objective was designed to report opioid and overall pain prescriptions use by different socio-demographics, geographical, clinical and economic factors among post -treatment cancer survivors.

VI. Among post -treatment cancer survivors: Distribution of pain prescriptions by different socio-demographics, geographical, clinical and economic factors.

A significant association was found between pain medication use and several demographic factors. Aging itself is an independent risk factor for pain. Studies have shown poor cancer pain management among elderly patients.[87] Both the dose and frequency of pain medication decreases as age increases.[60] As consistent with other studies the logit model from our study implies significantly higher odds of not receiving pain treatment among elderly compared to post-treatment cancer survivors age 18-34. Evidence exist that women seek health care services for pain at a higher rate than men.[88] However, a retrospective analysis of cancer patients referred for cancer pain treatment found no sex differences in pain disability or intensity.[104] Our study found non-significant association across sex and pain medication use. A pain management discrepancy exists among racial/ethnic minority patients compared to whites. It has been well documented that African Americans, Hispanics, and Asians are often undertreated.[89,105] Based on race/ethnicity, individuals were classified as: (i) non-Hispanic, Whites; (ii) non-Hispanic, Blacks; (iii) Hispanics; (iv) non-Hispanic, Other/multiple race. Consistent with other published studies, our study documented post-treatment cancer survivors belonging to non-Hispanic, Blacks race group received significant lower count [0.72 (0.55 - 0.95)] of pain prescriptions compared to non-Hispanic, Whites. Additionally, patients belonging to non-Hispanic, other races (Asian, American Indian, native Hawaiian, pacific islander, multiple race) had significantly higher odds of not receiving pain prescriptions [OR= 2.15 (1.03 - 4.48)] compared to non-Hispanic, Whites. Education was also documented to be associated with pain medication use. One of the concerns with prescribing pain medication is that the patient will slide into pattern of misuse because of lack of education and understanding. However, a non-significant association was obtained across education status and pain medication use. The literature suggests spouse

of cancer patients were more concerned about cancer pain[93]; hence, the assumption was married cancer survivors will report higher pain prescription claims. However, our study found non-significant association across marital status and pain medication use.

Based on geographical factors no significant difference in pain utilization was observed across regions. However, pain prescription counts were significantly lower among cancer survivors residing in urban compared to rural.

It was investigated that cancer survivors who continue smoking may experience more pain, and higher pain-related disruptions in daily lives compared to non-smokers.[96] Our study found that compared to non-smokers, post-treatment cancer survivors currently smoking reported significantly higher count of pain prescriptions. Overweight and obese have been related to poorer cancer outcomes.[106] Studies reported that obese individuals are more likely to experience pain; individuals with BMI of 30.0–34.9, 35.0–39.9 or over 40 kg/m^2 are 1.7, 1.9 and 2.3 times as likely as non-obese individuals to report severe pain.[97] Our study documented significant higher pain utilization among obese post-treatment cancer survivors compared to non-obese. Significant higher counts of pain prescription were reported by individuals currently experiencing high/severe pain and among those experiencing change in pain over time (from mild/moderate to high/severe and vice-versa) compared to post-treatment cancer survivors with no pain. Studies have shown that patients with cancer of visceral organs and bone have the highest prevalence of pain.[27] We did not found any significant relationship between type of cancer and pain medication use. Reports suggest that cancer survivors experience pain during or after cancer treatment and during early stage of diagnosis[32]; however, we did not find any significance across years since first cancer diagnosis and pain medication use. Chronic conditions are persistent; expected to last at least $\geq$ 12 months causes limitations in self-care, independent living, social interactions and/or in the need for ongoing medical intervention.[98,99] Chronic conditions require aggressive approaches to treatment and has been used in epidemiological studies as an indicator of higher medical expenditure and resource utilization. Our study found that the pain medication count was significantly higher among post-treatment cancer survivors with

arthritis compared to those without painful conditions. Since, mental health disorders are directly related to drug misuse, abuse, and addiction, cancer patients need to be carefully prescribed pain medication under supervision. The pain medication count was significantly higher among post-treatment cancer survivors with bipolar disorder compared to those without mental disorder. Whereas, the count was significantly lower among post-treatment cancer survivors with adjustment disorder compared to those without comorbid condition. No significant association was obtained across post-treatment cancer survivors with history of substance/drug abuse and pain medication use.

The financial factors like income, employment status and insurance status plays vital role in cancer survivorship. Situations such as unemployment, low income and lack of insurance present economic barriers and prevent many patients from getting optimal medical care. Our study found significant higher pain prescription count among post-treatment cancer survivors with higher income and among those with change in income compared to individuals with low family income. Employment was associated with significant lower count of pain prescription. A significant higher prescription count was reported by post-treatment cancer survivors with change in insurance status compared to uninsured.

VII. Among post -treatment cancer survivors: Distribution of Opioid prescriptions by different socio-demographics, geographical, clinical and economic factors.

Study conducted by Bernabei *et al.,* suggested the elderly cancer survivors with daily pain were more likely to receive no analgesia (OR=1.40, 1.13 – 1.73).[60] Previous studies showed that compared to younger, elderly cancer individuals were prescribed lower amount of opioids analgesic.[107,108] The logit model from our study implies significantly higher odds of not receiving opioid treatment across age groups 65-74, 75-84, compared to post-treatment cancer survivors age 18-34. This may be due to perception about pain prevalence among elderly. Many older adults feel pain just by natural part of aging. The fact that older patients handles medication differently in terms of absorption, distribution, metabolism and excretion compared to younger patients may be reason for undertreatment. With increasing age, the

kidney and liver functioning decreases and older individuals are at higher risk of side effects and developing toxicity associated with NSAIDs, opioids. Additionally, there is always fear of polypharmacy and drug-drug interactions. Having chronic medical comorbidity may again be a reason for poor cancer pain management among elderly. The reports published on sensitivity to opioids between the sexes found no difference in opioids use[109]. As consistent with other studies, we found non-significant association across sex and opioid medication use. Published study suggests that compared to whites, patients of minority races receive lower dose of opioids even tough pain severity levels are comparable.[89] Consistent with other studies, we found post-treatment cancer survivors belonging to non-Hispanic, other races had significantly higher odds [OR= 2.14 (1.03 - 4.43)] of not receiving opioid prescription compared to non-Hispanic, Whites.

The reasons for this discrimination in prescribing analgesic could include patient behavior or physician bias. The patient-related behavior could include how aggressive patient would be in expressing pain and asking pain relief, patient assertiveness, social distance, trust, patient-physician communication and language.[21,68,91] Physician-related barriers may include perception of patient, reluctant to prescribe opioids even if necessary, concerns about tolerance, abuse, side-effects, legal regulations, perception of negative public impression for opioids, administrative constraints, ignoring pain with greater focus on treatment of cancer, polypharmacy and drug reaction.[24,68] Additionally, some physicians may have prescribed less potent or non-opioids medication because of difficulties faced by some minorities in acquiring opioid prescription from pharmacy. However, the reasons and these dimensions were not explored in current study. One of the concerns with prescribing opioids is the patient will slide into pattern of misuse because of lack of education and understanding. It was shown that among US adults, lower education level were associated with higher opioid use.[92] Our study supports the previous findings and reported significant lower counts of opioid prescription among post-treatment cancer survivors with higher education compared to individuals with lower education. A non-significant association was obtained across marital status and opioid medication use.

Little has been investigated about opioid utilization among cancer survivors based on geographical factors. The prescribing trends of opioids in US was described by Olsen *et al*., according to which when compared to patients residing in west, those in northeast (OR=0.60 [95% CI 0.51 – 0.69]) or midwest (OR = 0.75 [95% CI 0.66 – 0.85]) had significantly lower odds of visit where opioid was prescribed.[94]

Based on geographical factors, findings from out study showed compared to post-treatment cancer survivors residing in northeast those residing in midwest had significant lower odds of not receiving opioid prescription. A non-significant association was obtained across MSA and opioid medication use.

Smoking has been linked to cause cancer and it has been investigated that cancer survivors who continues smoking experience more pain, and higher pain-related disruptions in daily lives compared to non-smokers.[96] Our study found that compared to non-smokers, post-treatment cancer survivors currently smoking had significantly higher count of opioid prescriptions. Adopting and maintaining healthy lifestyle has potential to increase survival and improve HRQoL. Excess body weight have been linked to cancer and related poorer outcomes.[106] Obese individuals are more likely to experience pain; individuals with BMI of 30.0–34.9, 35.0–39.9 or over 40 kg/m^2 are 1.7, 1.9 and 2.3 times as likely as non-obese individuals to report severe pain.[97]. Our study documented significant higher opioid counts among obese post-treatment cancer survivors compared to non-obese. Significant higher counts of opioid prescription was reported by individuals currently experiencing mild/moderate, high/severe pain and among those experiencing change in pain over time (from mild/moderate to high/severe and vice-versa) compared to post-treatment cancer survivors with no pain.

Cancer pain due to tumor is common and patients with cancer of visceral organs and bone have the highest prevalence of pain.[27] Unfortunately, we found no significant relationship between type of cancer and opioid medication use. Literature suggests that cancer survivors experience pain during or after cancer treatment and during early stage of diagnosis. We found that post-treatment cancer survivors with 1-5 years since first cancer diagnosis reported significant higher count of opioid prescription compared to

individuals diagnosed with less than a year. Comorbidities are tied to lowering health outcomes and mandate more complex treatment and clinical management. Our study found that the opioid medication count was significantly higher among post-treatment cancer survivors with arthritis compared to those without painful condition. Individuals with multi-painful comorbidities reported significant more count of opioid prescription. Surprisingly, fracture was associated significant lower count of opioid prescription. The logit model from the study implies significantly lower odds of not receiving opioid treatment across post-treatment cancer survivors with back and neck pain, connective tissue disorder and pelvic pain compared to individuals without respective painful conditions. Previous study suggest that individuals with mental health disorders (anxiety, mood, bipolar, depression) are more likely to prescribed opioids and are long term chronic users.[110] The relationship between opioid use and mental health disorder always has remained complicated as one of the concerns for prescribing opioids to individual with mental health disorder is the patient may slide into the pattern of opioid abuse. It has been well documented that mental conditions are associated with increased risk for chronic opioid use.[111] The results from our study showed the odds of not receiving opioid prescriptions among post-treatment cancer survivors with adjustment disorder and multi-mental comorbidity condition were significantly higher compared to individuals without respective mental condition. Whereas, among post-treatment cancer survivors with bipolar, the odds of not receiving opioid prescriptions were significantly lower compared to individuals without bipolar condition. Individuals having history of alcohol and substance abuse or dependence; history of mental disorder is at increased risk of switching back to behavior pattern and more likely to claim opioids. However, no significant association was obtained across post-treatment cancer survivors with history of substance/drug abuse and opioid medication use.

Pharmacological treatment to manage cancer pain is costly particularly prescriptions of narcotic analgesic combinations and opioids class of drugs. Having a diagnosis of cancer may limit employment opportunities, which in turn may affect insurance status. Many cancer survivors manage to continue work after treatment; however, nearly 37.0% of cancer survivors cannot because of the pain and long-term effect due to illness. In a systematic review conducted by Mehnert *et al*., 63.5% (range 24% - 94%) of

cancer survivors returned to work after treatment.[67] Cancer survivors who do not continue work either stay at home, are unemployed or retire early than planned. The financial factors like income, employment status and insurance status plays vital role in cancer survivorship. Situations such as unemployment, low income and lack of insurance present economic barriers and may prevent many patients from getting optimal medical care. It is also very likely that patients who were employed were having lower pain. Since, in this study we did not measure prevalence of pain among cancer survivors. In present study, employment was associated with significant lower count of pain prescription [0.65 (0.53 - 0.81)] and of opioid prescription [0.69 (0.51 - 0.92)] among post-treatment cancer survivors compared to unemployed. The reasons for increased use of pain medication among unemployed could be prevalence of pain years after treatment forcing post-treatment cancer survivors to make work-related changes and on the other side several studies have linked unemployment to pain killer abuse. Unemployed individuals are more likely to abuse opioids than full time workers. Hollingsworth *et al*., reported that:

"As the unemployment rate for a given county increases by one percentage point, the opioid death rate per 100,000 rises by 0.19 (3.6%) and the opioid overdose ED visit rate per 100,000 increases by 0.95 (7.0%)"[112]

Based on financial factors, our study found significant higher opioid prescription count among post-treatment cancer survivors with higher income and among those with change in income compared to individuals with low family income. A significant higher opioid prescription count was reported by post-treatment cancer survivors with change in insurance status compared to uninsured individuals.

Objective 3:

VIII. Work productivity

Studies showed that cancer survivorship was associated with substantial lost in productivity including decrease in work hours, employment disability and more missed work days.[113,114] Cancer survivors may experience fatigue, physical and emotional distress when pain unexpectedly persists years after completion of cancer related treatment. In one study, it was found that the cancer survivors experience these symptoms 10 years following cancer treatment limiting cancer survivor's productivity at home and at work.[64] In the Indiana cancer pain and depression study conducted by Kroenke *et al*., on average, 12 to 20 days per month cancer patients with pain were disabled; with 28.0% to 55.0% unable to work because of cancer.[70] Study conducted by Ekwueme *et al,* reported among cancer survivors who were employed from time since cancer diagnosis, malignancy or its treatment interfered with mental tasks required at work (14.0%), physical tasks (25.0%) and 3/4th of them reported productive at work.[115]

Study 3a:

Purpose of this study was to identify current patterns about pain medication use and productivity measures obtained from SF-12. A significant association was obtained across productivity measures and pain medication use. On question, *"during past 4 weeks, as result of physical health, limited in kind of work or other activities?"*, and findings from the study showed that nearly half (54.0%) of post-treatment cancer survivors experienced little to no work-related limitations. Among those who experienced no work limitation, significant higher proportion (73.0%) of respondents were non-users of pain medications. Among those who experienced work limitations most of the time (14.0%), significant higher proportion of respondents (42.8%) were chronic users of pain medications. Similar outcomes were obtained when asked*, "during past 4 weeks, as result of physical problems, accomplished less than would like?".*

On SF-12 question, *"during past 4 weeks, as result of mental problems, did work or other activities less carefully than usual*?", nearly 62.0 % of post-treatment cancer survivors experienced little/no work limitation; among those who experienced no work limitation, a significant higher proportion (64.5%) were non-users of pain medications. Among those who experienced work limitations most of the time (5.1%), significant higher proportion (43.2%) of respondents were chronic users of pain medications. Similar results with pain medication use was obtained for SF-12 question, "*during past 4 weeks, as result of mental problems, accomplished less than would like?*".

The role of opioids has always remained complex as clinically they are important to manage chronic pain; however, they are also known to alter brain function and negatively affect productivity. Employers are concerned that opioid use may have strong potential to cause impairment, health and safety hazards, absenteeism, lack of productivity, risk of injury at workplace, violence and increased employee turnover.[116] Our study found significant difference across various categories of productivity measures and opioid use. On SF-12 question, *"during past 4 weeks, as result of physical health, limited in kind of work or other activities?"*, findings from the study showed that nearly half of post-treatment cancer survivors experienced little to no work-related limitation; among which a significant higher proportion (83.7%) were non-users of opioid medications. Among those respondents who experienced work limitation most of the time (14.0%), significant higher proportion of respondents (42.8%) were non-users of opioid medications. A similar outcome was obtained when association between opioid use and productivity measure, *"during past 4 weeks, as result of physical problems, accomplished less than would like?* was checked.

When asked, *"during past 4 weeks, as result of mental problems, did work or other activities less carefully than usual*?", nearly 62.0 % of post-treatment cancer survivors experienced little/no work limitation; among which a significant higher proportion (77.3%) were non-users of opioid medications. Among those who experienced work limitation most of the time (5.1%), a significant higher proportion (44.6%) of respondents were non-users of opioid medications. A similar result was obtained for

productivity measure, "*during past 4 weeks, as result of mental problems, accomplished less than would like?*".

Study 3b:

Cancer survivors encounter challenges such as changes in work-related schedule, hours, wages, decline in productivity, more missed work days, risk for unemployment, less likely to be reemployed, job discrimination, retire early than planned.[113,114] In a systematic literature review about employment and work-related issues among cancer survivors, it was found between 50.0%-86.0% of cancer survivors experienced temporary changes in work schedules, work hours, wages and 63.5% (range 24 – 94%) returned to work.[117] Cancer survivors were significantly more likely to experience limitation of daily activities (OR=2.97), functional limitations (OR=1.74) and psychological disability (OR=2.18), compared to individuals without history of cancer.[75]

Using CSAQ productivity measures, we found 63.0% of post-treatment cancer survivors were employed of which nearly 50.0% did not make work-related changes. Among those who made work-related changes, 70.0% (n=142) took extended paid time off (vacation, sick time and/or disability) from work. Approximately, 46.0%, 20.0% and 10.0% respectively reported unpaid time off from work, work schedule change from full-time to part time and change to less demanding job. Around 12.0% of post-treatment cancer survivors retired earlier than planned. Among post-treatment cancer survivors who were employed at any time since cancer diagnosis, malignancy and its treatment interfered with ability to perform physical tasks (25.0%) and mental tasks (16.0%) required at work; one-fourth of post-treatment cancer survivors reported being less productive at work. These estimates were similar to study conducted by Ekwueme *et al,* whereby, the lost productivity among cancer survivors stratified by sex was reported.[115] According to this study, among cancer survivors who were employed from time since cancer diagnosis, malignancy or its treatment interfered with mental task required at work (14.0%), physical tasks (25.0%) and 75.0% of them reported productive at work.[115] A significant association was obtained

between the CSAQ productivity measures and pain medication use. Among post-treatment cancer survivors (80.0%) who did not made changes in work schedule from full-time to part-time, a significant higher proportion (53.5%) of respondents were non-users of pain medications. Similarly, among those (75.0%) who reported malignancy did not interfered with ability to perform physical tasks at job, a significant higher proportion (54.7%) of respondents were non-users of pain medications. When association between opioid use and productivity measures was checked, among post-treatment cancer survivors (75.0%) who do not felt less productive at work, a significant higher proportion (73.2%) of respondents were non-users of opioid medications.

Findings from our study and Ekwueme *et al* suggest that many post-treatment cancer survivors remained employed; cancer or treatment did not interfered with physical or mental task at work and they remained productive. We hypothesize that these post-treatment cancer survivors might be returning to work to maintain employer sponsored health insurance coverage. Job loss would result in losing health insurance thereby increasing financial burden on self/family and restricting access to optimal care.

IX. Limitation

Despite the strengths of large, US civilian non-institutionalized population-based database, there were several limitations with the study. The responses captured are typically provided by one respondent for the entire household; may not be able to report precisely presenting reporting bias. The cross-sectional design does not allow measuring the changes in variables over time. In general, the MEPS respondents are longitudinally followed up to 2.5 years. Some of inherent limitation working on MEPS database can be small sample size and missing data as it may preclude some analyses. The MEPS public release files provide clinical diagnosis codes which are broadly categorized in CCCs limiting ability to assess finer diagnostic gradations.

It was not possible to review patient specific clinical characteristics such as tumor size and extent of spread, tumor grade, lymph node involvement, presence of metastatic tumor and cancer staging limiting

our abilities to control for disease severity. These factors are associated with pain prevalence. The lack of information on cancer treatment initiation and its duration could have affected the interpretation of the results. The MEPS survey generally includes only small numbers of rare cancers and mainly comprise of long-term survivors participating many years after cancer diagnosis.[118] For confidentiality reasons, age variable is top-coded at 85 years. Top coding is the process whereby values on the higher end are grouped together. In MEPS, the age variable is top coded at 85 years for data privacy protection because comparatively few sampled respondents are older than 85 years. Any respondent with value 85 on age variables does not reflect age of 85 years; rather it means 85 years or over. Individuals with Age $\geq$ 85 were excluded from regression analysis as biased estimate would be generated in calculating years since first cancer diagnosis. Unfortunately, the VIF and Fishers Exact test that applies to complex survey data accounting for stratified multistage probability sample is not available and inferences were made using unweighted sample count. The diagnostic tests for comparing various types of regression model using survey database are still being developed in STATA; the goodness-of-fit tests for zero-inflated Poisson models using survey designs is not available. Findings obtained for productivity measures are to be carefully interpreted since we included work-related productivity and excluded productivity at home.

In spite of these limitations, this is the first retrospective study to report pain medication use among cancer survivors using population-based household survey database. The study has several strengths such as an algorithm was developed to identify cancer survivors using combination of self-report history and CCCs. Validation study have shown that identifying cancer survivors only through self-report question tend to underestimate cancer prevalence by false negative reports.[119] Pain medications were identified using drug name and not through 3-level nested Multum classification. Our study employed multiple years of the MEPS to report nationally representative estimates of pain medication utilization, expenditure, patient cost share, HRQoL and work productivity among adult cancer survivors.

X. Conclusion

Cancer survivors can feel pain at any stage from diagnosis, during treatment and even after cure. In order to manage cancer pain, WHO have outlined guidelines for the use of pain medications. This study documents substantial changes in the utilization of pain medications in the US over time. Compared to year 2008, the number and the percent of cancer survivors taking pain medications increased in year 2013. There was significantly higher pain medication use among cancer survivors compared to individuals without cancer history; particularly in the opioid and adjuvant class. The total cost to treat cancer pain increased and overall spending in terms of patient share decreased. The overall PCS scores were significantly lower among cancer survivors and MCS scores were not notably different from general population. Stratified by opioid exposure, the worst PCS and MCS scores were reported by opioid users.

The odds of not receiving pain medication were significantly higher among elderly, minorities belonging to non-Hispanic, other race group. From the count model, significant higher counts were reported by post-treatment cancer survivors currently smoking, experiencing high/severe pain or change in pain over time, unhealthy lifestyle (obese), having comorbidities such as arthritis, bipolar disorder; higher income or income change over time, insurance status change over time and significant lower counts of pain medications were reported by post-treatment cancer survivors, belonging to non-Hispanic Blacks, residing in urban, having adjustment disorder and currently employed.

The odds of not receiving opioid medications were significantly higher among elderly, minorities belonging to other race group, having adjustment disorder, more than one mental health condition. From the count model, significant higher counts were reported by post-treatment cancer survivors currently smoking; experiencing mild/moderate, high/severe pain or change in pain over time, having comorbidities such as arthritis, more than one painful conditions; higher income or income change over time, insurance status change over time and significant lower counts of opioid medication were reported by post-treatment cancer survivors with higher education and currently employed.

Nearly 54.0%-62.0% of post-treatment cancer survivors experienced little/no work limitation reported through SF-12 productivity measures. Among those who experienced no work limitation, significant higher proportion of respondents were non-users of pain medications and those who experienced work limitation most of the time, significant higher proportion of respondents were chronic users of pain medications. Significant difference existed across various categories of SF-12 productivity measures and opioid medication use. Among those who experienced no work limitation, significant higher proportions of respondents were non-users of opioids. From CSAQ productivity measures we found many post-treatment cancer survivors were employed, did not made work-related changes and remained productive.

APPENDICES

Appendix A: Types of Cancer Identified Using Clinical Classification Codes

Condition	ICD-9CM	CCC
Head/ Neck	**(a) Cancer of head and neck** 1400 1401 1403 1404 1405 1406 1408 1409 1410 1411 1412 1413 1414 1415 1416 1418 1419 1420 1421 1422 1428 1429 1430 1431 1438 1439 1440 1441 1448 1449 1450 1451 1452 1453 1454 1455 1456 1458 1459 1460 1461 1462 1463 1464 1465 1466 1467 1468 1469 1470 1471 1472 1473 1478 1479 1480 1481 1482 1483 1488 1489 1490 1491 1498 1499 1600 1601 1602 1603 1604 1605 1608 1609 1610 1611 1612 1613 1618 1619 1950 2300 2310 V1001 V1002 V1021	011
	(b) Cancer of brain and nervous system 1910 1911 1912 1913 1914 1915 1916 1917 1918 1919 1920 1921 1922 1923 1928 1929 V1085 V1086	035
	(c) Cancer of thyroid 193 25802 25803 V1087	036
Gastrointestinal	**(a) Cancer of esophagus** 1500 1501 1502 1503 1504 1505 1508 1509 2301 V1003	012
	(b) Cancer of stomach 1510 1511 1512 1513 1514 1515 1516 1518 1519 20923 2302 V1004	013
	(c) Cancer of colon 1530 1531 1532 1533 1534 1535 1536 1537 1538 1539 1590 20910 20911 20912 20913 20914 20915 20916 2303 V1005	014
	(d) Cancer of rectum and anus 1540 1541 1542 1543 1548 20917 2304 2305 2306 79670 79671 79672 79673 79674 79676 V1006	015
	(e) Cancer of liver and intrahepatic 1550 1551 1552 2308 V1007	016
	(f) Cancer of pancreas 1570 1571 1572 1573 1574 1578 1579	017
	(g) Cancer of other GI organs 1520 1521 1522 1523 1528 1529 1560 1561 1562 1568 1569 1580 1588 1589 1591 1598 1599 20900 20901 20902 20903 2307 2309 V1000 V1009	018
Lung/ bronchus	**(a) Cancer of bronchus, lung** 1622 1623 1624 1625 1628 1629 20921 2312 V1011	019
	(b) Cancer; other respiratory and intra-thoracic	020

	1620 1630 1631 1638 1639 1650 1658 1659 2311 2318 2319 V1012 V1020 V1022	
Breast	**(a) Cancer of breast** 1740 1741 1742 1743 1744 1745 1746 1748 1749 1750 1759 2330 V103	024
Gynecological	**(a) Cancer of uterus** 179 1820 1821 1828 2332 V1042	025
	(b) Cancer of cervix 1800 1801 1808 1809 2331 7950 V1041	026
	(c) Cancer of ovary 1830 V1043	027
	(d) Cancer of female genital organ 181 1832 1833 1834 1835 1838 1839 1840 1841 1842 1843 1844 1848 1849 2333 23330 23331 23332 23339 79516 V1040 V1044	028
	(e) Benign neoplasm of uterus 2180 2181 2182 2189 2190 2191 2198 2199	046
Prostate	**(a) Cancer of prostate** 185 2334 V1046	029
Urogenital	**(a) Cancer of testis** 1860 1869 V1047	030
	(b) Cancer of other male genital 1871 1872 1873 1874 1875 1876 1877 1878 1879 2335 2336 V1045 V1048 V1049	031
	(c) Cancer of bladder 1880 1881 1882 1883 1884 1885 1886 1887 1888 1889 2337 V1051	032
	(d) Cancer of kidney & renal pelvis 1890 1891 20924 V1052 V1053	033
	(e) Cancer of other urinary organs 1892 1893 1894 1898 1899 2339 V1050 V1059	034
Hematological	**(a) Leukemia** 20240 20241 20242 20243 20244 20245 20246 20247 20248 2031 20310 20311 20312 2040 20400 20401 20402 2041 20410 20411 20412 2042 20420 20421 20422 2048 20480 20481 20482 2049 20490 20491 20492 2050 20500 20501 2051 20510 20511 20512 2052 20520 20521 2053 20530 20531 2058 20580 20581 20582 2059 20590 20591 2060 20600 20601 20602 2061 20610 20611 20612 2062 20620 20621 20622 2068 20680 20681 20682 2069 20690 20691 20692 2070 20700 20701 20702 2071 20710 20711 20712 2072 20720 20721 20722 2078 20780 20781 20782 2080 20800 20801 2081 20810 20811 20812 2082 20820 20821 20822 2088 20880 20881 20882 2089 20890 20891 20892 V1060 V1061 V1062 V1063 V1069	039
	(b) Multiple Myeloma 2030 20300 20301 20302 2038 20380 20381	040

	(c) Hodgkins disease 20100 20101 20102 20103 20104 20105 20106 20107 20108 20110 20111 20112 20113 20114 20115 20116 20117 20118 20120 20121 20122 20123 20124 20125 20126 20127 20128 20140 20141 20142 20143 20144 20145 20146 20147 20148 20150 20151 20152 20153 20154 20155 20156 20157 20158 20160 20161 20162 20163 20164 20165 20166 20167 20168 20170 20171 20172 20173 20174 20175 20176 20177 20178 20190 20191 20192 20193 20194 20195 20196 20197 20198 V1072	037
	(d) Non-Hodgkins lymphoma 20000 20001 20002 20003 20004 20005 20006 20007 20008 20010 20011 20012 20013 20014 20015 20016 20017 20018 20020 20021 20022 20023 20024 20025 20026 20027 20028 20030 20031 20032 20033 20034 20035 20036 20038 20041 20042 20043 20044 20045 20046 20047 20048 20051 20052 20053 20054 20055 20056 20057 20058 20060 20061 20062 20064 20065 20066 20067 20068 20070 20071 20072 20073 20074 20075 20076 20077 20078 20080 20081 20082 20083 20084 20085 20086 20087 20088 20200 20201 20202 20203 20204 20205 20206 20207 20208 20210 20211 20212 20213 20214 20215 20216 20217 20218 20220 20221 20222 20223 20224 20225 20226 20227 20228 20270 20271 20272 20273 20274 20275 20276 20277 20278 20280 20281 20282 20283 20284 20285 20286 20287 20288 20290 20291 20292 20293 20294 20295 20296 20297 20298 V1071 V1079	038
Bone	**(a) Cancer of bone and connective tissue** 1700 1701 1702 1703 1704 1705 1706 1707 1708 1709 1710 1712 1713 1714 1715 1716 1717 1718 1719	021
Unspecified	**(a) Cancer, other and unspecified primary** 1640 1641 1642 1643 1648 1649 1760 1761 1762 1763 1764 1765 1768 1769 1900 1901 1902 1903 1904 1905 1906 1907 1908 1909 1940 1941 1943 1944 1945 1946 1948 1949 1951 1952 1953 1954 1955 1958 20230 20231 20232 20233 20234 20235 20236 20237 20238 20250 20251 20252 20253 20254 20255 20256 20257 20258 20260 20261 20262 20263 20264 20265 20266 20267 20268 20922 20925 20926 20927 2340 2348 2349 7951 79511 79512 79513 V1029 V1081 V1084 V1088 V1089 V109 V1091 V711	041
	(b) Secondary malignancies 1960 1961 1962 1963 1965 1966 1968 1969 1970 1971 1972 1973 1974 1975 1976 1977 1978 1980 1981 1982 1983 1984 1985 1986 1987 19881 19882 19889 20971 20972 20973 20974 51181 78951	042
	(c) Malignant neoplasm without specification 1990 1991 1992 20920 20929 20930 20970 20975 20979	043
	(d) Neoplasms of unspecified nature 2350 2351 2352 2353 2354 2355 2356 2357 2358 2359 2360 2361 2362 2363 2364 2365 2366 2367 23690 23691 23699 2370 2371 2372 2373 2374 2375 2376 2377 23770 23771 23772 23773 23779 2379 2380 2381 2382 2383 2384 2385 2386 2387 23877 2388 2389 2390 2391 2392 2393 2394 2395 2396 2397 2398 23981 23989 2399	044
	(e) Maintenance chemotherapy, radiotherapy V580 V581 V5811 V5812 V661 V662 V671 V672	045
	(f) Other and unspecified benign neoplasm	047

	20940 20941 20942 20943 20950 20951 20952 20953 20954 20955 20956 20957 20960 20961 20962 20963 20964 20965 20966 20967 20969 2100 2101 2102 2103 2104 2105 2106 2107 2108 2109 2110 2111 2112 2113 2114 2115 2116 2117 2118 2119 2120 2121 2122 2123 2124 2125 2126 2127 2128 2129 2130 2131 2132 2133 2134 2135 2136 2137 2138 2139 2140 2141 2142 2143 2144 2148 2149 2150 2152 2153 2154 2155 2156 2157 2158 2159 2160 2161 2162 2163 2164 2165 2166 2167 2168 2169 217 220 2210 2211 2212 2218 2219 2220 2221 2222 2223 2224 2228 2229 2230 2231 2232 2233 22381 22389 2239 2240 2241 2242 2243 2244 2245 2246 2247 2248 2249 2250 2251 2252 2253 2254 2258 2259 226 2270 2271 2273 2274 2275 2276 2278 2279 22800 22801 22802 22803 22804 22809 2281 2290 2298 2299 V1272	
Skin	**(a) Melanomas of skin** 1720 1721 1722 1723 1724 1725 1726 1727 1728 1729 V1082	022
Non-epithelial cancer of skin	**(a) Other non-epithelial cancer of skin** 17300 17301 17302 17309 17310 17311 17312 17319 17320 17321 17322 17329 17332 17339 17340 17341 17342 17349 17350 17351 17352 17359 17360 17361 17362 17369 17370 17371 17372 17379 17380 17381 17382 17389 17390 17391 17392 17399 20931 20932 20933 20934 20935 20936 2320 2321 2322 2323 2324 2325 2326 2327 2328 2329 V1083	023

Appendix B: Types of Cancer Identified Using Interview Questions

Condition	What kind of cancer?	Full-year Consolidated Data File	Longitudinal Data File
Head/ Neck	(a) Cancer of brain and nervous system	CABRAIN	CABRAIY1, CABRAIY2
	(b) Cancer of larynx	CALARYNX	CALARYY1, CALARYY2
	(c) Cancer of mouth	CAMOUTH	CAMOUTY1, CAMOUTY2
	(d) Cancer of throat	CATHROAT	CATHROY1, CATHROY2
	(e) Cancer of thyroid	CATHYROD	CATHYRY1, CATHYRY2
Gastrointestinal	(a) Cancer of esophagus	CAESOPH	CAESOPY1, CAESOPY2
	(b) Cancer of stomach	CASTOMCH	CASTOMY1, CASTOMY2
	(c) Cancer of colon	CACOLON	CACOLOY1, CACOLOY2
	(d) Cancer of rectum and anus	CARECTUM	CARECTY1, CARECTY2
	(e) Cancer of liver and intrahepatic	CALIVER/ CAGALLBL	CALIVEY1, CALIVEY2
	(f) Cancer of pancreas	CAPANCRS	CAPANCY1, CAPANCY2
Lung/ bronchus	(a) Cancer of bronchus, lung	CALUNG	CALUNGY1, CALUNGY2
Breast	(a) Cancer of breast	CABREAST	CABREAY1, CABREAY2
Gynecological	(a) Cancer of uterus	CAUTERUS	CAUTERY1, CAUTERY2
	(b) Cancer of cervix	CACERVIX	CACERVY1, CACERVY2;
	(c) Cancer of ovary	CAOVARY	CAOVARY1, CAOVARY2;
Prostate	(a) Cancer of prostate	CAPROSTA	CAPROSY1, CAPROSY2
Urogenital	(a) Cancer of bladder	CABLADDR	CABLADY1, CABLADY2
	(b) Cancer of kidney & renal pelvis	CAKIDNEY	CAKIDNY1, CAKIDNY2

	(c) Cancer of testis	CATESTIS	CATESTY1, CATESTY2
Hematological	(a) Blood cancer	CABLOOD	CABLOOY1, CABLOOY2;
	(b) Leukemia	CALEUKEM	CALEUKY1, CALEUKY2;
	(c) Lymphoma	CALYMPH	CALYMPY1, CALYMPY2
Bone	(a) Cancer of bone	CABONE	CABONEY1, CABONEY2;
	(b) Cancer of connective tissue/muscle/fat	CAMUSCLE	CAMUSCY1, CAMUSCY2
Unspecified	(a) Cancer, other and unspecified primary	CAOTHER	CAOTHEY1, CAOTHEY2
Skin	(a) Melanomas of skin	CAMELANO	CAMELAY1, CAMELAY2
Non-epithelial cancer of skin	(a) Other non-epithelial cancer of skin	CASKINNM	CASKNMY1, CASKNMY2
	(b) Unknown skin cancer	CASKINDK	CASKDKY1, CASKDKY2
Source: MEPS Documentation: Full-year Consolidated Data File, Longitudinal Data File			

Appendix C: MEPS Priority Conditions

Condition		ICD-9 CM	CCC
1.	**Asthma**	**(a) Asthma** 49300 49301 49302 49310 49311 49312 49320 49321 49322 49381 49382 49390 49391 49392	128
2.	**Chronic Bronchitis**	**(a) Chronic obstructive pulmonary disease and bronchiectasis/ Emphysema** 490 4910 4911 4912 49120 49121 49122 4918 4919 4920 4928 494 4940 4941 496	127
3.	**Heart disease**	**(a) Coronary atherosclerosis and other heart disease** 4110 4111 4118 41181 41189 412 4130 4131 4139 4140 41400 41401 41406 4148 4149 V4581 V4582	101
		(b) Congestive heart failure; non-hypertensive 39891 4280 4281 42820 42821 42822 42823 42830 42831 42832 42833 42840 42841 42842 42843 4289	108
		(c) Myocardial Infraction 4100 41000 41001 41002 4101 41010 41011 41012 4102 41020 41021 41022 4103 41030 41031 41032 4104 41040 41041 41042 4105 41050 41051 41052 4106 41060 41061 41062 4107 41070 41071 41072 4108 41080 41081 41082 4109 41090 41091 41092	100
4.	**Hypertension**	**(a) Essential hypertension** 4011 4019	098
		(b) Hypertension with complications and secondary hypertension 4010 40200 40201 40210 40211 40290 40291 4030 40300 40301 4031 40310 40311 4039 40390 40391 4040 40400 40401 40402 40403 4041 40410 40411 40412 40413 4049 40490 40491 40492 40493 40501 40509 40511 40519 40591 40599 4372	099
5.	**Stroke**	**(a) Occlusion or stenosis of pre-cerebral arteries** 4330 43300 4331 43310 4332 43320 4333 43330 4338 43380 4339 43390	110
		(b) Other and ill-defined cerebrovascular disease 4370 4371 4373 4374 4375 4376 4377 4378 4379	111
		(c) Transient cerebral ischemia 4350 4351 4352 4353 4358 4359	112
6.	**High cholesterol**	**(a) Disorders of lipid metabolism** 2720 2721 2722 2723 2724	053
Source: MEPS Documentation- Medical Conditions File			

Appendix D: List of Painful Conditions

Condition		ICD-9CM	CCC
1.	Arthritis	**(a) Infective arthritis and osteomyelitis (except that caused by tuberculosis or sexually transmitted disease)** 00323 00324 0261 03682 05671 71100 71101 71102 71103 71104 71105 71106 71107 71108 71109 71110 71111 71112 71113 71114 71115 71116 71117 71118 71119 71120 71121 71122 71123 71124 71125 71126 71127 71128 71129 71130 71131 71132 71133 71134 71135 71136 71137 71138 71139 71140 71141 71142 71143 71144 71145 71146 71147 71148 71149 71150 71151 71152 71153 71154 71155 71156 71157 71158 71159 71160 71161 71162 71163 71164 71165 71166 71167 71168 71169 71170 71171 71172 71173 71174 71175 71176 71177 71178 71179 71180 71181 71182 71183 71184 71185 71186 71187 71188 71189 71190 71191 71192 71193 71194 71195 71196 71197 71198 71199 73000 73001 73002 73003 73004 73005 73006 73007 73008 73009 73010 73011 73012 73013 73014 73015 73016 73017 73018 73019 73020 73021 73022 73023 73024 73025 73026 73027 73028 73029 73030 73031 73032 73033 73034 73035 73036 73037 73038 73039 73070 73071 73072 73073 73074 73075 73076 73077 73078 73079 73080 73081 73082 73083 73084 73085 73086 73087 73088 73089 73090 73091 73092 73093 73094 73095 73096 73097 73098 73099	201
		(b) Rheumatoid arthritis and related disorder 7140 7141 7142 71430 71431 71432 71433 7144 71481 71489 7149 7200	202
		(c) Osteoarthritis 71500 71504 71509 71510 71511 71512 71513 71514 71515 71516 71517 71518 71520 71521 71522 71523 71524 71525 71526 71527 71528 71530 71531 71532 71533 71534 71535 71536 71537 71538 71580 71589 71590 71591 71592 71593 71594 71595 71596 71597 71598 V134	203
		(d) Other non-traumatic joint disorders 7130 7131 7132 7133 7134 7135 7136 7137 7138 71600 71601 71602 71603 71604 71605 71606 71607 71608 71609 71620 71621 71622 71623 71624 71625 71626 71627 71628 71629 71630 71631 71632 71633 71634 71635 71636 71637 71638 71639 71640 71641 71642 71643 71644 71645 71646 71647 71648 71649 71650 71651 71652 71653 71654 71655 71656 71657 71658 71659 71660 71661 71662 71663 71664 71665 71666 71667 71668 71680 71681 71682 71683 71684 71685 71686 71687 71688 71689 71690 71691 71692 71693 71694 71695 71696 71697 71698 71699 71810 71811 71812 71813 71814 71815 71817 71818 71819 71820 71821 71822 71823 71824 71825 71826 71827 71828 71829 71850 71851 71852 71853 71854 71855 71856 71857 71858 71859 71865 71870 71871 71872 71873 71874 71875 71876 71877 71878 71879 71880 71881 71882 71883 71884 71885 71886 71887 71888 71889 71890 71891 71892 71893 71894 71895 71897 71898 71899 71900 71901 71902 71903 71904 71905 71906 71907 71908 71909 71910 71911 71912 71913 71914 71915 71916 71917 71918 71919 71920 71921 71922 71923 71924 71925 71926 71927 71928 71929	204

		71930 71931 71932 71933 71934 71935 71936 71937 71938 71939 71940 71941 71942 71943 71944 71945 71946 71947 71948 71949 71950 71951 71952 71953 71954 71955 71956 71957 71958 71959 71960 71961 71962 71963 71964 71965 71966 71967 71968 71969 7197 71970 71975 71976 71977 71978 71979 71980 71981 71982 71983 71984 71985 71986 71987 71988 71989 71990 71991 71992 71993 71994 71995 71996 71997 71998 71999	
2.	**Back/Neck pain**	**(a) Spondylosis; intervertebral disc disorders; other back problems** 7201 7202 72081 72089 7209 7210 7211 7212 7213 72141 72142 7215 7216 7217 7218 72190 72191 7220 72210 72211 7222 72230 72231 72232 72239 7224 72251 72252 7226 72270 72271 72272 72273 72280 72281 72282 72283 72290 72291 72292 72293 7230 7231 7232 7233 7234 7235 7236 7237 7238 7239 72400 72401 72402 72409 7241 7242 7243 7244 7245 7246 72470 72471 72479 7248 7249	205
		(b) Sprains and strains 8400 8401 8402 8403 8404 8405 8406 8407 8408 8409 8410 8411 8412 8413 8418 8419 84200 84201 84202 84209 84210 84211 84212 84213 84219 8430 8431 8438 8439 8440 8441 8442 8443 8448 8449 84500 84501 84502 84503 84509 84510 84511 84512 84513 84519 8460 8461 8462 8463 8468 8469 8470 8471 8472 8473 8474 8479 8480 8481 8482 8483 84840 84841 84842 84849 8485 8488 8489 9057	232
3.	**Chest pain**	**(a) Nonspecific chest pain** 78650 78651 78659	102
4.	**Connective tissue disease**	**(a) Other connective tissue disease: Fibromyalgia, Neuralgia, neuritis** 32752 56731 7105 725 7260 72610 72611 72612 72619 7262 72630 72631 72632 72633 72639 7264 7265 72660 72661 72662 72663 72664 72665 72669 72670 72671 72672 72673 72679 7268 72690 72691 72700 72701 72702 72703 72704 72705 72706 72709 7272 7273 72740 72741 72742 72743 72749 72750 72751 72759 72760 72761 72762 72763 72764 72765 72766 72767 72768 72769 72781 72782 72783 72789 7279 7280 72810 72811 72812 72813 72819 7282 7283 7284 7285 7286 72871 72879 72881 72882 72883 72884 72885 72886 72887 72888 72889 7289 7290 7291 7292 72930 72931 72939 7294 7295 7296 72981 72982 72989 7299 72991 72992 7819 78191 78192 78194 78199 7937 V135 V1359 V436 V4360 V4361 V4362 V4363 V4364 V4365 V4366 V4369 V437 V454 V481 V482 V483 V490 V491 V492 V495 V4960 V4961 V4962 V4963 V4964 V4965 V4966 V4967 V4970 V4971 V4972 V4973 V4974 V4975 V4976 V4977 V537	211
5.	**Diabetes**	**(a) Diabetes mellitus without complication** 24900 25000 25001 7902 79021 79022 79029 7915 7916 V4585 V5391 V6546	049
		(b) Diabetes mellitus with complications 24901 24910 24911 24920 24921 24930 24931 24940 24941 24950 24951 24960 24961 24970 24971 24980 24981 24990 24991 25002 25003 25010 25011 25012 25013 25020 25021 25022 25023 25030 25031 25032 25033 25040 25041 25042 25043 25050 25051 25052 25053 25060 25061 25062 25063 25070 25071 25072 25073 25080 25081 25082 25083 25090 25091 25092 25093	050
6.	**Fracture**	**(a) Pathological fracture** 7331 73310 73311 73312 73313 73314 73315 73316 73319 73393 73394 73395 73396 73397 73398 V1351	207

		V1352	
		(b) Fracture of neck of femur (hip) 82000 82001 82002 82003 82009 82010 82011 82012 82013 82019 82020 82021 82022 82030 82031 82032 8208 8209 9053 V5413 V5423	226
		(c) Skull and face fractures 80000 80001 80002 80003 80004 80005 80006 80009 80050 80051 80052 80053 80054 80055 80056 80059 80100 80101 80102 80103 80104 80105 80106 80109 80150 80151 80152 80153 80154 80155 80156 80159 8020 8021 80220 80221 80222 80223 80224 80225 80226 80227 80228 80229 80230 80231 80232 80233 80234 80235 80236 80237 80238 80239 8024 8025 8026 8027 8028 8029 80300 80301 80302 80303 80304 80305 80306 80309 80350 80351 80352 80353 80354 80355 80356 80359 80400 80401 80402 80403 80404 80405 80406 80409 80450 80451 80452 80453 80454 80455 80456 80459 9050	228
		(d) Fracture of upper limb 81000 81001 81002 81003 81010 81011 81012 81013 81100 81101 81102 81103 81109 81110 81111 81112 81113 81119 81200 81201 81202 81203 81209 81210 81211 81212 81213 81219 81220 81221 81230 81231 81240 81241 81242 81243 81244 81249 81250 81251 81252 81253 81254 81259 81300 81301 81302 81303 81304 81305 81306 81307 81308 81310 81311 81312 81313 81314 81315 81316 81317 81318 81320 81321 81322 81323 81330 81331 81332 81333 81340 81341 81342 81343 81344 81345 81347 81350 81351 81352 81353 81354 81380 81381 81382 81383 81390 81391 81392 81393 81400 81401 81402 81403 81404 81405 81406 81407 81408 81409 81410 81411 81412 81413 81414 81415 81416 81417 81418 81419 81500 81501 81502 81503 81504 81509 81510 81511 81512 81513 81514 81519 81600 81601 81602 81603 81610 81611 81612 81613 8170 8171 8180 8181 8190 8191 9052 V5410 V5411 V5412 V5420 V5421 V5422	229
		(e) Fracture of lower limb 82100 82101 82110 82111 82120 82121 82122 82123 82129 82130 82131 82132 82133 82139 8220 8221 82300 82301 82302 82310 82311 82312 82320 82321 82322 82330 82331 82332 82340 82341 82342 82380 82381 82382 82390 82391 82392 8240 8241 8242 8243 8244 8245 8246 8247 8248 8249 8250 8251 82520 82521 82522 82523 82524 82525 82529 82530 82531 82532 82533 82534 82535 82539 8260 8261 8270 8271 9054 V5414 V5415 V5416 V5424 V5425 V5426	230
		(f) Other fractures 80500 80501 80502 80503 80504 80505 80506 80507 80508 80510 80511 80512 80513 80514 80515 80516 80517 80518 8052 8053 8054 8055 8056 8057 8058 8059 80700 80701 80702 80703 80704 80705 80706 80707 80708 80709 80710 80711 80712 80713 80714 80715 80716 80717 80718 80719 8072 8073 8074 8075 8076 8080 8081 8082 8083 80841 80842 80843 80844 80849 80851 80852 80853 80854 80859 8088 8089 8090 8091 8280 8281 8290 8291 9051 9055 V540 V5401 V5402 V5409 V5417 V5419 V5427 V5429 V664	231
7.	**Headache**	**(a) Headache; including migraine** 33900 33901 33902 33903 33904 33905 33909 33910 33911 33912 33920 33921 33922 3393 33941 33942 33943 33944 33981 33982 33983 33984 33985 33989 3460 34600 34601 34602 34603 3461 34612 34613	084

		34610 34611 3462 34620 34621 34622 34623 34630 34631 34632 34633 34640 34642 34643 34651 34652 34653 34670 34671 34672 34673 3468 34680 34681 34682 34683 3469 34690 34691 7840	
8.	**Pelvic/ Abdominal pain**	**(a) Abdominal pain** 7890 78900 78901 78902 78903 78904 78905 78906 78907 78909 78960 78961 78962 78963 78964 78965 78966 78967 78969	251
		(b) Abdominal hernia 55000 55001 55002 55003 55010 55011 55012 55013 55090 55091 55092 55093 55100 55101 55102 55103 5511 55120 55121 55129 5513 5518 5519 55200 55201 55202 55203 5521 55220 55221 55229 5523 5528 5529 55300 55301 55302 55303 5531 55320 55321 55329 5533 5538 5539	143
		(c) Calculus of urinary tract: Renal colic 5920 5921 5929 5940 5941 5942 5948 5949 7880 V1301	160
		(d) Gastritis and duodenitis 5350 53500 53501 5351 53510 53511 5352 53520 53521 5353 5354 53540 53541 5355 53550 53551 5356 53560 53561 53571	140
		(e) Menstrual disorders 6253 6260 6261 6262 6263 6264 6265 6266 6268 6269	171
		(f) Menopausal disorders 25631 25639 6270 6271 6272 6273 6274 6278 6279 V074	173
Source: MEPS Documentation- Medical Conditions File			

Appendix E: Mental Health Diagnosis

Condition	ICD-9CM	CCC
Adjustment Disorder	**(a) Adjustment Disorder** 3090 3091 30922 30923 30924 30928 30929 3093 3094 30982 30983 30989 3099	650
Anxiety Disorder	**(a) Anxiety Disorder** 29384 30000 30001 30002 30009 30010 30020 30021 30022 30023 30029 3003 3005 30089 3009 3080 3081 3082 3083 3084 3089 30981 3130 3131 31321 31322 3133 31382 31383	651
Bipolar Disorder	**(a) Bipolar disorders** 29600 29601 29602 29603 29604 29605 29606 29610 29611 29612 29613 29614 29615 29616 29640 29641 29642 29643 29644 29645 29646 29650 29651 29652 29653 29654 29655 29656 29660 29661 29662 29663 29664 29665 29666 2967 29680 29681 29682 29689 29690 29699 **(b) Depressive disorders** 29383 29620 29621 29622 29623 29624 29625 29626 29630 29631 29632 29633 29634 29635 29636 3004	657
Conduct Disorder	**(a) Conduct disorder** 31200 31201 31202 31203 31210 31211 31212 31213 31220 31221 31222 31223 3124 3128 31281 31282 31289 3129 **(b) Oppositional defiant disorder/ Attention deficit disorder / Attention deficit hyperactivity disorder** 31400 31401 3141 3142 3148 3149	652
Personality Disorder	**(a) Personality disorders** 3010 30110 30111 30112 30113 30120 30121 30122 3013 3014 30150 30151 30159 3016 3017 30181 30182 30183 30184 30189 3019	658
Major Depressive Disorder	**(a) Schizophrenia and other psychotic disorders** 29381 29382 29500 29501 29502 29503 29504 29505 29510 29511 29512 29513 29514 29515 29520 29521 29522 29523 29524 29525 29530 29531 29532 29533 29534 29535 29540 29541 29542 29543 29544 29545 29550 29551 29552 29553 29554 29555 29560 29561 29562 29563 29564 29565 29570 29571 29572 29573 29574 29575 29580 29581 29582 29583 29584 29585 29590 29591 29592 29593 29594 29595 2970 2971 2972 2973 2978 2979 2980 2981 2982 2983 2984 2988 2989	659
Source: MEPS Documentation- Medical Conditions File		

Appendix F: Substance Use Diagnosis

Condition	ICD-9CM	CCC
Alcohol abuse or dependent	**(a) Alcohol-related disorders** 2910 2911 2912 2913 2914 2915 2918 29181 29182 29189 2919 30300 30301 30302 30303 30390 30391 30392 30393 30500 30501 30502 30503 76071 9800	660
Any substance abuse or dependent	**(a) Substance-related disorders** 2920 29211 29212 2922 29281 29282 29283 29284 29285 29289 2929 30400 30401 30402 30403 30410 30411 30412 30413 30420 30421 30422 30423 30430 30431 30432 30433 30440 30441 30442 30443 30450 30451 30452 30453 30460 30461 30462 30463 30470 30471 30472 30473 30480 30481 30482 30483 30490 30491 30492 30493 30520 30521 30522 30523 30530 30531 30532 30533 30540 30541 30542 30543 30550 30551 30552 30553 30560 30561 30562 30563 30570 30571 30572 30573 30580 30581 30582 30583 30590 30591 30592 30593 64830 64831 64832 64833 64834 65550 65551 65553 76072 76073 76075 7795 96500 96501 96502 96509 V6542	661
History of mental health disorder and substance abuse	**(a) Mental health disorder related codes** 33392 V110 V111 V112 V114 V118 V119 V154 V1541 V1542 V1549 V1582 V6285 V663 V701 V702 V7101 V7102 V7109 V790 V792 V793 V798 V799 **(b) Substance-related disorder codes** 3051 30510 30511 30512 30513 3575 4255 5353 53530 53531 5710 5711 5712 5713 7903 V113 V791	663
Source: MEPS Documentation- Medical Conditions File		

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