Impact of Cachexia on Resource Utilization and Costs in Patients with Pancreatic, Lung, and Colorectal Cancers

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Abstract

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Introduction:

Cancer cachexia or cancer anorexia-cachexia syndrome (CACS) is a wasting disease characterized by inadequate food intake, loss of muscle mass, weight loss, inactivity, and changes in metabolism. Cachexia is estimated to affect 70-80% of pancreatic cancer patients and approximately 50% of lung and colorectal cancer patients. There is limited literature describing the impact of this condition on healthcare resource utilization and costs in the US.

Objective:

The primary objective of this study was to compare the healthcare resource utilization (HRU) and direct health plan costs of colorectal, lung, and pancreatic cancer patients diagnosed with cachexia to matched cancer patients without a cachexia diagnosis.

Methods:

We conducted a retrospective cohort study in commercial and Medicare Merative™ MarketScan® claims database. Patients with cachexia were identified following a colorectal, lung, or pancreatic primary cancer diagnosis between October 1st, 2016 – December 31st, 2022. Controls with no cachexia diagnosis during the study period were 2:1 matched with cachexia cases. Mean annual healthcare resource utilization and direct health plan costs were calculated using Kaplan-Meier Sample Average (KMSA) to account for patients censored before the end of the 1-year observation period. Significant differences between groups were determined by bootstrap 95% confidence intervals. A cox proportional hazard model was conducted in the unmatched cohort to determine relative hazard of cachexia diagnosis in different cancer types.

Results:

After matching the sample included 34,882 cancer patients, 11,880 in the cachexia cohort and 23,002 in the control cohort. Overall healthcare costs were significantly higher in colorectal, lung, and pancreatic cancer patients with cachexia ($141,626, [95% CI: $138,004 - $144, 905]) compared to those without evidence of cachexia, ($99,104, [95% CI: $97,193 – $101,224]). Average annual hospital admissions (cachexia: 0.98 admissions, [95% CI: 0.94 – 1.02]; control: 0.60, [0.58 – 0.62]) and annual emergency room visits, (cachexia: 2.47 ER visits [95% CI: 2.38 – 2.58]; control: 1.33 [95% CI: 1.29 – 1.36]) were significantly higher among cancer patients with cachexia compared to controls. Average annual outpatient encounters (cachexia: 61.5 encounters [95% CI: 60.7 – 62.4]; control: 44.6 [95% CI: 44.0 – 45.2]) and annual prescription fills (cachexia: 37.7 fills [95% CI: 37.1 – 38.4]; control: 30.4 [95% CI: 30.0 – 30.8]) were also significantly higher in cachexia cancer patients compared to controls. Among patients who developed cachexia, pancreatic cancer patients had the shortest median time to cachexia diagnosis of 1.2 months (IQR: 0.1 - 5.1) and had a 2.9-fold greater risk of being diagnosed with cachexia compared to those with colorectal cancer, which had the lowest hazard (HR: 2.90, [95% CI: 2.79 – 3.02, p<0.0001]).

Conclusion:

Colorectal, lung, and pancreatic cancer patients in the US, with a concurrent diagnosis of cachexia were found to have higher healthcare resource utilization and cost of care in the year following cachexia diagnosis.

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2. Introduction

Cancer cachexia or cancer anorexia-cachexia syndrome (CACS) is a wasting disease characterized by inadequate food intake, loss of muscle mass, weight loss (with or without loss of fat mass), inactivity, and changes in metabolism.[1–3] The current consensus is that this condition cannot be cured or fully reversed with traditional nutritional support alone.[2] It is estimated that cachexia affects 70-80% of pancreatic cancer patients and approximately 50% of lung and colorectal cancer patients.[1,4] Cachexia has three clinically relevant stages: pre-cachexia, cachexia, and refractory cachexia.[2] Pre-cachexia is characterized by anorexia, early changes in metabolic function (impaired glucose tolerance) and involuntary weight loss of ≤5%.[2] Cachexia, is the stage of the syndrome with clear diagnostic criteria of weight loss >5% within 6 months or weight loss of >2% in patients with BMI <20, or patients with sarcopenia and any degree of weight loss.[2,5] Patients with refractory cachexia typically have low performance status, life expectancy of less than 3 months, and commonly coincides with aggressively progressing cancer unresponsive to treatment.[2] Not every patient experiences every stage as progression varies based on patient specific clinical factors such as baseline nutritional status, cancer type, stage, and increased systemic inflammation.[2,6] Cachexia negatively impacts patients physical functioning as well as their quality of life.[7] Several studies, across cancer types, have observed decreased survival in patients with weight loss and cachexia compared to those without cachexia.[8–10]

Cachexia negatively impacts patients 'physical functioning and their quality of life.[7] Current agents physicians may prescribe for appetite stimulation and to improve weight gain in patients with cancer anorexia-cachexia include olanzapine, progesterone analogs (megestrol acetate / medroxyprogesterone) and short courses of corticosteroids.[5,11] These supportive care agents have limited efficacy in improving weight gain, while also contributing to patients' overall cost of care.[12] There are currently no FDA approved medications or therapies in the United States (US) approved to treat cachexia.

The economic and healthcare resource utilization impact of cancer cachexia is not well characterized in the literature. A cross-sectional study of the 2009 Nationwide Inpatient Sample (NIS) assessed inpatient hospitalizations, length of stay, and inpatient mortality for patients with cachexia and several solid tumor types.[3] They found cancer patients in the US with cachexia had increased length of hospitalizations compared to those without cachexia (incident rate ratio 1.09, 95% CI: 1:08 - 1.10). The cost of an inpatient stay for people with lung cancer, was significantly higher in cachexia compared to non-cachexic lung cancer patients ($13,560 vs $13,190; p < 0.0001). They also found the odds of inpatient death was higher in lung cancer patients with cachexia (OR: 1.32, 95% CI: 1.20 - 1.46) and in all cancers combined (OR : 1.76, 95% CI: 1.67 – 1.85) compared to their non-cachexia counterparts. A retrospective observational study conducted in Optum claims found significantly higher overall per member per month (PMPM) cost of care in breast ($5,475 vs $3,900, p<0.0001), colorectal ($6,571 vs $5,113, p=0.0012), lung ($12,878 vs $10,440, p=0.0006), and prostate cancer patients ($4,354 vs $3,100, p<0.0001) with cachexia compared to those without cachexia.[17] Average costs of care were calculated based on the 12 month period following a patient's cancer diagnosis date. In their subgroup analysis of patients with metastases, those with a concurrent cachexia diagnosis had significantly higher costs in lung cancer (cachexia: $25,810 [SD: $27,882] vs no cachexia: $20,754 [SD: $29,267]; p=0.0198) and prostate cancer (cachexia: $10,913 [SD: $11,254] vs no cachexia: $5,892 [SD: $15,566); p=0.0020]. Metastatic breast (p=0.6143), colorectal (p= 0.1606), and pancreatic (p=0.2142) cancer patients found no significant difference in PMPM cost between cachexia and non-cachexia cohorts. [17]

Understanding how cancer patients with cachexia differ from those without cachexia can help us identify patients at risk of cachexia earlier, understand where their treatment needs differ, and improve care pathways to provide them more timely and appropriate healthcare. The existing literature provides minimal information on how healthcare services and resource utilization differ between cachexia and non-cachexia patients. This study aims to provide a detailed analysis of healthcare resource utilization and direct costs in colorectal, lung, and pancreatic cancer patients with and without cachexia to provide insights into cancer types and subgroup populations most impacted by cachexia, the health system economic burden of cachexia in the US, and the key healthcare settings where cachexia patients are requiring a larger quantity of care. This information is important in highlighting where interventions are needed to improve health outcomes for cancer patients with cachexia.

3. Methods

3.1 Study Design and Data Source

We conducted a retrospective cohort study to assess healthcare resource utilization and direct healthcare costs in colorectal, lung, and pancreatic cancer patients with and without cachexia in the United States between 2015 and 2023.

This study was conducted in Merative™ MarketScan® Commercial Claims and Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits (MDCR) Standard Edition Databases. The "Set B" version files from 2019-2023 were used which provides reimbursement data with no imputation. This database is comprised of active employees, early retirees, COBRA continuers, and dependents insured by employer sponsored commercial health plans and Medicare-eligible retirees with employer-sponsored Medicare Supplemental plans (which starting in 2020 includes Medicare advantage).

3.2 Patient Selection

The overall study period was October 1st, 2015, through December 31st, 2023. The start date of October 1st, 2015 reflects the start of the ICD-10 coding system. The end date of data availability was December 31st, 2023. Adults ages ≥18 years were included if they had a new diagnosis of colorectal, lung, or pancreatic cancer between October 1st, 2016, through December 31st, 2022 (patient identification period). Patients were identified in the CCAE and MDCR Standard Edition Databases based on the presence of ICD-10 codes in any billing position for a diagnosis of colorectal, lung, or pancreatic cancer. (Appendix A). Lung cancer patients included anyone with an ICD-10 code beginning with C34 indicating malignant neoplasm of bronchus and lung. Colorectal cancer patients were identified as anyone with an ICD-10 code beginning with C18 (malignant neoplasm of colon), C19 (malignant neoplasm of rectosigmoid junction), C20 (malignant neoplasm of rectum), or C21 (malignant neoplasm of anus and anal canal). Pancreatic cancer patients were identified as anyone with an ICD-10 code beginning with C25 indicating malignant neoplasm of the pancreas. A diagnosis required ≥2 outpatient claims ≥1 day(s) apart or ≥1 inpatient claim between October 1st, 2016, through December 31st, 2022. If diagnosed via an outpatient claim, the second of the 2 diagnosis dates was assigned as the primary cancer diagnosis date.

All patients were required to have continuous enrollment for 1 year prior to their primary cancer diagnosis date (baseline period). Patients were excluded if they had any claim with a diagnosis of cancer or cachexia within their 1-year baseline period. Any patients that were captured in multiple cancer types were only included for their first cancer diagnosis. (Figure 1: Study Timeline)

Cases

Cachexia diagnosis required ≥1 inpatient or outpatient claim with any of the following list of ICD-10 codes: R64: Cachexia (wasting syndrome), M62.50: Muscle wasting and atrophy, R63.0: Anorexia, R63.4: Abnormal weight loss, or R63.6: Underweight (Appendix A). These codes, apart from M62.50, were used previously in Aurther et.al. to identify patients with cachexia due to underdiagnosis of the condition.[3] The ICD-10 code for muscle wasting and atrophy (M62.50) was added to the expanded diagnosis of cachexia due to the muscle wasting and sarcopenia as part of Fearon 2011 criteria for diagnosis of cachexia.[2] Patients with the specific claim for cachexia (R64: cachexia) were marked with a "short cachexia diagnosis" flag for subgroup analysis. Patients' first claim with a diagnosis of cachexia was selected to serve as index date. Cases were excluded prior to matching if they did not have continuous enrollment from primary cancer diagnosis to 30 days after cachexia diagnosis date.

Controls

Controls were identified from the remaining cancer patients who never had a claim for cachexia. Controls were matched 2:1 using propensity score matching to cases. Controls were assigned a proxy cachexia diagnosis index date. The proxy index date was assigned for controls as the date "X" days after primary cancer diagnosis date. Where "X" equals the number of days from primary cancer diagnosis to cachexia diagnosis for their matched cachexia patient. After matching, any controls who did not have continuous enrollment from the primary cancer diagnosis date to 30 days after the assigned proxy index date were excluded.

Propensity Score Matching

Controls were matched to cachexia cases 2:1 with no replacement. Propensity scores were calculated based on a logistic regression model adjusted for gender (categorical), primary cancer type (categorical), age at primary cancer diagnosis (continuous), year of primary cancer diagnosis (categorical), baseline Charlson Comorbidity Index (CCI) score (continuous), insurance type (Medicare or commercial), region (categorical), metastatic cancer diagnosis at baseline (binary), and days from primary cancer diagnosis to disenrollment (continuous). Nearest neighbor matching method was used with adjustments for exact matching on gender and primary cancer type and caliper adjustments for age (caliper: 0.1), year (caliper: 2), and CCI score (caliper: 0.1). Once groups were assigned, any 2:1 matched group with a member that didn't have continuous enrollment from primary cancer diagnosis to 30 days after proxy index date were removed from the analysis. Days from primary cancer diagnosis to disenrollment was included as a matching variable to reduce the number of groups removed from the analysis. Balance checking was preformed via analysis of a Love plot to ensure that the absolute standardized mean differences of covariates between groups was less than 0.1. (Figure 2)

3.3 Study Measures and Outcomes

Baseline characteristics included age, gender, cancer type (colorectal, lung, pancreatic), metastatic status, year of primary cancer diagnosis, CCI score, insurance type (commercial, Medicare), and region (Northeast, North Central, South, West, Unknown). We calculated the Charlson Comorbidity Index over the 1-year baseline period prior to cancer diagnosis to be used for propensity score matching and at matched index date to assess any potential changes in comorbidities.

In MarketScan®, adjustment records are claims (their own line in an inpatient, outpatient, or pharmacy claims table) with negative financial variables to correct for a payment error, reversed claims, or any coding error. Adjustment records are intended to cancel out costs and other variables when those claims with the same service date are summed. However, there remained some claims with negative values that did not match existing claims. Prior to endpoint HRU and cost outcome assessment, unbalanced adjustment claims resulting in negative costs were removed using the following method. In the inpatient (s) and outpatient (o) claims tables, the NETPAY variable was summed by unique claim groups with the same enrollee ID, service date, procedure 1, and revenue code (ENROLID, SVCDATE, PROC1, and REVCODE) to calculate a total NETPAY for that claim encounter. Any claim encounter with a negative total NETPAY was removed from the analysis. The same process was applied to the pharmacy table defining a claim encounter as claims with the same unique combination of enrollee ID, service date, and drug NDC number (ENROLID, SVCDATE, and NDCNUM).

Primary Outcome: Healthcare Resource Use and Cost

The primary outcomes of interest of mean healthcare resource utilization (HRU) and costs were collected for up to one year post index date in cachexia versus control patients. The matched (cachexia diagnosis) index date served as the first day of month one for each patient. Each consecutive 30 days were counted as one month, for 12 months. HRU counts and costs were calculated for each patient for each month they maintained continuous enrollment in MarketScan®. Enrollment status was determined based on the monthly enrollment indicator (ENRIND1-12) variable from the MarketScan® Annual Enrollment Summary Table (A). Each patient was required to be continuously enrolled from one year prior to primary cancer diagnosis to 30 days post index date. This ensured each patient contributed at least one month of HRU and cost data.

Outpatient services were evaluated from the outpatient services tables, pharmacy fills from the pharmacy claims table, and emergency encounters were calculated from claims in both the inpatient and outpatient services tables. Healthcare resource utilization endpoints included mean number of hospitalizations per patient per year (PPPY), mean length of stay per hospitalization (days), mean number of emergency department visits PPPY, mean number of outpatient encounters PPPY, and mean number of prescriptions filled PPPY. Outpatient encounters were further characterized into care visits, lab visits, skilled nursing/assisted living claims, and hospice claims (further defined in Appendix B). Prescription fills were further characterized by the class of medication filled, anti-infectives, antiemetics, antineoplastic, non-opioid analgesics, opioid analgesics, and others.

The primary cost endpoints were the mean annual total costs, inpatient costs, outpatient costs, and average annual pharmacy costs in cachexia patients versus controls (Appendix C). Costs were inflation adjusted to 2024 USD using the Consumer Price Index for All Urban Consumers (CPI-U).

Secondary Outcome: Time to Cachexia Diagnosis

The time variables used in calculating the time to cachexia diagnosis, cachexia-free survival curves, and cox-proportional hazard model are described in detail in Appendix D. Date of disenrollment was defined as the first day of the month where a patient was no longer continuously enrolled in the MarketScan® database after their primary cancer diagnosis. If a patient was enrolled until the end of the study, this date was defined as December 31st, 2023 (end of study period). Months from primary cancer diagnosis date to disenrollment date (or cachexia diagnosis date) were calculated by retrieving the number of days between the respective dates and dividing those days by 30. The "time to event" variable used in both models was defined for the cachexia cohort as - the time, in months, from primary cancer diagnosis date to cachexia diagnosis date. For control cohort "time to event" was defined as – the time, in months, from primary cancer diagnosis date to disenrollment date. The "event" variable was defined as "1" for patients who were diagnosed with cachexia and "0" for those who were not.

3.4 Statistical Analysis

Baseline characteristics were summarized by means and standard deviation (SD) for the continuous variables, age and CCI score. Categorical variables were reported as frequencies and percentages. Differences in baseline variables between the cachexia and the control cohort were assessed with chi-squared tests for categorical variables and t-tests for continuous variables.

Primary Outcome

The primary outcomes of interest were mean healthcare resource utilization (HRU), and costs collected in the year post index date in cachexia versus control patients. The Kaplan-Meier sample average (KMSA) technique was used to account for censoring patients who were lost to follow up prior to the end of the 12-month observation period.[18] The average cost or HRU count was calculated for each month after index, then multiplied by the survival probability for that month. The adjusted averages for each of the 12 months were then summed to calculate the annual total of the outcome. To estimate uncertainty around costs and HRU counts, balanced bootstrapping with replacement was performed with 1,000 replications to generate 95% confidence intervals.[19] The difference in average length of stay between cachexia and control cohorts was assessed using a two sample t-test.

Secondary Outcome

Mean and median time from primary cancer diagnosis to cachexia diagnosis, in months, was calculated for each cancer type. Kaplan-Meier survival curves were created to visualize cachexia-free survival time for each cancer type (colorectal, lung, and pancreatic). Hazard ratios were calculated using a cox proportional hazard model to compare cachexia-free survival between cancer types, using colorectal cancer as the reference group.

4. Results

4.1 Baseline Characteristics

From the Merative™ MarketScan® CCAE and MDCR tables we identified 164,027 individuals with a primary colorectal, lung, or pancreatic cancer diagnosis between October 1st, 2015 and December 31st, 2022 (Figure 3). From this population, after applying exclusion criteria, 15,778 cancer patients with cachexia were identified and 79,485 controls. In the unmatched cohort we identified 41,933 colorectal patients (5,793 long diagnosis and 462 short diagnosis of cachexia), 40,666 lung cancer patients (6,214 long diagnosis and 727 short diagnosis of cachexia), and 12,664 pancreatic cancer patients (3,771 long diagnosis and 433 short diagnosis of cachexia) and included them for matching.

After matching the total study population was 34,882. Of which, 11,880 (4,665 (39%) colorectal, 4,455 (38%) lung, 2,760 (23%) pancreatic) were in the cachexia cohort and 23,002 (9,277 (40%) colorectal, 8,872 (39%) lung, 4,853 (21%) pancreatic) were in the control cohort. Due to limited sample size, these proportional differences in cancer type between the cachexia and control matched cohorts were statistically significant ($p<0.001$). The baseline characteristics for cachexia and control patients by cancer type is outlined in Appendix E.

Baseline characteristics after matching described in Table 1, reveal the mean age of both cohorts was 65 years ($p=0.8$) and females made up 48% of the population ($p=0.4$). Twenty-six percent of each group had a metastatic cancer diagnosis at baseline ($p>0.9$). At baseline, both cohorts had an average CCI score of 4.4 ($p=0.6$). Individuals with commercial insurance made up 55% of each cohort ($p=0.7$). The proportion of patients in different regions and year of primary cancer diagnosis were different between the case and control groups ($p<0.001$).

4.2 Healthcare Resource Utilization

Of the 11,880 cachexia patients in this study 11,661 (98%) had outpatient healthcare encounters. Cachexia patients had a significantly higher number of encounters of 61.52 encounters PPPY (95% CI: 60.71 – 62.36), compared to controls (44.59 encounters PPPY, [95% CI: 44.03 – 45.15]). Outpatient encounters are characterized by encounter type in Table 2, by care visits (i.e. office visits, outpatient surgery…), lab visits, hospice claims, and skilled nursing / assisted living claims. Patient care visits made up the largest proportion of outpatient encounters in each group. One patient could have more than one outpatient encounter per service date.

10,638 (90%) of cachexia patients had at least 1 prescription drug claim compared to 18,462 (80%) of controls. The average number of cachexia prescriptions filled was significantly higher in the cachexia group, with 37.72 fills per year (95% CI: 37.11 – 38.38) versus 30.39 fills per year (95% CI: 29.98 – 30.78) in the controls. When looking into specific therapeutic classes commonly used in cancer patients, we noticed the difference in average number of prescriptions filled per year was significantly higher in cachexia patients by 0.16 fills per year for anti-infectives (95% CI: 0.09 - 0.23, $p<0.001$), 0.28 antiemetic fills per year (95% CI: 0.19-0.37, p<0.001), 0.61 opioid prescriptions per year (95% CI: 0.48-.74, p<0.001) and a difference of 0.39 fills per year for other prescription types (95% CI: 0.07 - 0.70, p=0.0166). There was no significant difference in the number of non-opioid analgesic prescriptions filled per year (0.07 difference, 95% CI: -0.03 – 0.16, p=0.1609). Outpatient prescriptions for antineoplastics per year was lower in patients with cachexia compared to controls by -0.55 fills per year (95% CI: -0.73 – -0.38, p<0.0001). More information on how therapeutic class codes were defined in Appendix B.

The mean number of hospital emergency room visits per patient per year was significantly higher in the cachexia group with 2.47 visits (95% CI: 2.38 -2.58) than the control group, which had an average of 1.33 visits per year (95% CI: 1.29 – 1.36) visits per person per year. The mean number of hospital admissions per patient per year was also significantly higher in the cachexia cohort 0.98 (95% CI: 0.94 – 1.02) compared to the control cohort 0.60 (95% CI: 0.58 – 0.62). The mean length of stay for a hospital admission was 6.12 days (95% CI: 5.98 - 6.26) in the cachexia cohort versus 5.62 days (95% CI: 5.50 - 5.74) in the control group (p<0.0001). This relationship of significantly higher resource utilization in cachexia held when assessed for each cancer subgroup. (Figure 4a-d)

4.3 Direct Healthcare Costs

Average annual direct health plan costs were significantly higher in the cancer patients with cachexia compared to their control counterparts for each cost category evaluated, overall costs, inpatient, outpatient, and pharmacy claims. Significance was determined by no overlap of the 95% confidence interval for cachexia and controls. The total annual healthcare cost was $141,626 (95% CI: $138,004 - $144,905) for cachexia patients and $99,104 ($97,193 – $101,224) for controls. Annual inpatient direct costs were $78,330 (95% CI: $74,774 – $81,786) and $44,498 (95% CI : $42,855 – $46,282) for cachexia and controls respectively. Annual outpatient costs were found to be $86,271 (95% CI: $83,785 – $88,854) for cachexia patients and $61,958 (95% CI: $60,449 – $63,469) controls. Lastly, annual outpatient pharmacy costs were $12,304 (95% CI: $11,538 – $13,176) and $9,991 (95 % CI: $9,566 – $10,479) for controls. (Table 3) Annual costs were highest in the pancreatic cancer patient subgroup with total annual costs of $170,297 (95% CI: $162,977 – $178,090) in those with cachexia and $130,122 ($124,960 – $135,424) in controls.

4.4 Time to Cachexia Diagnosis

The overall median time from primary cancer diagnosis to cachexia diagnosis was 2.6 months (IQR: 0.4 – 9.5). Pancreatic cancer patients had the shortest median time to cachexia diagnosis of 1.2 (IQR: 0.1 - 5.10) months (Table 4). The median time to diagnosis was similar in the colorectal and lung cancer groups, 3.2 months (IQR: 0.4 - 11.6) and 3.3 months (IQR: 0.7 - 10.9), respectively. Kaplan Meier survival curves indicate that the likelihood of being diagnosed with cachexia is highest in the months immediately following cancer diagnosis and decreases as the time from primary cancer diagnosis increases (Figure 5).

The results of the cox-proportional hazard model indicated, when compared to colorectal cancer patients, lung cancer patients had a 1.25-fold increase risk of cachexia diagnosis (HR: 1.25, [95% CI: 1.21 – 1.29, p<0.0001]), while pancreatic cancer patients had a 2.90 fold increased risk of cachexia diagnosis (HR: 2.90, [95% CI: 2.79 – 3.02, p<0.0001]).

5. Discussion

We conducted a retrospective cohort study using Merative™ MarketScan® commercial and Medicare claims data, to identify patients with diagnoses of colorectal, lung, and pancreatic cancers and compare healthcare resource utilization and costs among those with a diagnosis of cachexia compared to those without. In this study, cancer patients with a cachexia diagnosis had significantly higher annual healthcare costs and resource utilization than controls on all endpoints. Cachexia patients had higher annual direct healthcare costs paid by their health plan for inpatient, outpatient, and pharmacy claims. The average annual total cost of care for cachexia patients was $141,626 (95% CI: $138,004 - $144,905) compared to $99,104 (95% CI: $97,193 – $101,224) for those with no cachexia diagnosis. Cancer patients with cachexia had on average 61.52 encounters PPPY versus controls 4.59 encounters PPPY. These visits contributed to the increased average annual outpatient costs $86,271 (95% CI: $83,785 – $88,854) for cachexia patients compared to $61,958 average outpatient spend for controls (95% CI: $60,449 – $63,469). These results highlight the increased burden of illness cancer patients with cachexia face compared to their counterparts without a cachexia diagnosis.

We also observed higher outpatient pharmacy prescriptions filled with 37.72 prescriptions filled per year (95% CI: 37.11 – 38.38) for cachexia patients that added up to an average $12,304 (95% CI: $11,538 – $13,176) per year. Controls had on average, 7 less prescriptions filled per year (30.39 [95%

CI: 29.98 – 30.78]) that results in a significantly lower outpatient drug spend of $9,991 (95 % CI: $9,566 – $10,479). Of concern, cachexia patients were found to have 0.61 more opioid prescriptions per year than patients without cachexia (p<0.0001). As well as, 0.28 more antiemetic prescriptions (p<0.0001), 0.16 more anti-infectives (p<0.0001), and 0.39 more prescriptions of other classes (p=0.0166) indicating a higher pill burden, while also receiving significantly less antineoplastics compared to controls (-0.55 fills per year, p<0.0001). Two studies have suggested that cachexia diagnosis is associated with dose reduction or discontinuation of chemotherapy. [15,16] This exceeds the scope of this study, but an important next step will be to dive deeper into each cancer type to better understand if true differences in cancer treatment patterns exist.

Cachexia patients demonstrated higher hospital resource utilization through increased annual hospital admissions (cachexia: 0.98 [95% CI: 0.94 – 1.02] vs control: 0.60 [95% CI: 0.58 – 0.62]), increased length of stay by 0.5 days on average (95% CI: 0.31-0.68, p<0.0001), and higher hospital emergency room visits per year (cachexia: 2.47 [95% CI: 2.38 - 2.58] vs control: 1.33 [95% CI: 1.29 – 1.36]). Identifying the primary reason for emergency room visit or hospital admission is beyond the scope of this study, but important for understanding the clinical factors driving cachexia patients' need for additional hospital care.

This study contributes to the limited body of evidence, evaluating both healthcare resource utilization and direct costs in cancer patients with cachexia in the United States. Two abstracts of cancer cachexia healthcare resource utilization have been published using the Optum® Market Clarity Database. [4,17] Dagenais et.al. found significantly higher per member per month (PMPM) costs in patients with breast, colorectal, lung, and prostate cancers when comparing patients with cachexia versus those without.[17] They did not find a difference in PMPM costs for those with pancreatic cancer, which differs from what we found looking at costs on an annual basis, where pancreatic cancer patients with cachexia had higher overall cost of care $170,297 (95% CI: $162,977 – $178,090) compared to pancreatic cancer patients with no cachexia diagnosis $130,122 (95% CI: $124,960 – $135,424). This difference held true when evaluating inpatient, outpatient, and pharmacy costs. That study also did not detect a difference between cachexia and controls for inpatient hospital costs in patients with colorectal and pancreatic cancer patients where our study did. Ali et.al. evaluated healthcare resource utilization on a monthly basis and did not detect a difference in number of inpatient hospital admissions for colorectal, lung, or pancreatic cancer patients.[4] However when we evaluated these differences in each of these cancer types, we found a significant difference in annual hospitalizations to be higher in patients with cachexia compared to those without.

A large limitation in this study is our ability to accurately capture cachexia patients using ICD-10 codes alone, as the diagnosis of cachexia is under coded, and likely underdiagnosed. To address this diagnosis issue, prior studies in the Optum® Market Clarity Database had weight measures and applied the Fearon diagnostic criteria[2] of those who had ≥5% weight loss between ≥2 weight measurements 150-210 days apart (at least 1 after cancer diagnosis) to identify cancer patients with cachexia.[4,17] As a weight measurement wasn't available in this dataset, we used the approach of a basket of ICD-10 codes (R64: Cachexia (Wasting syndrome), M62.50: Muscle wasting and atrophy, R63.0: Anorexia, R63.4: Abnormal weight loss, or R63.6: Underweight), informed by Aurther et.al. and the Fearon cachexia diagnostic criteria, as our primary method of identifying patients with cachexia.[2,3] In the unmatched cohort we observed the "short" R64 ICD-10 code diagnosis in 462 of the 41,933 colorectal patients (1.1%), 727 of the 40,666 lung cancer patients (1.8%) and 433 of the 12,664 pancreatic cancer patients (3.4%). Our expanded diagnostic definition estimated the frequency of cachexia, over this eight-year study period, to be 13.7% (5,793/41,933) of colorectal cancer patients, 15.3% (6,214/40,666) of lung cancer patients, and 29.8% (3,771/12,664) of pancreatic cancer patients. The previously reported prevalence of this disease in colorectal and lung is 50% and 70-80% for pancreatic cancer patients.[1,4] Even using the expanded ICD-10 code definition, we suspect based on disease prevalence, that there are still true cachexia patients in the control cohort that could be artificially increasing the average costs and HRU among controls. This further justified our use of the expanded ICD-10 definition of cachexia to increase the likelihood of capturing true cachexia cases. If cachexia cases were only defined as the short definition (R64: cachexia - wasting syndrome), we are likely only capturing those with the most severe cachexia disease and risk inflating the true annual cost per cancer patient with cachexia.

Additional limitations exist with this dataset, as it only captures commercial patients and those who receive supplemental Medicare insurance through their employer, these results may not be generalizable to the entire US population. In this dataset, we also did not have information on mortality. This would have been valuable to use as a censoring event to better estimate cachexia- free survival and those who are no longer contributing to the KMSA. Without death as a censoring event, patients who died outside of the hospital setting often continue enrollment in their health plan until the plan is canceled or not renewed. This can artificially lower the average cost of care, because it looks like they are enrolled but not engaging with the healthcare system. In this study, the first break in continuous enrollment status was used to signify patients who have left the system. Death is an important competing event in this analysis because this cancer patient population has a high risk of death. Cachexia in cancer patients is associated with further decreased survival and can further bias results if patients who die are not appropriately censored from the cachexia cohort's cost and HRU analysis. [8–10]

6. Conclusion

Colorectal, lung, and pancreatic cancer patients in the US, with a concurrent diagnosis of cachexia were found to have higher healthcare resource utilization and cost of care within 1 year after cachexia diagnosis. These results emphasize the economic burden of increased healthcare resource utilization among cancer patients with cachexia in the US healthcare system.

7. Tables

7.1 Table 1. Baseline Demographics Matched vs Unmatched

	Unmatched			Matched		
Baseline Characteristics	**Cachexia** (n=15,778)	**Control** (n=79,485)	p-value	**Cachexia** (n=11,880)	**Control** (n=23,002)	p-value
Gender, n (%)			<0.001			0.4
Male	8,241 (52%)	39,287 (49%)		6,185 (52%)	11,854 (52%)	
Female	7,537 (48%)	40,198 (51%)		5,695 (48%)	11,148 (48%)	
Age (years), n(%)						0.8
Mean (SD)	66 (13)	64 (13)	<0.001	65 (13)	65 (13)	
18 – 24	30 (0.2%)	198 (0.2%)		20 (0.2%)	35 (0.2%)	
25 - 34	149 (0.9%)	882 (1.1%)		108 (0.9%)	197 (0.9%)	
35 - 44	608 (3.9%)	3,627 (4.6%)		501 (4.2%)	951 (4.1%)	
45 - 54	2,192 (14%)	13,387 (17%)		1,731 (15%)	3,340 (15%)	
55 - 64	5,468 (35%)	28,523 (36%)		4,174 (35%)	8,166 (36%)	
65 - 74	2,868 (18%)	12,980 (16%)		2,171 (18%)	4,168 (18%)	
75 - 84	3,223 (20%)	13,708 (17%)		2,335 (20%)	4,513 (20%)	
85 +	1,240 (7.9%)	6,180 (7.8%)		840 (7.1%)	1,632 (7.1%)	
Primary Cancer Diagnosis, n (%)			<0.001			<0.001
Colorectal	5,793 (37%)	36,140 (45%)		4,665 (39%)	9,277 (40%)	
Lung	6,214 (39%)	34,452 (43%)		4,455 (38%)	8,872 (39%)	
Pancreatic	3,771 (24%)	8,893 (11%)		2,760 (23%)	4,853 (21%)	
Metastatic Cancer Diagnosis at Baseline[1], n (%)			<0.001			>0.9
Yes	4,674 (30%)	20,148(25%)		3,111 (26%)	6,023 (26%)	
Charlson Comorbidity Index at Baseline[1], n (%)						
Mean (SD)	4.67 (2.46)	4.53 (2.50)	<0.001	4.41(2.30)	4.40 (2.28)	0.6
2	3,853 (24%)	22,413 (28%)		3,180 (27%)	6,194 (27%)	
3	3,053 (19%)	15,106 (19%)		2,457 (21%)	4,796 (21%)	
4	1,779 (11%)	8,792 (11%)		1,392 (12%)	2,651 (12%)	
≥5	7,093 (45%)	33,174 (42%)		4,851 (41%)	9,361 (41%)	
Year of Primary Cancer Diagnosis, n (%)			<0.001			<0.001

2016	891 (6%)	4,233 (5%)		637 (5%)	1,105 (5%)	
2017	3,274 (21%)	15,564 (20%)		2,414 (20%)	4,615 (20%)	
2018	2,747 (17%)	13,905 (17%)		2,117 (18%)	4,262 (19%)	
2019	2,023 (13%)	11,184 (14%)		1,592 (13%)	3,225 (14%)	
2020	2,488 (16%)	11,490 (14%)		1,832 (15%)	3,321 (14%)	
2021	2,298 (15%)	11,491 (15%)		1,596 (13%)	3,592 (16%)	
2022	2,057 (13%)	11,543 (15%)		1,692 (14%)	2,882 (12%)	
Insurance Type, n (%)			<0.001			0.7
Commercial Insurance	8,411 (53%)	46,606 (59%)		6,520 (55%)	12,667 (55%)	
Medicare Supplemental	7,367 (47%)	32,879 (41%)		5,360 (45%)	10,335 (45%)	
Region, n (%)			<0.001			<0.001
Northeast	3,233 (20%)	15,980 (20%)		2,118 (18%)	4,766 (21%)	
North Central	5,265 (33%)	24,591 (31%)		3,813 (32%)	7,575 (33%)	
South	5,766 (37%)	30,052 (38%)		4,636 (39%)	8,448 (37%)	
West	1,463 (9%)	8,591 (11%)		1,279 (11%)	2,175 (10%)	
Unknown	51 (0%)	271 (0%)		38 (0%)	43 (0%)	
Short Definition Cachexia	1,622 (10%)	0	>0.9	1,142 (10%)	0	>0.9
Colorectal	462 (2.9%)			331 (2.8%)		
Lung	727 (4.6%)			509 (4.3%)		
Pancreatic	433 (2.7%)			302 (2.5%)		

[1] Measurement taken at time of primary cancer diagnosis. [2] Short cachexia diagnosis, are those have a claim with the specific ICD-10 code R64 indicating cachexia wasting disease.
Continuous variables p-values were attained using unpaired two-sample t-test. Categorical variables p-values were attained using chi-squared test.

7.2 Table 2. Healthcare Resource Utilization by Cachexia Status

Table 2. Annual Healthcare Resource Utilization Cachexia Status for all cancer types.

	Cachexia (n=11,880)	**Control** (n=23,002)	Significance
Outpatient Services			
People with ≥1 Outpatient Encounter, n (%)	11,661 (98%)	19,856 (86%)	-
Encounters (PPPY), mean (95% CI)	61.52 (60.71 – 62.36)	44.59 (44.03 – 45.15)	Yes[1]
Encounters by Type, n (%)			
Care Visit	485,329 (87.88%)	722,924 (89.98%)	-
Lab	33,611 (6.09%)	55,004 (6.85%)	-
Hospice Claim	13,285 (2.41%)	10,338 (1.29%)	-
Skilled Nursing/ Assisted Living	20,067 (3.63%)	15,204 (1.89%)	-
People with ≥1 Prescription Fill, n (%)	10,638 (90%)	18,462 (80%)	-
Prescription Fills (PPPY), mean (95% CI)	37.72 (37.11 – 38.38)	30.39 (29.98 – 30.78)	Yes[1]
Prescription Fills (PPPY) by Drug Class, mean (95% CI)			
Anti-Infectives	2.82 (2.76 – 2.88)	2.66 (2.62 – 2.70)	p<0.0001[2]
Antiemetics	3.07 (3.00 – 3.14)	2.79 (2.73 – 2.85)	p<0.0001[2]
Antineoplastics	3.32 (3.19 – 3.45)	3.88 (3.76 – 4.00)	p<0.0001[2]
Non-Opioid Analgesics	2.19 (2.11 – 2.27)	2.12 (2.07 – 2.17)	p=0.16[2]
Opioid Analgesics	4.09 (3.99 – 4.19)	3.48 (3.40 – 3.56)	p<0.0001[2]
Other	15.45 (15.19 – 15.71)	15.06 (14.87 – 15.25)	p=0.0166
People with ≥1 Emergency Room (ER) Visit, n (%)	6,620 (56%)	9168 (40%)	
ER Visits (PPPY), mean (95% CI)	2.47 (2.38 – 2.58)	1.33 (1.29 – 1.36)	Yes[1]
Inpatient Admissions			
Hospital Admissions (PPPY), mean (95% CI)	0.98 (0.94 – 1.02)	0.60 (0.58 – 0.62)	Yes[1]
Length of Stay (days), mean (95% CI)	6.12 (5.98 - 6.26)	5.62 (5.50 - 5.74)	p<0.0001[2]
Patients with ≥1 admissions, n (%)	4,305 (36.2%)	6,298 (27.4%)	-
1, n (%)	2,160 (18.2%)	3,698 (16.1%)	-
2, n (%)	1,120 (9.4%)	1,525 (6.6%)	-
3, n (%)	555 (4.7%)	596 (2.1%)	-
4+, n (%)	470 (4.0%)	479 (2.1%)	-

[1]Average calculated using KMSA methods and 95% CI calculated using bootstrapping. Difference was significant (yes) if Bootstrap 95% Confidence intervals for the 2 group KMSA were not overlapping. [2] Unpaired two-sample t-test was used to test difference in means.
PPPY: Per person per year

7.3 Table 3. Annual Healthcare Costs

Table 3. Healthcare Costs by Cachexia Status and Primary Cancer Diagnosis. All costs expressed in 2024 US dollars.

KMSA Annual Average Healthcare Costs				
	Total	**Inpatient**	**Outpatient**	**Pharmacy**
Total Population				
Cachexia, mean (95% CI) n= 11, 880	$141,626 ($138,004 -$144, 905)	$78,330 ($74,774–$81,786)	$86,271 ($83,785 – $88,854)	$12,304 ($11,538 – $13,176)
Control, mean (95% CI) n= 23,002	$99,104 ($97,193 – $101,224)	$44,498 ($42,855 – $46,282)	$61,958 ($60,449 – $63,469)	$9,991 ($9,566 – $10,479)
Colorectal Cancer				
Cachexia, mean (95% CI) n= 4,665	$133,817 ($128,324 – $139,315)	$85,982 ($80,410 – $92,858)	$78,041 ($74,536 – $82,464)	$10,029 ($8,814 – $11,384)
Control, mean (95% CI) n= 9,277	$86,290 ($83,249 – $89,376)	$41,994 ($39,936 – $44,847)	$53,222 ($51,060 – $55,407)	$7,085 ($6,521 – $7,685)
Lung Cancer				
Cachexia, mean (95% CI) n= 4,455	$132,882 ($127,288 – $138,973)	$55,494 ($51,372 – $60,067)	$86,173 ($81,700 – $90,862)	$14,667 ($13,209 – $16,260)
Control, mean (95% CI) n= 8,872	$95,812 ($92,474 – $99,104)	$33,651 ($31,543 – $35,678)	$62,579 ($59,893 – $65,052)	$12,722 ($11,802 – $13,670)
Pancreatic Cancer				
Cachexia, mean (95% CI) n= 2,760	$170,297 ($162,977 – $178,090)	$109,497 ($100,544 – $118,545)	$100,315 ($95,530 – $105,297)	$12,784 ($11,749 – $14,243)
Control, mean (95% CI) n= 4,853	$130,122 ($124,960 – $135,424)	$75,509 ($70,629 – $81,556)	$76,541 ($73,306 – $79,872)	$10,496 ($9,767 – $11,232)

All averages calculated using KMSA methods and 95% CIs calculated using bootstrapping.

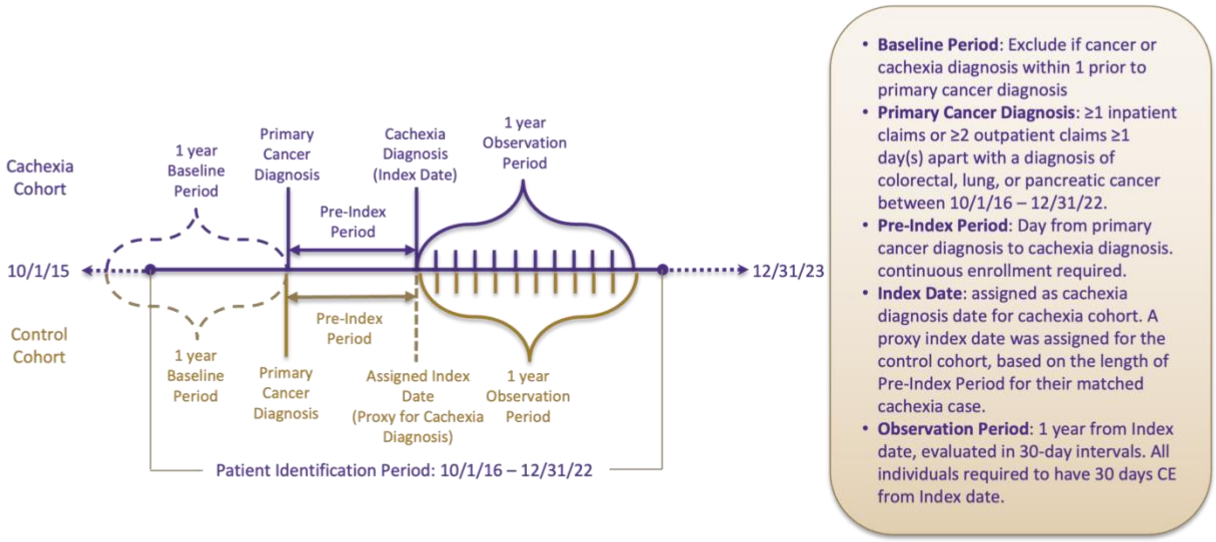
7.4 Table 4. Time from Cancer Diagnosis to Cachexia Diagnosis

Table 4. Healthcare Costs by Cachexia Status and Primary Cancer Diagnosis. All costs expressed in 2024 US dollars.

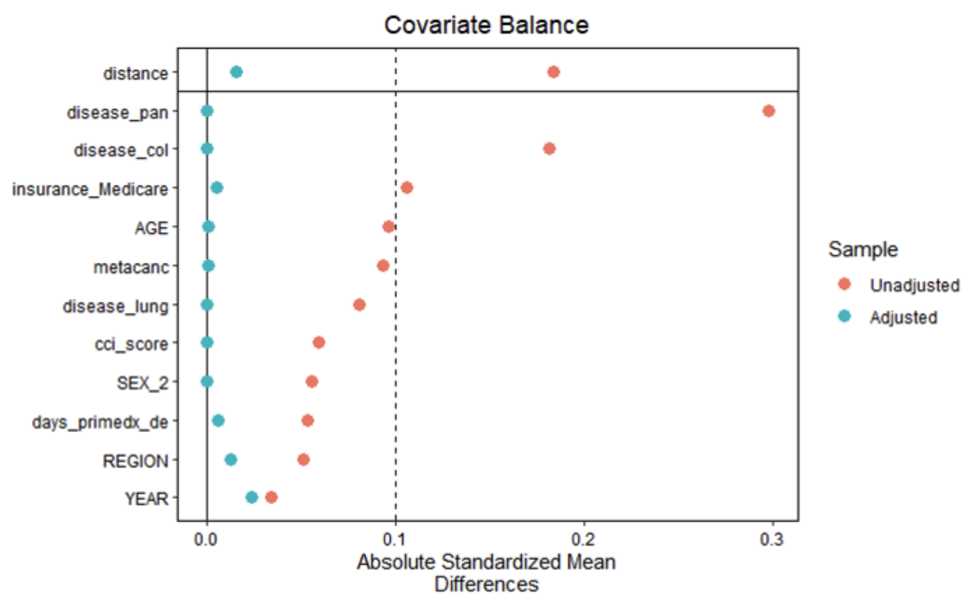
Total Unmatched Population (N = 95,263)	**Colorectal** (N=41,933)	**Lung** (N=40,666)	**Pancreatic** (N=12,664)
Cachexia, n (%)	5,793 (14%)	6,214 (15%)	3,771 (30%)
Time to Cachexia Diagnosis (months)			
Average (SD)	8.85 (13.08)	8.11 (11.47)	4.62 (8.60)
Median (IQR)	3.23 (0.40, 11.57)	3.33 (0.67, 10.93)	1.23 (0.10, 5.10)
Cox Proportional Hazard of Cachexia Diagnosis			
Hazard Ratio (95% CI, value)	Reference	1.25 (1.21 – 1.29, <0.001)	2.90 (2.79 – 3.02, <0.001)

8. Figures

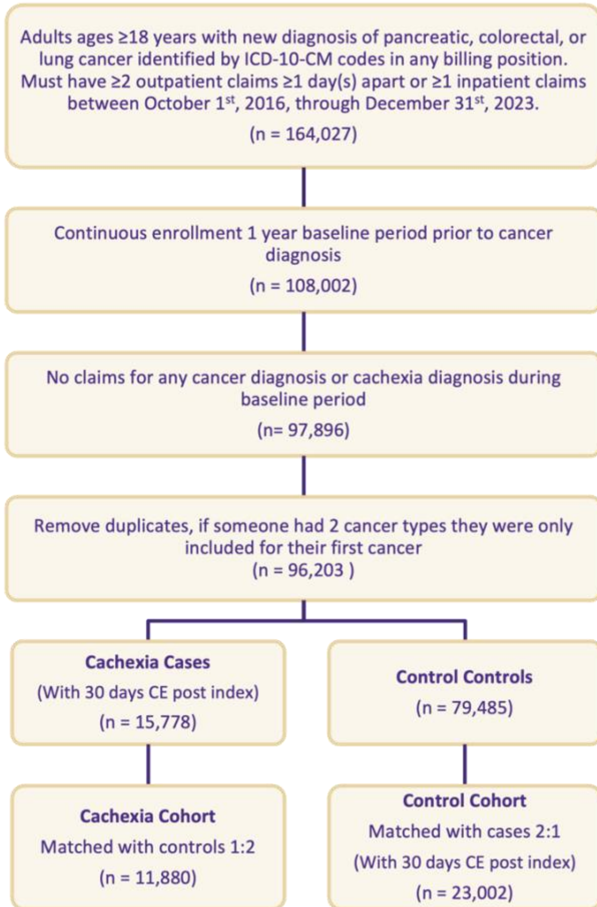
8.1 Figure 1. Study Timeline



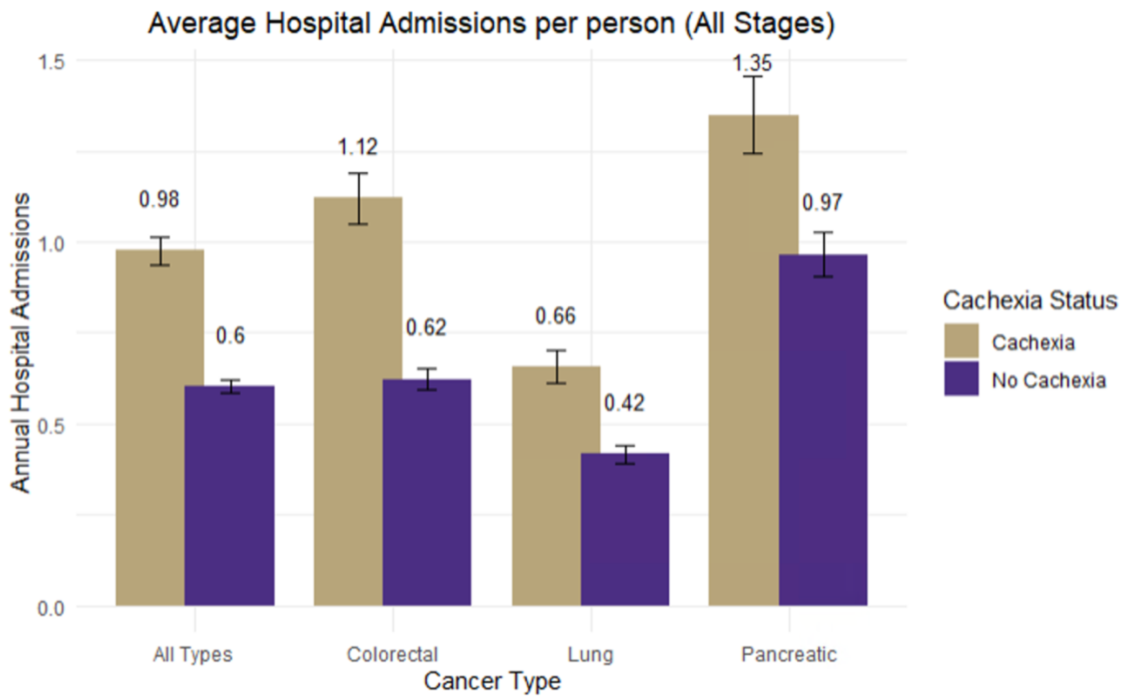
8.2 Figure 2. Matched Cohort Love Plot



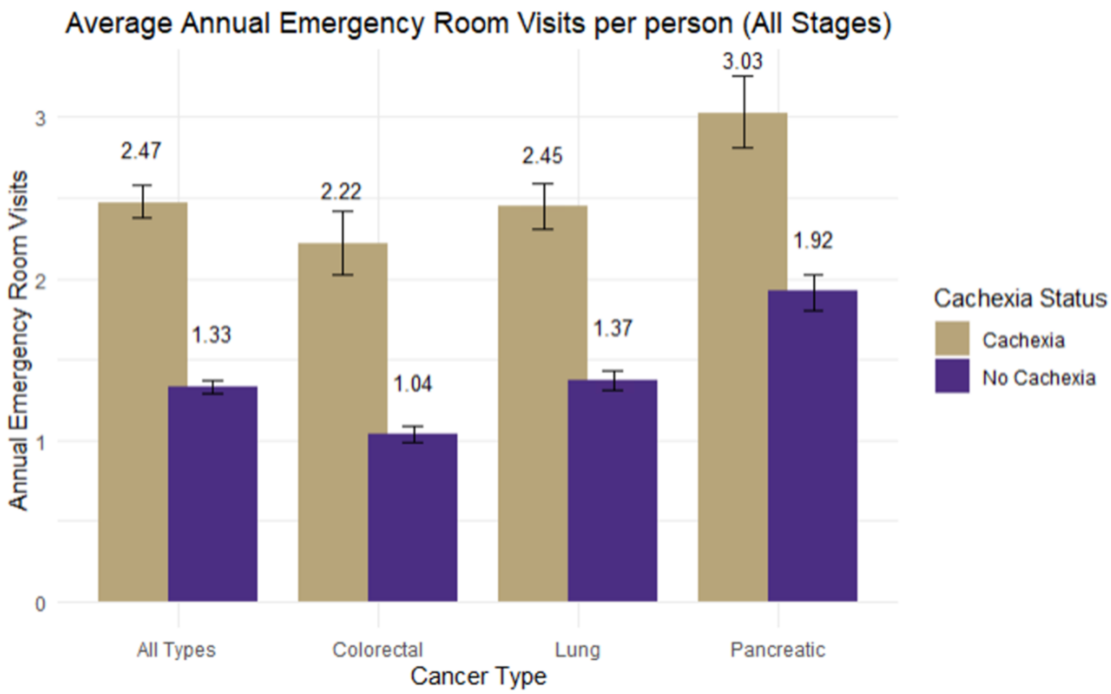
8.3 Figure 3. Cohort Selection Process



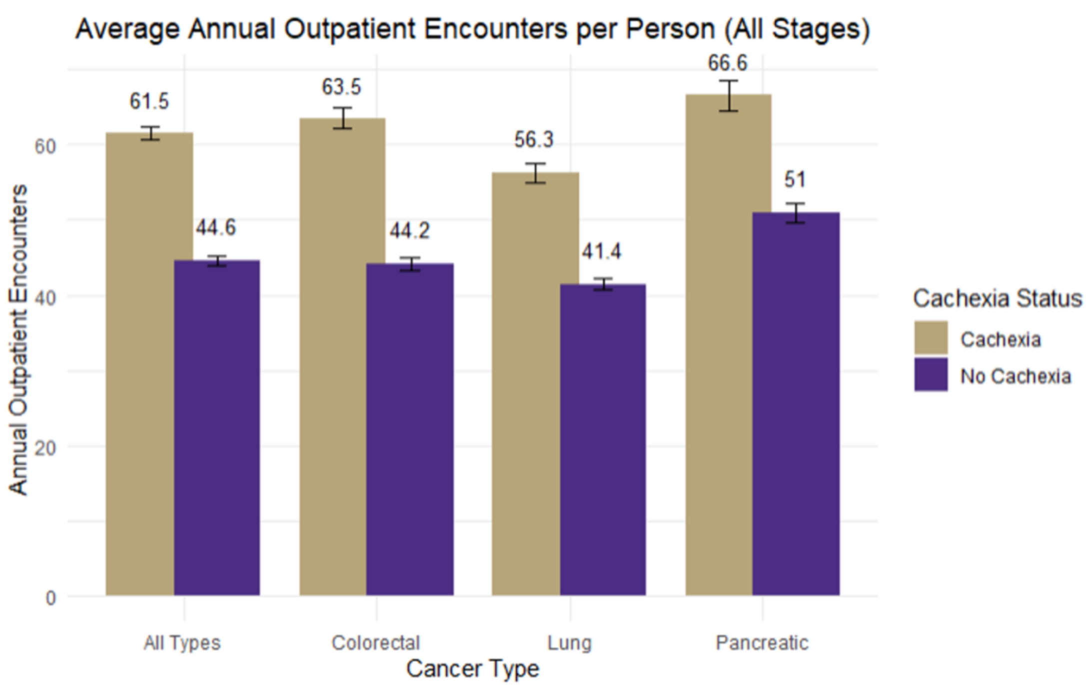
8.4 Figure 4a. Healthcare Resource Utilization by Cancer Type: Annual Hospitalization Admissions



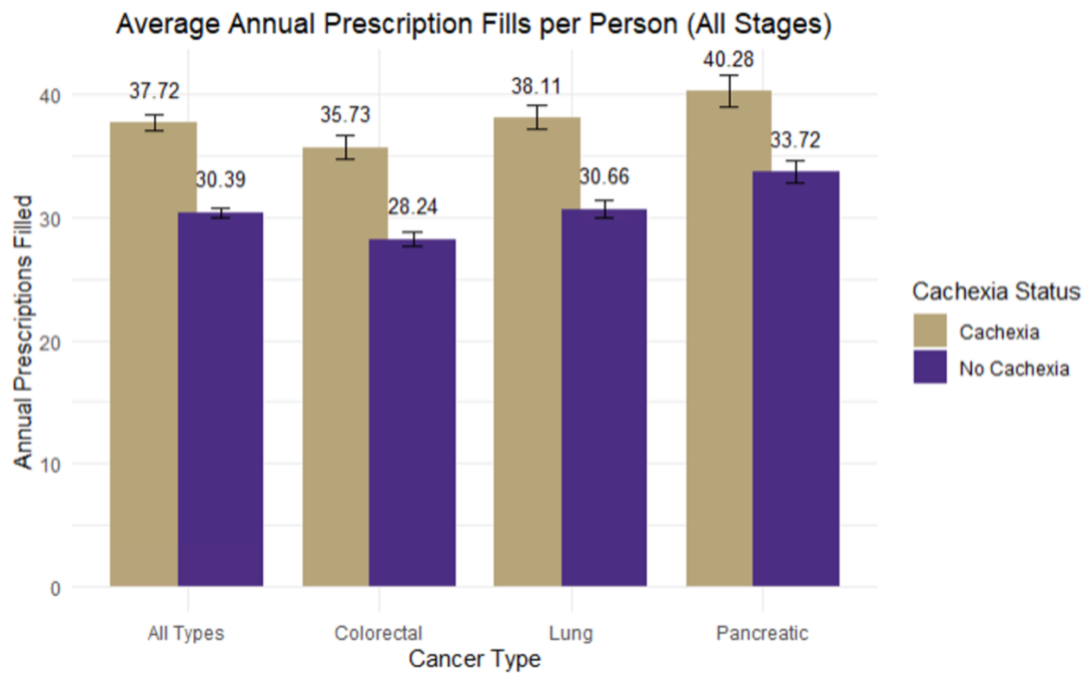
8.5 Figure 4b. Healthcare Resource Utilization by Cancer Type: Annual Hospital Emergency Room Visits



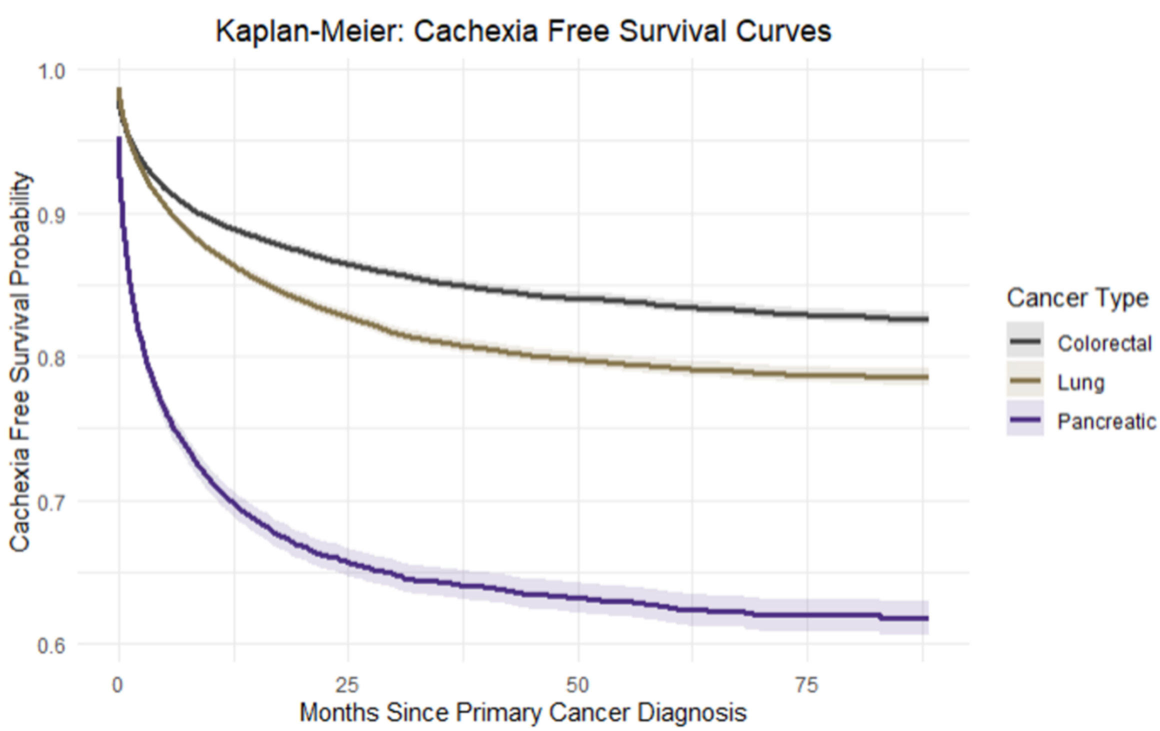
8.6 Figure 4c. Healthcare Resource Utilization by Cancer Type: Annual Outpatient Encounters



8.7 Figure 4d. Healthcare Resource Utilization by Cancer Type: Annual Prescription Fills



8.8 Figure 5. Cachexia Free Survival Curves



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10. Appendices

10.1 Appendix A: ICD-10 Diagnosis Codes

Variable	Created Variable Name	Coded Variable	Table(s)	Operational Definition
Inpatient, Outpatient, and Pharmacy Service Date	NA	SVCDATE	O,D,S	Used to identify dates for diagnosis, when claims happen SVCDATE (Service Date) – used to designate date of diagnosis for outpatient claims
Diagnosis Definitions				
Primary Cancer Diagnosis				
Pancreatic Cancer	cancer_type = “pan”	ICD-10-CM: C25.x Malignant neoplasm of pancreas	S,O	1 inpatient claim or ≥2 outpatient claims ≥1 days apart
Colorectal Cancer	cancer_type = “col”	ICD-10-CM: C18.x: Malignant neoplasm of colon, OR C19.x: Malignant neoplasm of rectosigmoid junction, OR C20.x: Malignant neoplasm of rectum, OR C21.x: Malignant neoplasm of anus and anal canal	S,O	1 inpatient claim or ≥2 outpatient claims ≥1 days apart
Lung Cancer	cancer_type = “lung”	ICD-10-CM: C34.x: Malignant neoplasm of bronchus and lung	S,O	1 inpatient claim or ≥2 outpatient claims ≥1 days apart
Primary cancer diagnosis date	prime_dx_date	SVCDATE	S,O	SVCDATE for first inpatient claim OR second of 2 outpatient claims ≥30 days apart
Metastatic Cancer Diagnosis				

Metastatic Cancer at baseline	metacanc	ICD-10-CM: C77.x: Secondary and unspecified malignant neoplasm of lymph nodes, OR C78: Secondary malignant neoplasm of respiratory and digestive organs, OR C79: Secondary malignant neoplasm of other and unspecified sites	S,O	1 inpatient claim or 1 outpatient claims on day of primary cancer diagnosis Metacanc = Create metastatic marker variable for 0: no metastatic disease, 1: metastatic disease at baseline – Used for CCI calculation and propensity score matching
Metastatic Cancer Status at index	met_status = 1, 0	ICD-10-CM: C77.x: Secondary and unspecified malignant neoplasm of lymph nodes, OR C78: Secondary malignant neoplasm of respiratory and digestive organs, OR C79: Secondary malignant neoplasm of other and unspecified sites	S,O	1 inpatient claim or ≥2 outpatient claims ≥1 days apart between (same ICD codes) Created variable to use for metastatic subgroup analysis and index characteristics
Metastatic Cancer diagnosis date	met_dx_date	SVCDATE	S,O	SVCDATE of first metastatic cancer diagnosis between primary cancer dx date and matched index date
Cachexia Diagnosis				
Specific Definition	short_cachexia_dx_flag	ICD-10-CM: R64: Cachexia (Wasting syndrome)	S,O	≥1 inpatient claim or ≥1 outpatient claims after primary cancer diagnosis (or secondary malignancy diagnosis) Created flag for specific cachexia diagnosis
Expanded Definition	cachexia	ICD-10-CM: R64: Cachexia (Wasting syndrome), OR M62.50: Muscle wasting and atrophy, OR R63.0: Anorexia, OR R63.4: Abnormal weight loss, OR R63.6: Underweight	S,O	≥1 inpatient claim or ≥1 outpatient claims after primary cancer diagnosis (or secondary malignancy diagnosis) Cachexia variable = 0: controls, 1: cachexia

Date of cachexia diagnosis	initial_cc_dx_date	SVCDATE	S,O	SVCDATE of cachexia diagnosis claim

10.2 Appendix B: Healthcare Resource Utilization Outcome Codes

Measure	Variables	Table	Notes	If missing
Number of Inpatient Admissions	CASEID	I	Number of unique inpatient admissions per month = number of unique combinations of ENROLID and CASEID in the inpatient admissions table. Unique admissions per month were used to calculate average admissions per year.	
Hospitalization Length of Stay	DAYS	I	LOS for each unique CASEID and SVCDATE	
Number of Outpatient Encounters	SVCDATE, STDPLAC, visit_group	O	Number of unique outpatient encounters per month is the number of unique combinations of ENROLID, SVCDATE, and visit_group. Unique visits per month were used to calculate average visits per year. visit_group = **"Care visit"** when STDPLAC = 5 Indian Hlth Svc Free-stand Fac 6 Indian Hlth Svc Prov-based Fac 7 Tribal 638 Free-standing Fac 8 Tribal 638 Provider-based Fac 11 Office 12 Patient Home 15 Mobile Unit 17 Walk-in Retail Health Clinic 18 Place of Employment-Worksite 19 Outpatient Hospital-Off Campus 20 Urgent Care Facility 22 Outpatient Hospital-On Campus 24 Ambulatory Surgical Center 26 Military Treatment Facility 49 Independent Clinic 50 Federally Qualified Health Ctr 53 Community Mental Health Center 54 Intermed Care/Intellect Disab 57 Non-resident Subst Abuse Facil 60 Mass Immunization Center 62 Comprehensive Outpt Rehab Fac 65 End-Stage Renal Disease Facil 71 State/Local Public Health Clin 72 Rural Health Clinic 95 Outpatient (NEC)	If STDPLAC missing, visit_group = "Other"

			"Labs" when STDPLAC = 81 Independent Laboratory "Assisted living" when STDPLAC = 13 Assisted Living Facility 14 Group Home 31 Skilled Nursing Facility 32 Nursing Facility 33 Custodial Care Facil 35 Adult Living Care Facility 55 Residential Subst Abuse Facil 56 Psych Residential Treatmnt Ctr **"Hospice"** when STDPLAC = 34 Hospice	
Number of ER Visits	SVCDATE, STDPLAC	O, S	Filter claims where STDPLAC, place of service = 23 (Emergency room – hospital) Number of unique emergency room visits per month is the number of unique combinations of ENROLID and SVCDATE. Unique visits per month were used to calculate average visits per year.	
Drug Utilization (number of prescription fills)	NDCNUM, SVCDATE	D	Number of prescriptions fills per month = number of unique combinations of ENROLID, NDCNUM, and SVCDATE. Unique fills per month was used to calculate average fills per year.	
Number of Fills per month by therapeutic class	thercls_group	D	Used to calculate average annual fills per year of specific class types. thercls_group = "**Antineoplastic**" when THERCLS = 21-22, 260-265 "**Anti-infective**" when THERCLS = 2-20 "**Antiemetics**" when THERCLS = 160 "Non-opioid Analgesics" when THERCLS = 58-59, 62, 203 "**Opioid Analgesics**" when THERCLS = 60-61 "**Other**" = All other THERCLS	If THERCLS Missing will categorize as other

10.3 Appendix C: Cost Outcome Codes

Measure	Variables	Table	Notes	If missing
Total Monthly Cost	NETPAY: The portion of the charge for a	S,O,D	Sum of NETPAY for inpatient, outpatient, pharmacy cost	NETPAY: Exclude

Monthly inpatient cost	healthcare service that the carrier paid to the employee or assigned provider. NETPAY is calculated by MarketScan as PAY minus DEDUCT minus COPAY minus COINS minus COB.	S	Sum of NETPAY for all claims where SVCDATE falls between the first and last day of the month per ENROLID.	
Monthly outpatient cost		O	Sum of NETPAY for all claims within 1 month per ENROLID	
Monthly pharmacy cost		D	Sum of NETPAY for all claims within 1 month per ENROLID	

10.4 Appendix D: Calculated Date Variable Codes

Variable	Calculated Variable Name	Table(s)	Operational Definition	Missing Variable
Primary cancer diagnosis date	prime_dx_date	S,O	PRIMEDX_DATE created from SVCDATE for first inpatient claim OR second of 2 outpatient claims ≥1 days apart	No SVCDATE exclude
Metastatic cancer diagnosis date	met_dx_date	S,O	METDX_DATE created from SVCDATE for first inpatient or outpatient claim with secondary malignancy	
Cachexia diagnosis date	initial_cc_dx_date	S,O	CCDX_DATE created from SVCDATE for first inpatient or outpatient claim with secondary malignancy	
Crude time from Primary cancer diagnosis to cachexia diagnosis	days_primedx_cc	-	Created Variable (Primary cancer diagnosis date) – (cachexia diagnosis date) Used for assigning proxy index date in control group	
	months_primedx_cc	-	days_primedx_cc / 30	
Crude time from Primary cancer diagnosis to Disenrollment	TIME_PRIMEDX_2DE	-	Created Variable (Primary cancer diagnosis) – (Disenrollment date)	
	months_primedx_de	-	days_primedx_cc / 30	
Index date	proxy_index		Assigned after propensity score matching If cachexia = 1, proxy_index = initial_cc_dx_date, if cachexia = 0, proxy_index= prime_dx_date + days_primedx_cc(from their cachexia case match)	
Month Windows within observation period	Month1_start, Month1_end through Month12_start,	-	Month1_start = proxy_index Month1_end = proxy_index + 29 days Month2_start = proxy_index + 30 days…	

	Month12_end			
Disenrollment Date	DISENROLL_DATE	A	(Reference variables) For each year of enrollment, ENRIND1-ENRIND12: flag that indicates that an individual was enrolled in the specified month DISENROLL_DATE is the first day of the first month with a break of continuous enrollment	No enrollment data: Exclude
Month of Disenrollment	Disenroll_month	-	Disenroll_date may fall in the middle of an observation month. Disenroll_month was assigned as the month after disenroll_date was captured between MonthX_start and MonthX_end of an observation month. (Disenroll month = X + 1). This was to ensure that any costs within the observation month between monthX_start and disenroll_date were captured, before the patient becomes censored from the KMSA. Month X+1 is their disenroll month where they will have will not have expenses or HRU.	NA
Time to event for survival analysis	Time_to_event	-	If cachexia = 1, time_to_event = months_primedx_cc, if else (cachexia = 0), time_to_event = months_primedx_de	

10.5 Appendix E: Baseline Demographics by Cancer Type (Matched Cohort)

	Colorectal		Lung		Pancreatic	
Baseline Characteristics	**Cachexia** (n=4,665)	**Control** (n=9,277)	**Cachexia** (n=4,455)	**Control** (n=8,872)	**Cachexia** (n=2,760)	**Control** (n=4,853)
Gender, n (%)						
Male	2,406 (51.6%)	4,781 (51.5%)	2,241 (50.3%)	4,460 (50.3%)	1,538 (55.7%)	2,613 (53.8%)
Female	2,259 (48.4%)	4,496 (48.5%)	2,214 (49.7%)	4,412 (49.7%)	1,222 (44.3%)	2,240 (46.2%)
Age (years), n (%)						
Mean (SD)	62.9 (14.7)	62.9 (14.6)	67.9 (11.3)	67.9 (11.1)	63.8 (11.7)	63.7 (11.5)
18–24	12 (0.3%)	23 (0.2%)	5 (0.1%)	5 (0.1%)	3 (0.1%)	7 (0.1%)
25–34	76 (1.6%)	145 (1.6%)	15 (0.3%)	27 (0.3%)	17 (0.6%)	25 (0.5%)
35–44	354 (7.6%)	692 (7.5%)	55 (1.2%)	108 (1.2%)	92 (3.3%)	151 (3.1%)
45–54	949 (20.3%)	1,881 (20.3%)	374 (8.4%)	735 (8.3%)	408 (14.8%)	724 (14.9%)

55–64	1,479 (31.7%)	2,971 (32.0%)	1,536 (4.5%)	3,079 (34.7%)	1,159 (42.0%)	2,116 (43.6%)
65–74	593 (12.7%)	1,185 (12.8%)	1,062 (23.8%)	2,115 (23.8%)	516 (18.7%)	868 (17.9%)
75–84	773 (16.6%)	1,550 (16.7%)	1,123 (25.2%)	2,231 (25.1%)	439 (15.9%)	732 (15.1%)
85+	429 (9.2%)	830 (8.9%)	285 (6.4%)	572 (6.4%)	126 (4.6%)	230 (4.7%)
Metastatic Cancer, n (%)						
No Metastatic Cancer	3,626 (77.7%)	7,264 (78.3%)	3,046 (68.4%)	6,066 (68.4%)	2,097 (76.0%)	3,649 (75.2%)
Metastatic Cancer	1,039 (22.3%)	2,013 (21.7%)	1,409 (31.6%)	2,806 (31.6%)	663 (24.0%)	1,204 (24.8%)
Charlson Comorbidity Index						
Mean (SD)	3.98 (2.14)	3.96 (2.12)	4.85 (2.38)	4.84 (2.36)	4.44 (2.28)	4.40 (2.28)
2, n (%)	1,720 (36.9%)	3,439 (37.1%)	794 (17.8%)	1,587 (17.9%)	666 (24.1%)	1,168 (24.1%)
3, (n%)	886 (19.0%)	1,769 (19.1%)	966 (21.7%)	1,925 (21.7%)	605 (21.9%)	1,102 (22.7%)
4, (n%)	438 (9.4%)	869 (9.4%)	569 (12.8%)	1,137 (12.8%)	385 (13.9%)	645 (12.8%)
5+, (n%)	1,621 (34.7%)	3,200 (34.5%)	2,126 (47.7%)	4,223 (47.6%)	1,104 (40.0%)	1,938 (39.9%)
Year of Primary Cancer Diagnosis, n (%)						
2016	268 (5.7%)	429 (4.6%)	231 (5.2%)	449 (5.1%)	138 (5.0%)	227 (4.7%)
2017	941 (20.2%)	1,908 (20.6%)	921 (20.7%)	1,824 (20.6%)	552 (20.0%)	883 (18.2%)
2018	852 (18.3%)	1,813 (19.5%)	782 (17.6%)	1,548 (17.4%)	483 (17.5%)	901 (18.6%)
2019	681 (14.6%)	1,354 (14.6%)	503 (11.3%)	1,132 (12.8%)	408 (14.8%)	739 (15.2%)
2020	683 (14.6%)	1,286 (13.9%)	760 (17.1%)	1,369 (15.4%)	389 (14.1%)	666 (13.7%)
2021	615 (13.2%)	1,423 (15.3%)	607 (13.6%)	1,438 (16.2%)	374 (13.6%)	731 (15.1%)
2022	625 (13.4%)	1,064 (11.5%)	651 (14.6%)	1,112 (12.5%)	416 (15.1%)	706 (14.5%)
Region, n (%)						
Northeast	788 (16.9%)	1,867 (20.1%)	813 (18.2%)	1,873 (21.1%)	507 (18.4%)	1,026 (21.1%)
North Central	1,405 (30.1%)	2,926 (31.5%)	1,593 (35.8%)	3,260 (36.7%)	819 (29.7%)	1,389 (28.6%)
South	1,930 (41.4%)	3,534 (38.1%)	1,641 (36.8%)	3,075 (34.7%)	1,062 (38.5%)	1,839 (37.9%)
West	530 (11.4%)	940 (10.1%)	389 (8.7%)	651 (7.3%)	360 (13.0%)	584 (12.0%)
Unknown	12 (0.3%)	10 (0.1%)	19 (0.4%)	13 (0.1%)	12 (0.4%)	15 (0.3%)
Insurance Type, n (%)						
Commercial	2,862 (61.4%)	5,704 (61.5%)	1,984 (44.5%)	3,946 (44.5%)	1,674 (60.7%)	3017 (62.2%)
Medicare	1,803 (38.6%)	3,573 (38.5%)	2,471 (55.5%)	4,926 (55.5%)	1,086 (39.3%)	1836 (37.8%)
Short Definition Cachexia	331 (7.1%)	0	509 (11.4%)	0	302 (10.9%)	0

[1] Measurement taken at time of primary cancer diagnosis. [2] Short cachexia diagnosis, are those have a claim with the specific ICD-10 code R64 indicating cachexia wasting disease.