ECONOMIC BURDEN OF CANCER: ANALYSIS OF OUT-OF-POCKET EXPENDITURE FOR ALL-CANCER, SKIN CANCER AND HEPATOCELLULAR CARCINOMA PATIENTS

A Dissertation

by

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ABSTRACT

Cancer is the second major cause of death in the US which exerts significant morbidity, mortality and economic burden. In this dissertation I focused on the financial toxicity of cancer. I conducted three studies examining the out-of-pocket (OOP) costs and underinsurance among insured all-cancer, skin cancer and hepatocellular carcinoma patients. Since identification of financially vulnerable groups is important, the predictors of OOP and underinsurance were also investigated.

In the first study, insured cancer patients were identified (n_{total} = 6280, $n_{non\text{-}elderly}$ = 2738 and $n_{elderly}$ = 3542) from Medical Expenditure Panel Survey (MEPS) data. Nearly 13% were underinsured, with a higher proportion of elderly patients (16.4%) than non-elderly patients (8.8%). Nearly all (98%) patients had some OOP expenditures, with mean adjusted OOP per person per year of $1623 overall, $1552 for non-elderly and $1669 for elderly patients. Higher expenditure patterns were observed in older adults, females, non-Hispanic whites, patients with a college degree and patients with higher income compared to respective counterparts, for both elderly and non-elderly cohorts. In the second study, similar study design was adopted for skin cancer patients (n_{total} = 1825, n_{NMSC} = 1566 and $n_{melanoma}$ = 259) using MEPS data. Adjusted mean total OOP estimates for all skin cancer patients and only NMSC patients were $1766 and $1763, respectively, and the probability of underinsurance estimates were 13.1% and 13.2%, respectively. In the analysis of significant predictors, 60-64 years age group, females, people with some college education or a college degree and people with high income

demonstrated higher all-cause total OOP expenditure compared to their respective counterparts. Weighted descriptive analyses was repeated stratifying the sample by skin cancer type.

The third study used Surveillance, Epidemiology, and End Results (SEER)-Medicare data to examine the estimates and predictors of OOP incurred by HCC patients (n_{total} = 9942, $n_{satisfying\_Milan\_criteria}$ = 2905 and $n_{not\_satisfying\_Milan\_criteria}$ = 7037). Adjusted mean per person per month (PPPM) OOP estimates for the full sample, cohort satisfying and cohort not satisfying the Milan criteria were $903, $797 and $949, respectively. Among the covariates, race/ethnicity, Metro/non-metro status, NCI comorbidity index, stage at diagnosis, cirrhosis duration and presence of ascites were significant predictors of PPPM OOP costs.

Excessive OOP burden that results in financial toxicity may impact the life of a cancer patient in several ways. Consequences of excess OOP includes foregoing basic necessities, experiencing excessive psychological stress and forgoing necessary medical care. Insured patients are not immune to the detrimental effects of financial toxicities of cancer. In this dissertation I have examined the OOP expenditure and underinsurance affecting cancer patients to get a better understanding of the financial toxicity. The three studies presented here investigate these issues in three different scenarios, namely all-cancer, skin cancer and hepatocellular carcinoma. The outcomes of these studies will fill the gap in current cancer OOP costs related knowledge and will help patients, physicians and policy makers make well-informed decisions.

DEDICATION

I dedicate this work to my family. You always had faith in me and motivated me to be a better person. Thank you.

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NOMENCLATURE

AAP	Average Adjusted Prediction
AME	Average Marginal Effect
ASCO	American Society of Clinical Oncology
CCS	Clinical Classifications Software
CPI	Consumer price index
FI	Family income
FPL	Federal poverty level
FYC	Full year consolidated
HCC	Hepatocellular carcinoma
MC	Managed care
MEPS	Medical Expenditure Panel Survey
NCI	National Cancer Institute
NMSC	Non melanoma skin cancer
OOP	Out-of-pocket
PPPM	Per person per month
SEER	Surveillance, Epidemiology, and End Results
SES	Socioeconomic status

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1. INTRODUCTION

Although substantial progress has been achieved against cancer in terms of incidence and mortality in the last few decades, the condition remains a public health issue of significant concern in the United States.[1] An estimated 1.8 million new cancer cases are expected to occur in the US in 2020.[2] 40% of all men and 39% or all women are at the risk of being diagnosed with some type of cancer in their lifetime.[1] The condition imposes morbidity and mortality burden on the affected population at a tremendous scale. Cancer associated financial burden on the health system and financial toxicity affecting the patients are also overwhelming.[3,4]

Different estimates of national total direct burden of cancer range from around $62 billion to $173 billion per year and estimates of total indirect burden range from around $18 billion to $94 billion per year.[1,4-6] The out-of-pocket (OOP) burden, for which the patients are directly responsible, has also been examined in several studies.[7-10] However, issues such as underinsurance resulting from excess OOP expenditure and the services utilization pattern in conjunction with OOP expenditure are not well reported in the literature. Moreover, OOP studies on specific cancer types are scarce. I have addressed these cancer OOP related issues in my dissertation. Three studies concerning with three different aspects of cancer related OOP constitutes this dissertation: the first study focuses on all-cancer types, the second study focuses on skin cancer and the third study focuses on hepatocellular carcinoma (HCC) which is the most common type of liver cancer.

1.1. OVERVIEW

Cancer treatment is usually costly and the financial burden may adversely affect diagnosed individuals. There are certain mechanisms to alleviate financial burden affecting low-income and uninsured patients suffering from certain cancer types. The Breast and Cervical Cancer Prevention and Treatment Act (BCCPTA) passed in The Congress in 2000 enabled all 50 states to extend Medicaid coverage to eligible financially insolvent breast or cervical cancer patients diagnosed through the National Breast and Cervical Cancer Early Detection Program (NBCCEDP).[11] This model of assisting needy cancer survivors, however, stands out as an exception and individuals with other cancer types may not get such assistance. The Affordable Care Act (ACA) though it's several provisions has contributed in reducing the number of uninsured individuals in the US, and brought 13.5 million individuals under insurance coverage during the 2013-2018 time period.[1,12] Though increasing insurance coverage may help cancer patients in financial needs that may not be adequate to protect patients against the financial toxicity of cancer. They added financial onus resulting from non-cancer related comorbid conditions may further deteriorate the financial well-being of a cancer patient. A 2013 study by Zafar et al. on 254 patients with various insurance status reported reduced spending on basic necessities like food and clothing by 46% of the participants and skipping of prescription filling by 24% of the participants.[13] In a 2019 study based on 2011-2016 data, 22% of privately insured cancer patients and 33% of publicly insured cancer patients reported some type of material hardship experienced (i.e. needing to borrow money or being unable to pay cost sharing amount or declaring bankruptcy).[10]

This demonstrates the need to have a better understanding of the financial burden affecting insured cancer patients. In my dissertation I have focused on the issue of out-of-pocket expenditure related financial toxicity affecting insured cancer patients. My research questions investigated financial toxicity among all-cancer patients in general, which has been presented in Section 2 of this dissertation; skin cancer patients, which has been presented in Section 3 of this dissertation; and hepatocellular carcinoma patients, which has been presented in Section 4 of this dissertation. In each study presented in Section 2, 3 and 4, I have investigated the predictors, estimates and extent of economic burden caused by respective cancer types.

1.1.1. OOP Expenditure Burden on All Cancer Patients

The first study of this dissertation examines the issue of financial toxicity among all cancer patients. First, the extent of high burden expressed through the underinsurance indicator is examined. Then, OOP expenditure responsible for the underinsurance is examined. Finally the services utilization that are responsible for incurring OOP expenditure are examined. The analysis is stratified by age specific Medicare eligibility (age <65 years versus ≥65 years). Data provided by a nationally representative survey, Medical Expenditure Panel Survey (MEPS), was used in this study.

1.1.2. OOP Expenditure Burden on Skin Cancer Patients

The second study of this dissertation examines the issue of financial toxicity affecting skin cancer patients. Skin cancer is the most prevalent cancer in the USA which has two major sub-types: melanoma and non-melanoma skin cancer (NMSC).[14,15] Cost related studies of skin cancer is challenging because the major sub-type, NMSC, is not tracked by the cancer registries. Thus, linking prevalence data with claims data, such as Medicare claims, is not possible for NMSC unlike other cancer types. Although NMSC is less deadly compared to melanoma, financial burden caused by this cancer type is not trivial.[16] Although previous studies have examined total burden of skin cancer, studies on OOP burden and underinsurance affecting skin cancer patients is lacking.[16-18] In the second study of this dissertation, I have addressed these issues using MEPS data. Due to limited sample size, the study was not stratified by age. Rather, the study was stratified by skin cancer sub-type. Covariate adjusted analysis was restricted to full sample and NMSC sample.

1.1.3. OOP Expenditure Burden on Hepatocellular Carcinoma Patients

The third study in this dissertation examines the issue of financial toxicity among the patients with hepatocellular carcinoma (HCC). HCC accounts for 80% of all primary liver cancers and has very low survival rate.[19] 2-year and 5-year survival rate of HCC in the United States is <50% and 10% respectively.[19,20] To analyze the OOP burden of HCC, linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database was used. This study provided insights into the out of pocket cost aspects of a high mortality cancer type.

1.2. CONCLUDING REMARKS

Financial toxicity is a grave concern for cancer patients, physicians, health systems and policy makers. The studies presented in the current dissertation will facilitate better informed patient-physician interactions, treatment decision discussions and cancer-cost related policy discussions.

2. OUT-OF-POCKET EXPENDITURE, UNDERINSURANCE AND HEALTH SERVICES UTILIZATION AMONG CANCER PATIENTS

2.1. INTRODUCTION

Despite the decreasing mortality in the last 25 years, cancer remains a deadly disease which is expected to cause an estimated 606,520 deaths in the USA in 2020.[2] In addition to high mortality, cancer is associated with significant morbidity, with an adverse impact on the quality of life of the survivors.[21,22] Besides its mortality and morbidity impact, the adverse financial impact of cancer on patients, oftentimes called ‘financial toxicity’, has become a matter of grave concern among patients, providers, and policy makers.[23-25] With the rising cost of healthcare, fueled by the introduction of new technologies and medications, patients are prone to high out-of-pocket costs.[26-28] The high cost of services may negatively impact the care received and overall well-being of patients. Studies have reported non-compliance, forgone medication purchases and high level of hardship experienced by cancer patients related to financial toxicity.[29,30]

All cancer patients, either insured or uninsured, experience some form of financial distress.[31] Due to the heterogeneity in coverage in health plans and no out-of-pocket maximum provision of traditional Medicare, out-of-pocket (OOP) expenditure burden on cancer patients with insurance coverage could become substantial.[7,9]

2.2. BACKGROUND

Although many studies on financial hardship have focused on patients of low socioeconomic status including uninsured patients, those with insurance are not immune to the financial toxicity of cancer care.[31] The coverage pattern between health plans varies, with many plans inadequately covering OOP expenditure, which may result in considerable economic burden on the patients.[7,9] Moreover, the OOP burden may vary depending on cancer management strategies.[32,33] These factors may contribute in rendering a cancer patient underinsured when the patient incurs a substantial amount of OOP expenditure despite having insurance coverage. In addition to cancer-specific costs, unrelated medical care for comorbid conditions may exacerbate financial burden.[34] Alternatively, financial toxicity may lead to lower use of beneficial but "non-essential" services such as preventive medical care or dental care.

The American Society of Clinical Oncology (ASCO) Guidance on Cost of Cancer Care identified patient-provider discussions about costs of medical care as a key component of high quality care.[35] There have also been calls for patient engagement in treatment planning.[25,36] It is important for clinicians to communicate the financial aspects of therapy options, along with their clinical suitability, to make patients aware of the complete impact of all treatment options. Information on differing pattern of services utilization and expenditure among patient subgroups may provide physicians a holistic context to communicate expenditure-related information to their patients. Prior studies have reported high financial burden of medical care among cancer survivors, although there are limited data examining how service-specific OOP and utilization pattern varies among subgroups.[7,9,10,37-40]

In the current study I investigated underinsurance, OOP expenditure and service utilization among a large nationally representative sample of insured cancer patients in the United States.

2.3. DATA AND METHODS

2.3.1. Data Source

I used the Household Component (HC) of the Medical Expenditure Panel Survey (MEPS) for the years 2011 to 2015. MEPS is a survey on a nationally representative sample of civilian non-institutionalized population in the USA.[41] There are multiple data files provided by MEPS, among which the Full Year Consolidated (FYC) file containing sociodemographic and expenditure information and the Medical Condition (MC) file containing medical condition information were used for this analysis (Figure 2-1).

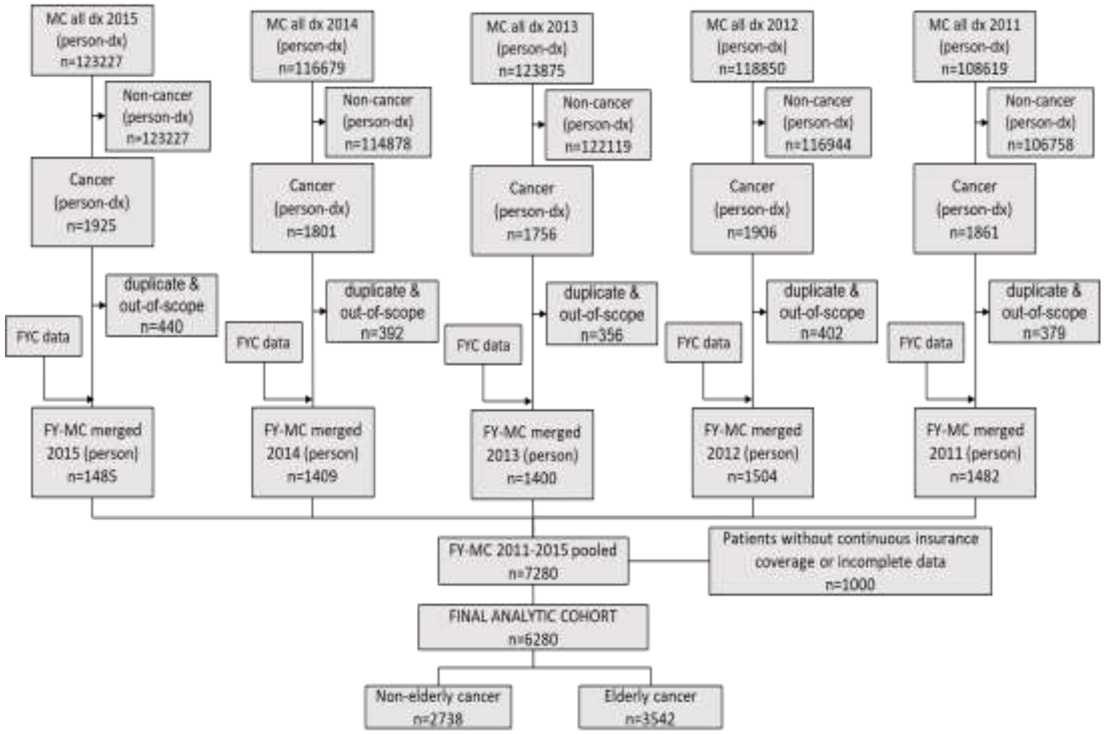

Figure 2-1: Construction of analytic cohort (all cancer) - dataflow

2.3.2. Study Sample

In my study, I identified adult (≥18 years) cancer patients form MEPS-HC using Clinical Classifications Software (CCS) codes (21-45) for whom cancer is reported as a current condition (n = 6280). Only patients with full year insurance coverage and having complete data were included. MEPS employs a multistage survey design and oversamples minority racial/ethnic groups (Blacks, Hispanics and Asians).[42] My analyses were performed adjusting for the complex survey design of MEPS by incorporating appropriate person-level weight, strata and primary sampling unit variables in each model and employing survey specific commands in Stata (i.e. svyset, svy etc.) which enabled me to produce national level estimates. [41,43]

My analysis was performed on two cohorts of cancer patients: non-elderly (age 18 to 64 years, n = 2738) and elderly (age ≥ 65 years, n = 3542) patients (Figure 2-1). I studied subgroup variation in underinsurance, expenditure and utilization for each of the two cohorts.

2.3.3. Measures

Underinsurance. Following previous studies, underinsurance was defined using an indicator variable based on the ratio of total OOP and family income. Specifically, it was defined as total OOP ≥5% of family income (FI) for FI <200% federal poverty level (FPL) or ≥10% of FI for FI ≥200% FPL, for the individuals having full year insurance coverage.[44,45] This concept of underinsurance has the advantage of quantifying financial inadequacy based on varying OOP to family income ratio,[44-47] versus the commonly reported threshold of OOP ≥20% of FI among all patients.[7,10,40] However, I performed several sensitivity analyses using several different underinsurance thresholds: the three fixed thresholds were at OOP ≥5% of FI, ≥10% of FI and ≥20% of FI, for all income levels and the five sliding thresholds had varying OOP-to-FI ratio for FI <125%, 125% to <200%, 200% to <400% and >400% of FPL, respectively.

Total and service-specific OOP expenditure. Total OOP is the sum of a cancer patient's expenditure for all health services utilized in a given year.[41] Additionally, separate service-specific OOPs were estimated in my analysis for the following service categories: ambulatory clinical (office based + outpatient), non-ambulatory clinical (inpatient + ER), prescription medications, dental services and other health services (home health + vision + device + others).

Service-specific utilization. Services utilization was quantified separately for each service category except for other health services (data not available in MEPS). Ambulatory and dental care utilization represents the number of visits for those services; non-ambulatory utilization represents the number of inpatient discharges and ER visits; and prescription medication utilization represents the number of prescriptions purchased per person over one year period.

Covariates. Age, sex, race/ethnicity, marital status, income level, education and insurance status were included as covariates in each model. Number of MEPS reported comorbid conditions (except cancer and Attention Deficit Hyperactivity Disorder) summarized in four categories was included as a categorical variable to control for comorbidities. Self-reported health status and census region variables were also included. All covariates were categorical (Appendix A, Table 1 and Appendix A, Table 2).

2.3.4. Analysis

As stated above, I evaluated three outcomes: underinsurance, OOP expenditure and service utilization. Prevalence of underinsurance was estimated using a multivariable logistic regression model. Total and service-specific OOPs were estimated using two-part regression models (logistic and GLM with log link and gamma distribution).[48] GLM-only sensitivity analyses were performed to test the effect of estimation method variation. Service-specific utilization were estimated using negative binomial models, in which total number of events per year was the dependent variable for each service type. Average Adjusted Prediction (AAP) and Average Marginal Effect

(AME) measures were used to quantify all estimates.[48-50] I conducted subgroup analyses by sociodemographic factors including age, sex, race/ethnicity, education, income, and insurance status. Income and expenditure dollar values were inflated to 2018 US dollars using consumer price index (CPI) and values were rounded.[51] Statistical significance was defined at a 5% level. All analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC) and Stata 13.1 (StataCorp, College Station, TX).

2.4. RESULTS

2.4.1. Patient Characteristics

Of 6280 eligible patients, 2738 were non-elderly and 3542 were elderly. The overall weighted sample was majority white (85.8%), female dominant (53.8%) and most had non-managed care insurance coverage (71.7%). The non-elderly cohort had a higher proportion of female, Black and Hispanic patients compared to the elderly cohort (Appendix A, Table 1).

2.4.2. Prevalence and Correlates of Underinsurance

Overall, 13.2% of patients were underinsured, although this was more common among elderly cancer patients than the non-elderly. Even after adjusting for relevant covariates, underinsurance among the elderly cohort (16.4% [SE, 0.8 percentage point (pp)]) was almost two times higher than the prevalence observed among the non-elderly cohort (8.8% [SE, 0.7 pp]).

In subgroup analyses, underinsurance was more common in older adults aged 60-64 years (13% vs 6.2%, $p<0.01$), elderly females (17.9% vs 14.5%, $p<0.01$) and non-Hispanic whites (non-elderly: 9.8% vs 4.6%, $p<0.01$, elderly: 17.5% vs 10.6%, $p<0.01$)

compared to those aged 18-49 years, elderly males and Blacks, respectively. Underinsurance was less common among middle- and high-income individuals compared to those with low income (non-elderly: 5.8% and 0.7% vs 45.4%, both $p<0.01$; elderly: 8.2% and 1.6% vs 49.2%, both $p<0.01$) both in the non-elderly and the elderly cohort. However surprisingly, it was more common in patients with higher educational attainment, such that patients with a college degree were more likely to be underinsured (non-elderly: 11.1% vs 7.4%, $p<0.05$; elderly: 19.9% vs 14.3%, $p<0.01$) than those with a high-school education; and this pattern was common among the non-elderly and elderly cohorts. Non-elderly cancer patients with Medicaid and Medicare/dual-eligibility were less likely to be underinsured compared to private managed-care patients (3.7% and 6.5% vs 12%, both $p<0.01$), but <65 private non-managed care patients did not show any significant difference. No variation in underinsurance was observed among elderly patients across insurance types (Table 2-1).

2.4.3. Total OOP Expenditures

Nearly all (98%) patients had some OOP expenditure, with mean adjusted OOP per person per year for the overall, non-elderly, and elderly samples being $1623 [SE, $60], $1552 [SE, $86] and $1669 [SE, $74], respectively. OOP variation among sociodemographic subgroups generally paralleled underinsurance patterns with a couple notable exceptions. For example, non-elderly females incurred significantly higher total OOP expenditure than non-elderly males ($1676 vs $1379, $p<0.01$) but their probability of underinsurance did not reflect this pattern. Females (vs. males), patients with a college degree (vs. those with a high school education/diploma) and patients with medium or high income (vs. those with low income) spent significantly higher OOP, whereas black and Hispanic patients (vs. non-Hispanic whites) spent significantly lower OOP, in both non-elderly and elderly cohorts. Although patients with Asian/others race/ethnicity spent significantly higher OOP vs. non-Hispanic whites in the non-elderly cohort, no such pattern was observed in the elderly cohort. Older sub-groups in each age-cohort: patients aged 50-59 years and 60-64 years (vs. those aged 18-49 years) in the non-elderly cohort and patients aged ≥85 years (vs. those aged 65-74 years) in the elderly cohort incurred significantly higher OOP expenditure. Patients covered by Medicaid in the non-elderly cohort (vs. <65 Private managed-care) and covered by Medicare FFS without other private insurance in the elderly cohort (vs. ≥65 Medicare managed-care with other private) incurred significantly higher OOP expenditure All results are presented in Table 2-1 (demographics) and Table 2-2 (socioeconomic status).

Table 2-1: Adjusted OOP and probability of underinsurance by demographic variables for non-elderly and elderly cancer patients (weighted).

Variable and Categories	Total OOP				Probability of underinsurance			
	non-elderly cancer (n=2738)		**elderly cancer (n=3542)**		**non-elderly cancer (n=2738)**		**elderly cancer (n=3542)**	
	OOP ($)†	***p***	**OOP ($)†**	***p***	**Prob. (%)‡**	***p***	**Prob. (%)‡**	***p***
Age								
18-49 years [ref.]	1255				6.21			
50-59 years	1487	0.046			8.17	0.114		
60-64 years	1922	0.000			13.02	0.000		
65-74 years [ref.]			1543				15.61	
75-84 years			1596	0.627			15.79	0.907
>=85 years			2401	0.016			19.78	0.064
Sex								
Male [ref.]	1379		1563		9.09		14.53	
Female	1676	0.008	1785	0.035	8.68	0.696	17.94	0.004
Race/ethnicity								
non-Hispanic white [ref.]	1638		1733		9.8		17.47	
Black	931	0.000	1032	0.000	4.57	0.000	10.59	0.000
Hispanic	1250	0.014	800	0.000	7.79	0.117	9.29	0.000
Asian/others	1183	0.030	1664	0.851	6.21	0.047	12.82	0.152
Marital status								
Not Married [ref.]	1572		1771		10.26		16.58	
Married	1544	0.843	1604	0.237	7.44	0.049	16.15	0.750

Abbreviations: HS, high school; MC, Managed care.

Note: †Adjusted mean from two-part model (logistic and GLM with log link and gamma distribution). ‡ Adjusted mean from logistic model. All estimation models were adjusted for age, sex, race/ethnicity, marital status, income level, education, census region, insurance status, number of MEPS priority conditions and self-reported health status. *p*-value Represents significant difference compared to the reference category (the first row) of each variable.

Table 2-2: Adjusted OOP and probability of underinsurance by socioeconomic status (SES) variables for non-elderly and elderly cancer patients (weighted).

Variable and Categories	Total OOP				Probability of underinsurance			
	non-elderly cancer (n=2738)		**elderly cancer (n=3542)**		**non-elderly cancer (n=2738)**		**elderly cancer (n=3542)**	
	OOP ($)†	***p***	**OOP ($)†**	***p***	**Prob. (%)‡**	***p***	**Prob. (%)‡**	***p***
Education								
HS education/diploma [ref.]	1338		1429		7.46		14.37	
Some college	1422	0.513	1597	0.156	9.37	0.142	18.13	0.007
College degree or above	1788	0.005	2015	0.001	11.07	0.021	19.87	0.001
Income level								
Low income [ref.]	1131		1350		45.36		49.24	
Middle income	1368	0.035	1675	0.006	5.77	0.000	8.24	0.000
High income	1743	0.000	1863	0.001	0.7	0.000	1.59	0.000
Insurance status								
<65 Private MC [ref.]	1479				11.99			
<65 Private non-MC	1691	0.080			11.86	0.941		
<65 Medicaid	451	0.000			3.65	0.000		
<65 Medicare/dual eligible	1415	0.794			6.54	0.008		
65+ Medicare MC with other private [ref.]			1910				16.86	
65+ Medicare MC w/o other private			1703	0.296			17.97	0.603
65+ Medicare FFS with other private			1660	0.129			17.26	0.830
65+ Medicare FFS w/o other private			1451	0.028			13.55	0.113

Abbreviations: HS, high school; MC, Managed care. Note: †Adjusted mean from two-part model (logistic and GLM with log link and gamma distribution). ‡ Adjusted mean from logistic model. All estimation models were adjusted for age, sex, race/ethnicity, marital status, income level, education, census region, insurance status, number of MEPS priority conditions and self-reported health status. Low income represents <200% of Federal poverty level (FPL), Middle income represents 200% to <400% of FPL and High income represents ≥ 400% of FPL.

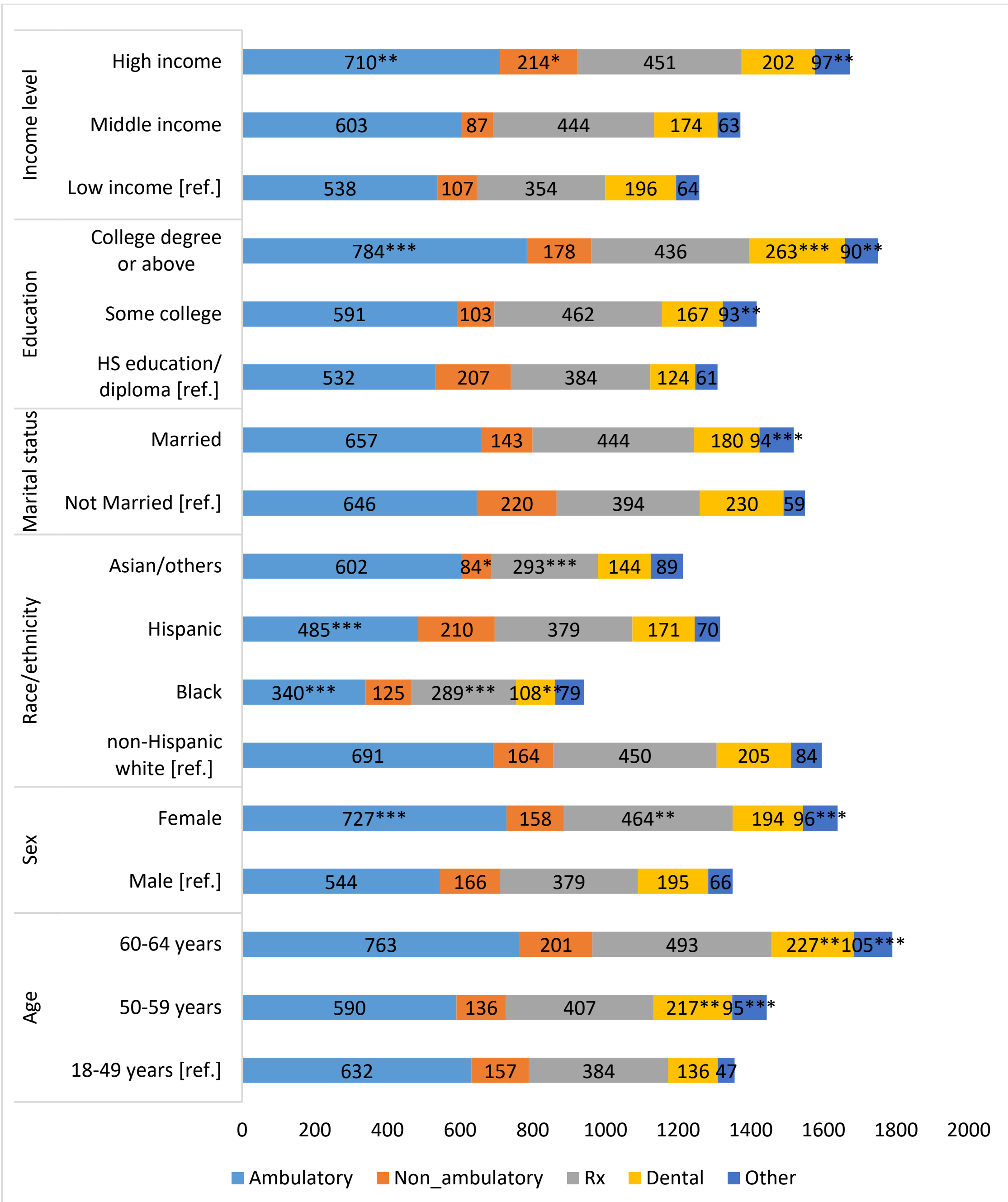

Figure 2-2: Mean OOP by sociodemographics and service categories, non-elderly cancer patients ($ per person per year)

2.4.4. Service-specific OOP Expenditures

Adjusted mean OOP expenditures for ambulatory, non-ambulatory, prescription, dental and other health services incurred by all patients were $515 [SE, $20], $117 [SE, $23], $490 [SE, $17], $309 [SE, $23] and $174 [SE, $25] respectively; whereas OOP incurred by non-elderly and elderly patients separately for the same services were $653 [SE, $29] and $415 [SE, $23], $161 [SE, $43] and $82 [SE, $15], $428 [SE, $29] and $534 [SE, $22], $194 [SE, $17] and $391 [SE, $36], and, $83 [SE, $7] and $240 [SE, $42] respectively. Compared to the elderly cancer patients, non-elderly patients spent a higher proportion of their total OOP on ambulatory, non-ambulatory and prescription services. The trend was reversed for dental and other services, for which non-elderly patients spent lower proportions of their total OOP expenditure (Figure 2-2).

OOP expenditure pattern for different health services varied by sociodemographic subgroups with patients aged 50-59 years and 60-64 years spending more on dental ($217 and $227 vs $136, both $p<0.05$) and other health services ($95 and $105 vs $47, both $p<0.01$) compared to those aged 18-49 years; females spending more on ambulatory ($727 vs $544, $p<0.01$) and prescription services ($464 vs $379, $p<0.05$) compared to males; and non-Hispanic whites spending more on ambulatory ($691 vs $340, $p<0.01$) and prescription services ($450 vs $289, $p<0.01$) compared to Black patients in the non-elderly cohort. Cancer patients with high socioeconomic status (SES) generally had higher OOP expenditure for health services with non-elderly cancer patients with a college degree ($784 vs $532, $p<0.01$) and high income ($710 vs $538, $p<0.05$) spending more on ambulatory services compared to patients with high school education and low income respectively (Figure 2-2). Similar OOP expenditure pattern was observed among the elderly sociodemographic sub-groups (Figure 2-3). Additionally, variation in insurance status was associated with service-specific OOP expenditure for health services. Compared to private managed-care patients, non-elderly Medicaid patients had significantly lower OOP expenditure for all health service types, whereas elderly Medicare managed-care patients having other private insurance spent ($565 [SE, $ 56]) more than any other insurance sub-groups for ambulatory care (Appendix A, Figure 1).

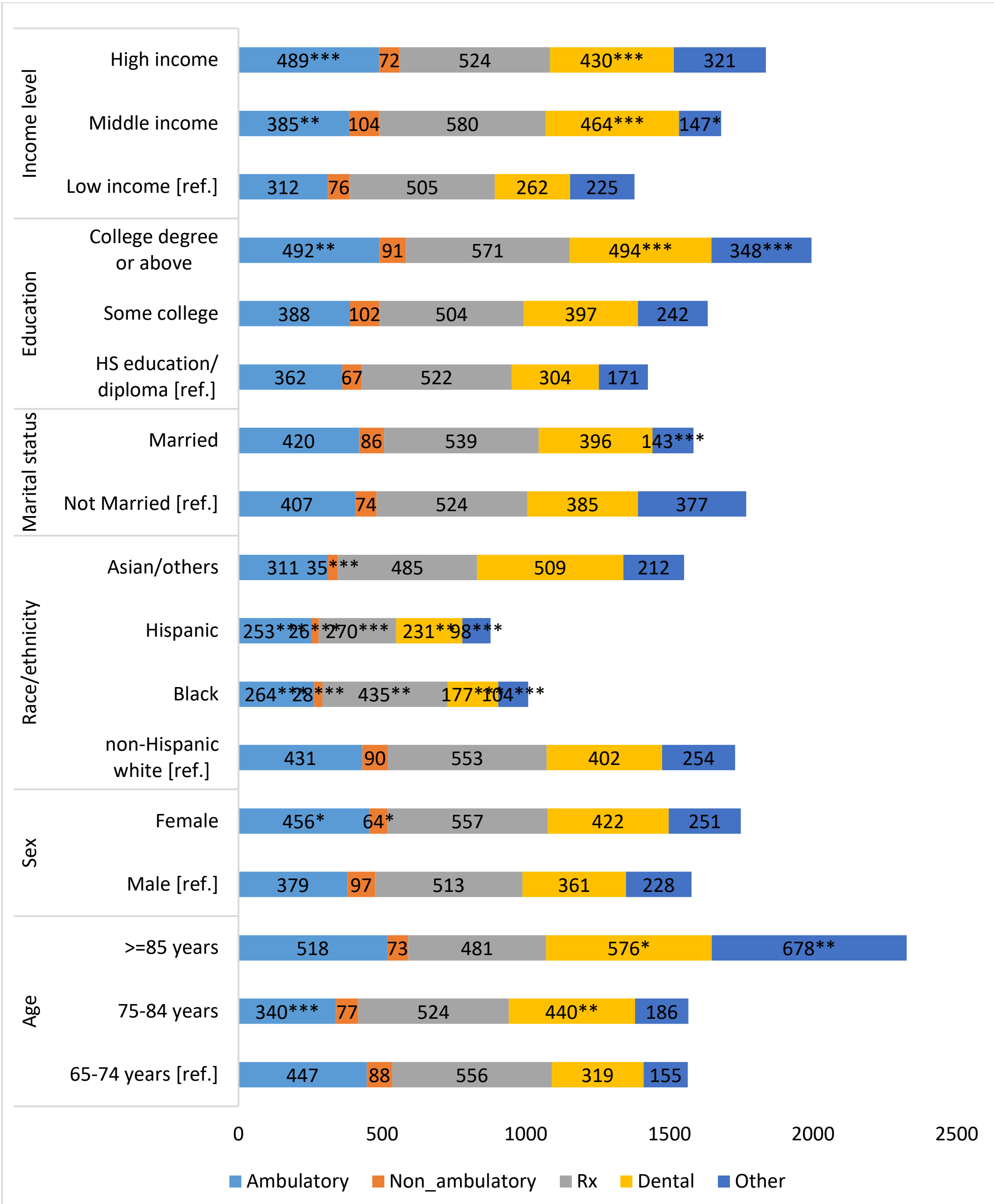

Figure 2-3: Mean OOP by sociodemographics and service categories, elderly cancer patients ($ per person per year)

2.4.5. Service-specific Utilization

Adjusted mean number of events for ambulatory, non-ambulatory, prescription and dental services for non-elderly and elderly patients were 14 [SE, 0.4] and 19 [SE, 0.5], 0.51 [SE, 0.03] and 0.64 [SE, 0.03], 24 [SE, 1] and 30 [SE, 0.7], and, 1.4 [SE, 0.05] and 1.6 [SE, 0.67] respectively. Utilization of several health services, such as ambulatory and dental care, were significantly lower among racial/ethnic minority patients and patients with high school education compared to their respective counterparts. I also observed differential utilization patterns of prescription medications by socioeconomic status (SES), where elderly patients with a college education or middle to high income used less prescription medications than their lower SES counterparts, while utilization of all other health services were similar or increased with higher SES in both age-cohorts (Appendix A, Table 3; Appendix A, Table 4 and Appendix A, Figure 2).

2.4.6. Sensitivity Analysis

I performed several sensitivity analyses to check the robustness of my estimates. Adjusted probabilities of underinsurance for non-elderly and elderly were 2.9% [SE, 0.4%] and 4.5% [SE, 0.5%] respectively for a fixed threshold of OOP ≥20% of FI; and were 6.4% [SE, 0.5%] and 11.6% [SE, 0.7%] respectively for a sliding threshold of OOP ≥5%, ≥10%, ≥15% and ≥20% of FI. Additional results are presented in Table 2-3.

Table 2-3: Sensitivity analyses results – probability of underinsurance for various OOP-to-FI thresholds.

Alternative definitions of underinsurance	**Probability of underinsurance**	
	Non-elderly cancer (%)	**Elderly cancer (%)**
Fixed thresholds		
OOP ≥5% of FI for all income levels	13.2	22.8
OOP ≥10% of FI for all income levels	5.9	10.5
OOP ≥20% of FI for all income levels	2.9	4.5
Sliding thresholds		
OOP ≥5% and ≥10% of FI, for FI <200% and ≥200% of FPL, respectively **(base case)**	8.8	16.4
OOP ≥5%, ≥6%, ≥7% and ≥8% of FI, for FI <125%, 125% to <200%, 200% to <400% and ≥400% of FPL, respectively	9.7	18.1
OOP ≥5%, ≥6.5%, ≥8% and ≥9.5% of FI, for FI <125%, 125% to <200%, 200% to <400% and ≥400% of FPL, respectively	8.7	16.6
OOP ≥5%, ≥7%, ≥9% and ≥11% of FI, for FI <125%, 125% to <200%, 200% to <400% and ≥400% of FPL respectively	8.2	15.1
OOP ≥5%, ≥8%, ≥11% and ≥14% of FI, for FI <125%, 125% to <200%, 200% to <400% and ≥400% of FPL respectively	7.4	13.9
OOP ≥5%, ≥10%, ≥15% and ≥20% of FI, for FI <125%, 125% to <200%, 200% to <400% and ≥400% of FPL respectively	6.4	11.6

A GLM-only model for total OOP instead of a two-part model of the base case found very similar estimates, although service-specific OOP estimates had greater variations. The mean total OOP estimates from two-part and GLM-only models were:

$1551.9 [SE, $85.6] and $1558.7 [SE, $85.7] respectively for the non-elderly cohort, and $1668.6 [SE, $73.6] and $1669.2 [SE, $73.7] respectively for the elderly cohort.

2.5. DISCUSSION

My study highlights that many insured cancer patients require high service utilization, resulting in high out-of-pocket expenditures. Of particular concern, I found nearly 13% of cancer patients are underinsured, relative to their income level. The issues of financial toxicity varied across patient subgroups, with underinsurance and high OOP expenditures more likely among older adults, females, and those of low SES.

The findings reinforce data from prior studies suggesting ambulatory and prescription medication utilization largely drive Medicare beneficiaries' total costs.[52] In my study, these services accounted for 32% and 31% of OOP costs respectively for all adults. Prescription medication costs have come under increased scrutiny given the upward trend in cancer therapy pricing. High-cost therapies like targeted oral agents and biologics have made $10,000+ per month for cancer drugs a relatively common phenomenon.[23,53,54] There are several industry practices like companies increasing prices of anticancer medications after obtaining desired market share or insurance companies placing high-cost drugs in the highest cost-sharing tier that may exacerbate financial toxicity of prescription medications.[55-57] In addition to high resultant OOP costs, high drug costs may also result in medication non-adherence as a means to control OOP.[29,58] These issues are not only important for clinicians to consider when selecting between medication choices but also highlight a need for policy changes to curb rising medication costs, particularly patient OOP portions. However, I also found non-cancer related services, like dental care, constitute a substantial portion of financial burden for cancer patients. My study shows that dental care utilization disparity among subgroups is common both in elderly and non-elderly cancer patients; and socially disadvantaged groups almost always utilize less dental care. This may be an indication of financial toxicity of cancer negatively affecting utilization of non-essential but beneficial services by cancer patients.

Some consistent findings were observed in subgroup analyses that are worth highlighting. First, older adults nearing Medicare eligibility (i.e. age 60-64 years) have increased underinsurance, higher OOP and significantly higher service utilization than younger patients. In fact, their patterns are more consistent with Medicare eligible patients >65 years, likely related to increased comorbidity severity, suggesting a need for specific insurance reform for this age group. Second, I observed consistently lower utilization, OOP costs, and underinsurance among racial/ethnic minorities and patients of low SES. This was surprising given the preponderance of data showing increased disease burden and worse clinical outcomes in these groups;[59-62] however, this pattern was likely driven by increased barriers and decreased access to health care.

The Affordable Care Act (ACA) had a major impact on cancer prevention and care in the USA by making cancer screening more affordable and expanding Medicaid. ACA has increased preventive services utilization and early stage detection of several cancers,[63,64] potentially leading to better health outcomes; however, the economic impact of the ACA on cancer patients needs further investigation. My study shows non-elderly Medicaid patients incurring significantly less out-of-pocket expenditure, although I was unable to distinguish between pre- and post-ACA data due to sample size limitations. An investigation of whether ACA had any impact on underinsurance rate should be the next logical step in my research.

Although my study investigated several important aspects of financial burden in cancer patients, I would like to note a few limitations. First, MEPS expenditure and utilization data are patient-reported, with only a sub-sample cross-checked with providers, so there is potential recall bias.[65] Second, underinsurance estimates may have been underestimated because high-deductible cases could not be identified; although prior MEPS-based studies reported use of similar underinsurance measures.[66] Finally, MEPS does not provide tumor stage or treatment-specific data so these could not be included in analyses.

In this study many cancer patients were found to have high service utilization and OOP expenditures, resulting in nearly 13% being underinsured. These data must be taken into consideration by providers when making decisions about cancer therapies and inform the continued need for further policy changes in health insurance coverage in the United States.

3. ESTIMATES AND PREDICTORS OF OUT-OF-POCKET EXPENDITURE INCURRED BY SKIN CANCER PATIENTS

3.1. INTRODUCTION

Skin cancer is the most common cancer in United States. An estimated 3.3 million new patients were diagnosed with non-melanoma skin cancer (NMSC) in 2018, while melanoma caused more than 90 thousand estimated new cases in the same year.[67] NMSC is further divided into basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) where BCC represents 80% of NMSC cases. The total prevalence of skin cancer is greater than all other cancer types combined. Although mortality from certain skin cancers (e.g. NMSC) is lower than other cancer types, skin cancer conditions are responsible for more than 60% of total mortality caused by all skin disorders.[68] The aggregated financial burden of the condition is also substantial with a staggering total national burden of $8.1 billion per year incurred due to skin cancer during 2007-2011 period.[69]

Estimation of NMSC prevalence has proven difficult because, although US cancer registries usually track melanoma related information, they do not record information on NMSC. As a result, unlike other cancers, linked SEER-Medicare data sources providing treatment, outcome and cost related information on NMSC for patients aged ≥65 years is not available.

Many studies have attempted to estimate skin cancer related costs using Medicare data, private payer data or nationally representative survey data.[17,70,71] These studies however are not reflective of the total financial burden experienced by skin cancer patients because they usually focus only on cancer related healthcare costs rather than all-source healthcare costs. Moreover, out-of-pocket expenditure is sparsely reported in skin cancer cost related literature. Adequacy of insurance coverage, in terms of overall health related cost burden relative to patient's income, is another under-investigated topic in context of skin cancer. Moreover no reported study to-date has investigated the sociodemographic predictors of either total OOP expenditure incurred or underinsurance/high-burden experienced by skin cancer patients.

In the current study, I examined all-cause health related out-of-pocket expenditure incurred by insured skin cancer patients and estimated the level of total burden in terms of cost to income ratio (i.e. underinsurance). Additional analyses focused on clinical healthcare related OOP expenditure (i.e. excluding services not directly related to cancer, such as dental care) were also performed.

3.2. BACKGROUND

The estimated prevalence of all skin cancer cases in US was about 2 million in 2004, which increased to an estimated 3.4 million average annual treated cases in 2007-2011 period.[69,72] Among major sub-types, melanoma is less prevalent but more deadly with more than 6800 expected deaths in 2020 and non-melanoma skin cancers (NMSC) are more prevalent but less deadly with around 2000 deaths per year in the USA.[14,15] Although the mortality from skin cancer, especially NMSC, is lower compared to other cancer types, the sheer number of cases makes skin cancer a substantial financial challenge for the healthcare system. A significant number of US residents are prone to suffering from skin cancer in their lifetime with one in five Caucasian Americans expected to have NMSC by the time they reach the age of 70.[73] Most of these cancer cases would cause varying degrees of cost burden on the patients. Additionally, skin cancer patients may suffer from other comorbid conditions, which may drive the total out-of-pocket healthcare costs even higher.

Several previous studies have investigated the total financial burden of skin cancer. Because an overwhelming share of skin cancer types (NMSC) are non-deadly, this cancer type has drawn relatively less attention than other cancer types in economic burden studies. A 2001 study estimated total burden on the Medicare population with NMSC to be $426 million per year. The study also estimated the overall cost incurred per episode of NMSC treated in physician's office, outpatient and inpatient settings to be $492, $1043 and $5537, respectively. However this study did not explore OOP costs. The analysis was based on relatively old (1991-1995) Medicare Current Beneficiary Survey (MCBS) data that conducted only weighted descriptive analysis.[70] Most older skin cancer studies (NMSC or melanoma) used data from late nineties or early two-thousands and many of them adopted descriptive approaches.[71,74-77]

Another study published in 2010 that used 1991-1996 SEER-Medicare data to investigate the economic burden of melanoma on the elderly estimated annual total expenditure of $249 million at the national level, with an average per-case lifetime cost of $28,210. The study stratified cost estimates by cancer stage and phase, but did not address OOP expenditure.[71]

Among the relatively recent papers, Chen et al. focused on NMSC among Medicare population by investigating expenditure variations related to treatment practice differences,[16] whereas Ruiz et al. undertook similar analysis among Medicare population for all skin cancer subtypes; but neither of them shed light on sociodemographic variation in expenditure.[17]

All the above mentioned studies explore cancer attributable costs, but do not address the issue of financial toxicity associated with high level of OOP experienced by skin cancer patients. One method to quantify an excessive OOP burden for insured cancer patients is the indicator for underinsurance, which expresses total OOP in terms of income.[66] In the current study I focused on an all-cause approach to estimate the OOP burden and on the resultant phenomenon of underinsurance among skin cancer patients. The sociodemographic factors associated with these two measures were also identified.

3.3. DATA AND METHODS

3.3.1. Data Source

The same data source used for the all-cancer study, Medical Expenditure Panel Survey (MEPS), was also used for the skin cancer study. Similar to the all-cancer analysis, Full Year Consolidated File (FYC) and Medical Condition file (MC) were used for the main analysis. For all-cause expenditure analysis, medical conditions file for each year was linked to full year consolidated file and all the health related expenditure for all conditions incurred to a skin cancer patient were taken into account. This linking was repeated for each year from 2011 to 2015 and the resultant year-specific linked files were pooled together to generate the analytic file.

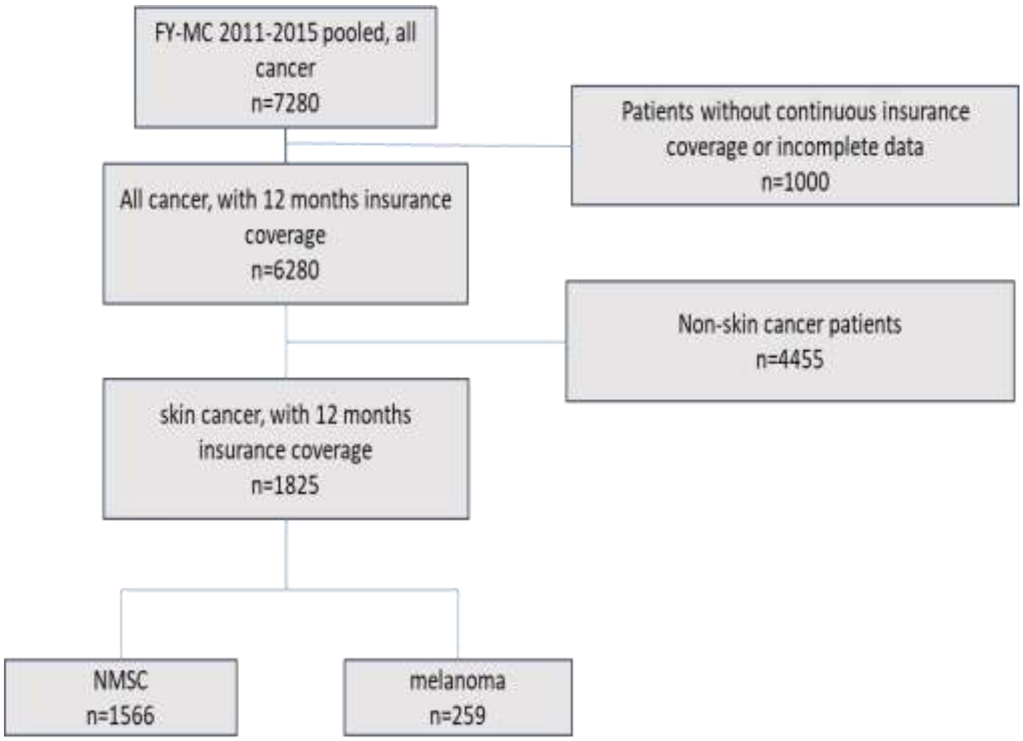

Figure 3-1: Construction of analytic cohort (skin cancer) - dataflow

3.3.2. Study Sample

Skin cancer cases were identified using CCS codes 22 (melanoma) and 23 (NMSC) from the Medical Condition file and the conditions were linked to full year consolidated file using a common identifier. While pooling linked FYC-MC data for the years 2011 to 2015, person level probability weights were adjusted by dividing the weight by the number of pooled years as recommended by MEPS.[78] Since the probability of underinsurance warrants inclusion of the individuals who had continuous insurance coverage for 12 consecutive months, only those individuals were retained in the analytic file. All included individuals were adult (≥18 years) skin cancer survivors (n_{total} = 1825, n_{NMSC} = 1566 and $n_{melanoma}$ = 259) (Figure 3-1).

3.3.3. Measures

Expenditure and income. MEPS reported out-of-pocket expenditures for all health services related to identified skin cancer patients were summed to obtain the total OOP expenditure. While analyzing clinical healthcare relate OOP, dental, vision and other non-essential OOP were subtracted from the total. To determine underinsurance, MEPS reported family income was used. All dollar values were inflated to 2018 US$ using consumer price index (CPI) and were rounded.

Underinsurance. In accordance with the prior literature, underinsurance indicator variable was defined based on the ratio of total OOP-to-family income using the following definition: total OOP ≥ 5% of family income (FI) for FI < 200% federal poverty level (FPL) or FI ≥ 10% of FI for FI ≥ 200% FPL, for those individuals continuous 12 month insurance coverage in a year.[44,45] The same definition was applied to generate an indicator for clinical healthcare related high burden. In this scenario, dental, vision and other services not directly related to skin cancer were omitted from the OOP calculation. Since this measure was less than the total OOP cost, the term high-burden instead of underinsurance was used for this cases.

Covariates. Sociodemographic variables age, sex, race/ethnicity, marital status, income level, education and insurance status were included as predictors in each estimation model. Similar to the all-case cancer analysis, the number of MEPS priority conditions (i.e. comorbid conditions enumerated by MEPS) coded as a categorical variable was incorporated in each model. To account for potential confounding effect of health status variation and regional variation, self-reported health status and census region variables were incorporated as controls.

All independent variables in each model were categorical. Age (18-49 [ref., non-elderly), 50-59, 60-64, 65-74, 75-84 and ≥85 years), sex (male [ref.], female), marital status (not married [ref.], married), education (high school diploma or less [ref.], some college, college degree or above), income (poor/low income (<200% FPL) [ref.], middle income (200% to 400% FPL) and high income (≥ 400% FPL)), priority condition (zero [ref.], one, two, ≥three), census region (northeast [ref.], Midwest, south, west) and self-reported health status (poor/fair [ref.], good, very good/excellent) had the same categorization as was used in the all-cancer study. Due to smaller sample size, insurance status variable had only three categories (private managed care [ref.], private non-managed-care, any public, uninsured/intermittently insured). Skin cancer patients are overwhelmingly white. Because of that the race/ethnicity variable was split into only two categories (non-Hispanic white [ref.], non-white) in the current study. Too many categories in the insurance or race/ethnicity variables would have created categories with very few observations; in certain cases having less than 5% of total unweighted observations in some categories.

3.3.4. Analysis

Statistical analysis. Descriptive analysis was conducted to identify sample characteristics. Mean unadjusted OOP cost for all patients and patients with a positive expenditure were estimated applying survey weights. Additionally, covariate adjusted analyses were performed using multivariable generalized linear models (GLM) incorporating all key independent variables of interest, along with potential confounding variables. The multivariable GLM model was used to assess the simultaneous effect of the independent variables and to quantify the covariate adjusted mean OOP. In the literature, GLM with log link and gamma distribution has been widely reported as one of the appropriate methods to estimate expenditure due to its skewed nature.[48] In my analysis, a modified park test was employed to determine the variance structure of the error terms. The following equation represents the linear predictor part of the gamma GLM estimation model:

$$E(\mathbf{Y}|\mathbf{X}) = \exp(\boldsymbol{\beta}\mathbf{X})$$

Where, $\boldsymbol{\beta}$ represents the vector of parameters and $\mathbf{X}$ represents the matrix of covariate values. Errors are distributed as a function of the predicted values.

Probability of underinsurance (in case of total OOP) or high-burden (in case of clinical healthcare related OOP) were estimated using logistic models.

The all-cancer analysis presented in Section 2 was used as a basis for predictor selection. Potential demographic variation in skin cancer prevalence among various sub-groups which were also taken into account. Incremental effect size across categories of a predictor and their statistical significance were determined using average marginal effect (AME) for both GLM and logistic models. Parameter coefficients from the GLM models and odds ratio from logistic models are presented in the appendix (Appendix A, Table 5). The significance level was set at 5%.

Incremental dollar value estimates and incremental underinsurance estimates were quantified using Average Marginal Effect (AME).[79]

As described in the all-cancer analysis methods segment in Section 2, all base case analyses were performed accounting for the complex survey design of MEPS. After setting-up the data in Stata using 'svy' command (i.e. specifying the strata, primary sampling unit (PSU) and personal weight variables) to account for the survey design, Stata's "svy" prefix for applicable procedures was used throughout the analysis, MEPS oversampled minority groups (Blacks, Hispanics and Asians) and to get consistent population level estimates, employing appropriate survey specific analytical procedures is necessary.[41]

3.4. RESULTS

3.4.1. Descriptive Statistics

There were significant differences in age and race/ethnicity distribution between NMSC and melanoma cases. Notably, proportion of 18-49 years olds was higher whereas the proportion of ≥85 years olds was lower in melanoma cohort vs the NMSC cohort. In regards to race/ethnicity distribution, proportion of non-Hispanic whites was substantially lower in the melanoma cohort (Table 3-1).

In unadjusted analysis when only non-zero cases were considered, survey weighted total all-cause OOP in 2018$ were higher for melanoma ($1808, SE $184) vs. NMSC ($1754, SE $117). NMSC OOP was slightly lower than all skin cancer cases combined ($1761, SE $106) (Figure 3-2).

Table 3-1: Distribution of skin cancer patients (weighted).

Variable	Categories	all skin cancer (n=1825)	NMSC (n=1566)	Melanoma (n=259)	*p*†
age	18-49 years	6.9%	6.3%	10.3%	0.048
	50-59 years	16.0%	16.0%	16.5%	
	60-64 years	11.7%	11.1%	15.7%	
	65-74 years	31.2%	31.0%	32.8%	
	75-84 years	24.4%	25.1%	20.1%	
	≥85 years	9.7%	10.5%	4.6%	
sex	Male	52.0%	52.2%	50.9%	0.785
	Female	48.0%	47.8%	49.1%	
race/ethnicity	non-Hispanic white	96.8%	97.8%	90.1%	0.000
	non-white	3.2%	2.2%	9.9%	
marital status	Not Married	32.6%	32.0%	35.9%	0.377
	Married	67.4%	68.0%	64.1%	
education	HS education/diploma	31.2%	32.5%	23.4%	0.057
	Some college	26.7%	25.7%	32.9%	
	College degree or above	42.1%	41.8%	43.8%	
income level	Low income	20.3%	20.8%	17.4%	0.431
	Middle income	23.0%	23.1%	21.8%	
	High income	56.7%	56.1%	60.8%	
insurance status	Private – MC	15.3%	14.9%	17.9%	0.545
	Private - non MC	61.3%	61.3%	61.4%	
	Public	23.3%	23.8%	20.7%	
# of comorbidities	none	6.5%	5.7%	11.3%	0.059
	one	11.8%	11.4%	14.0%	
	two	17.0%	17.2%	16.1%	
	three or more	64.7%	65.7%	58.7%	
census region	northeast	16.3%	16.4%	15.6%	0.797
	midwest	24.2%	24.1%	25.1%	
	south	36.6%	37.2%	33.2%	
	west	22.8%	22.3%	26.1%	
health status	poor or fair	14.9%	14.4%	17.7%	0.445
	good	28.4%	28.3%	29.1%	
	very-good or excellent	56.7%	57.3%	53.3%	

Abbreviations: HS, high school; MC, Managed care;
Note: Weighted descriptive statistics based on the analysis of Medical Expenditure Panel Survey data (2011-2015).
†p-value from chi-squared test of independence (survey-weighted) among categorical variables in NMSC vs melanoma cases.

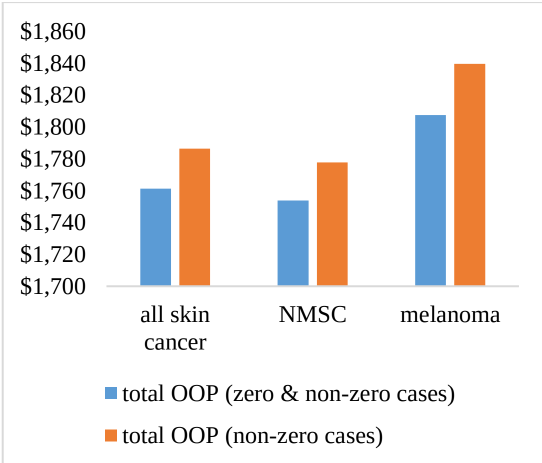

Figure 3-2: Unadjusted mean OOP (total), in 2018$

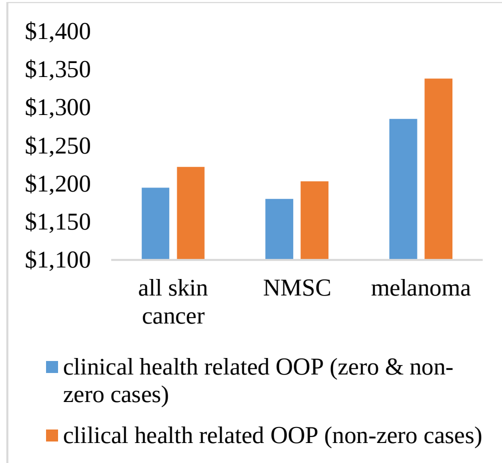

Figure 3-3: Unadjusted mean OOP (clinical healthcare related), in 2018$

Survey weighted total OOP for non-zero cases in 2018$ was higher for melanoma ($1338, SE $165) vs. NMSC ($1202, SE $89), when only clinical healthcare related costs were considered. NMSC OOP was slightly lower than all skin cancer cases combined ($1222, SE $81). When both zero and non-zero expenditure cases were included in the analysis, similar trend with slightly lower dollar value for each subtype was observed (Figure 3-3).

3.4.2. Adjusted OOP Expenditure and Underinsurance

Average adjusted predictions (AAP) from the analysis show that all-cause total OOP per person per year was $1766 and the probability of being underinsured was 13.1% on-average for a skin cancer survivor, considering all skin cancer cases. The average adjusted total OOP value and probability of underinsurance remained very similar with values of $1763 and 13.2% respectively when only the NMSC cases were considered. Covariate adjusted OOP and underinsurance analysis were not conducted for melanoma skin cancer cases separately due to the small sample size.

3.4.3. Sociodemographic Factors Associated With Total OOP Expenditure

When all skin cancer cases were grouped together, 60-64 years age group, females, people with some college education or a degree and high income people demonstrated higher all-cause total OOP expenditure compared to respective counterparts. Estimated AMEs from the GLM model show that among all skin cancer cases, 60-64 years age group spent $623 more than 18-49 years age group [ref.] ($p<0.05$), females spent $390 more than males [reference group] ($p<0.01$), people with some college education and with a college degree spent $374 and $910 more than people with high school education/diploma [ref.] (both $p<0.01$), respectively, the high income group (≥400% FPL) spent $435 more than the low income group (<200% FPL) [ref.] ($p<0.05$) and people with non-managed-care private insurance spent $334 more than people with managed-care private insurance [ref.] ($p<0.05$) on-average per person per year (Table 3-2).

When only NMSC cases are considered, the same sociodemographic categories as observed in all-skin cancer showed similar variation, with the only exception of non-white race/ethnicity, vs. respective counterparts in total OOP. Although all-cause total OOP did not vary significantly among non-Hispanic whites vs non-whites when all skin cancer analysis, significantly lower OOPs were observed for non-whites when only NMSC cases were considered (Table 3-2).

Table 3-2: Variation in all-cause total OOP by sociodemographic factors among skin cancer patients (weighted).

		all skin cancer (n=1825)		NMSC (N=1566)	
Variable	**Category**	**All-cause ΔOOP ($)†**	***p***	**All-cause ΔOOP ($)†**	***p***
Age	18-49 years [ref.]				
	50-59 years	88	0.780	126	0.715
	60-64 years	623	0.033	809	0.017
	65-74 years [ref.]	87	0.761	193	0.556
	75-84 years	187	0.533	244	0.433
	≥85 years	864	0.062	915	0.043
Sex	Male [ref.]				
	Female	390	0.007	359	0.017
Race/ethnicity	non-Hispanic white [ref.]				
	non-white	-159	0.650	-718	0.001
Marital status	Not Married [ref.]				
	Married	-146	0.440	-148	0.472
Education	HS education/diploma [ref.]				
	Some college	374	0.009	313	0.035
	College degree or above	910	0.000	957	0.000
Income level	Low income [ref.]				
	Middle income	326	0.084	222	0.266
	High income	435	0.024	409	0.041
Insurance status	Private MC [ref.]				
	Private non-MC	334	0.027	309	0.048
	Public	195	0.392	211	0.378

Abbreviations: HS, high school; MC, Managed care.

Note: †Incremental adjusted mean from a GLM model with log link and gamma distribution. All estimation models were adjusted for age, sex, race/ethnicity, marital status, income level, education, census region, insurance status, number of MEPS priority conditions and self-reported health status. *p*-value Represents significant difference compared to the reference category (first row) of each variable.

Parameter coefficients from the estimated GLM model that was used to estimate AMEs also demonstrated statistical significance for the same covariates in similar direction for both all skin-cancer and NMSC models (Appendix A, Table 7).

3.4.4. Sociodemographic Factors Associated With Underinsurance

The AMEs estimated from the logit model show that among all skin cancer cases, female gender was associated with 3.9 percentage point (pp) higher probability vs. male [ref.] ($p<0.01$), 60-64 years age group was associated with 8.5 pp higher probability vs. 18-49 years age group [ref.] ($p<0.05$), non-white race/ethnicity was associated with 8.3 pp lower probability vs. non-Hispanic white [ref.] ($p<0.01$), and, middle and high income status was associated with 38.3 pp and 47.6 pp lower probability (both $p<0.01$) respectively vs. low income status [ref.] of being underinsured on average (Table 3-3).

When only NMSC cases were considered, the same sociodemographic categories, namely 60-64 years old, female, non-white race/ethnicity, middle income and high income status showed similar variation in underinsurance with slightly different percentage point variation (Table 3-3).

Table 3-3: Variation in probability of underinsurance by sociodemographic factors among skin cancer patients (weighted).

		all skin cancer (n=1825)		NMSC (n=1566)	
Variable	**Category**	**Incremental probability of underinsurance (%) †**	***p***	**Incremental probability of underinsurance (%) †**	***p***
Age	18-49 years [ref.]				
	50-59 years	1.5%	0.671	2.7%	0.390
	60-64 years	8.5%	0.029	11.9%	0.001
	65-74 years [ref.]	2.4%	0.445	4.3%	0.129
	75-84 years	2.0%	0.517	4.0%	0.147
	≥85 years	5.4%	0.154	6.6%	0.056
Sex	Male [ref.]				
	Female	3.9%	0.003	3.3%	0.011
Race/ethnicity	non-Hispanic white [ref.]				
	non-white	-8.3%	0.000	-10.9%	0.000
Marital status	Not Married [ref.]				
	Married	0.0%	0.979	0.6%	0.686
Education	HS education/diploma [ref.]				
	Some college	2.7%	0.073	2.6%	0.073
	College degree or above	2.6%	0.177	2.1%	0.352
Income level	Low income [ref.]				
	Middle income	-38.3%	0.000	-39.6%	0.000
	High income	-47.6%	0.000	-48.1%	0.000
Insurance status	Private MC [ref.]				
	Private non-MC	1.3%	0.526	1.3%	0.572
	Public	-0.2%	0.911	0.3%	0.884

Abbreviations: HS, high school; MC, Managed care.

Note: †Incremental adjusted mean from a logistic model.
All estimation models were adjusted for age, sex, race/ethnicity, marital status, income level, education, census region, insurance status, number of MEPS priority conditions and self-reported health status. *p*-value Represents significant difference compared to the reference category (first row) of each variable.

3.4.5. Clinical Healthcare Related OOP and High Burden

In an addition to total OOP analysis, a clinical health related OOP analysis was also performed. In this scenario, dental, vision and other services which are not directly related to skin cancer were omitted from OOP calculation. The adjusted mean total OOP pertaining to clinical healthcare was $1196.85 and probability of high burden was 9.15% when all skin cancer cases were considered together; and these values were $1181.98 and 9.05%, respectively, when only NMSC cases were considered.

3.4.6. Sociodemographic Factors Associated With Clinical Healthcare Related OOP Expenditure and High Burden

In each scenario where all skin cancers were grouped together and only NMSC were considered, females and college educated individuals spent higher, whereas non-whites incurred lower clinical healthcare related OOP compared to respective reference categories. Unlike all-cause OOP, no variation across income groups were observed (Table 3-4).

In each scenario where all skin cancers were grouped together and only NMSC were considered, 60-64 years old age group and females had higher probability of high-burden, whereas non-whites, middle income and high income individuals had lower probability of high-burden vs respective reference category, when only clinical health related OOPs were considered. Unlike the clinical healthcare related OOP analysis, no variation across educational attainment were observed (Table 3-5).

Table 3-4: Variation in clinical health related total OOP by sociodemographic factors among skin cancer patients (weighted).

		all skin cancer (n=1825)		NMSC (n=1566)	
Variable	**Category**	**Clinical health related ∆OOP ($)†**	***p***	**Clinical health related ∆OOP ($)†**	***p***
Age	18-49 years [ref.]				
	50-59 years	24	0.936	26	0.936
	60-64 years	525	0.078	628	0.064
	65-74 years [ref.]	-222	0.417	-125	0.684
	75-84 years	-391	0.144	-241	0.433
	≥85 years	-37	0.901	57	0.863
Sex	Male [ref.]				
	Female	352	0.001	367	0.001
Race/ethnicity	non-Hispanic white [ref.]				
	non-white	-355	0.041	-343	0.068
Marital status	Not Married [ref.]				
	Married	-189	0.140	-162	0.245
Education	HS education/diploma [ref.]				
	Some college	96	0.279	30	0.751
	College degree or above	522	0.000	477	0.002
Income level	Low income [ref.]				
	Middle income	154	0.279	39	0.776
	High income	148	0.307	164	0.310
Insurance status	Private MC [ref.]				
	Private non-MC	227	0.041	213	0.073
	Public	2	0.985	-24	0.849

Abbreviations: HS, high school; MC, Managed care.
Note: †Incremental adjusted mean from a GLM model with log link and gamma distribution.
All estimation models were adjusted for age, sex, race/ethnicity, marital status, income level, education, census region, insurance status, number of MEPS priority conditions and self-reported health status. p-value Represents significant difference compared to the reference category (the first row) of each variable.

Table 3-5: Variation in probability of high burden considering clinical healthcare related total OOP by sociodemographic factors among skin cancer patients (weighted).

		all skin cancer (n=1825)		NMSC (n=1566)	
Variable	**Category**	**incremental probability of high burden (%)†**	***p***	**incremental probability of high burden (%)†**	***p***
Age	18-49 years [ref.]				
	50-59 years	1.8%	0.607	2.4%	0.424
	60-64 years	8.2%	0.048	11.3%	0.004
	65-74 years [ref.]	1.7%	0.592	3.0%	0.262
	75-84 years	-1.3%	0.657	0.6%	0.800
	≥85 years	1.8%	0.618	3.2%	0.329
Sex	Male [ref.]				
	Female	2.9%	0.036	2.8%	0.042
Race/ethnicity	non-Hispanic white [ref.]				
	non-white	-6.6%	0.000	-6.7%	0.000
Marital status	Not Married [ref.]				
	Married	-0.1%	0.956	0.0%	0.987
Education	HS education/diploma [ref.]				
	Some college	-0.1%	0.916	-0.8%	0.570
	College degree or above	0.9%	0.638	-1.0%	0.615
Income level	Low income [ref.]				
	Middle income	-30.4%	0.000	-31.0%	0.000
	High income	-35.7%	0.000	-34.5%	0.000
Insurance status	Private MC [ref.]				
	Private non-MC	0.9%	0.657	0.2%	0.938
	Public	-1.1%	0.618	-1.7%	0.438

Abbreviations: HS, high school; MC, Managed care.
Note: †Incremental adjusted mean from a logistic model.
All estimation models were adjusted for age, sex, race/ethnicity, marital status, income level, education, census region, insurance status, number of MEPS priority conditions and self-reported health status. p-value Represents significant difference compared to the reference category (first row) of each variable.

3.5. DISCUSSION

In the current study, an all-cause cost approach was adopted to investigate the financial burden on skin cancer patients. Survey weighted OOP expenditure incurred by all adult insured skin cancer patients were estimated and analyses was repeated by stratifying the sample by skin cancer types (i.e. NMSC and melanoma). These analyses show that melanoma patients incurred higher OOP expenditure relative to NMSC patients when all sources of expenditures were considered. This difference was smaller when only clinical healthcare related expenses were considered (i.e. services such as dental and vision care costs are excluded). Cancer versus non-cancer related expenses were not differentiated in these analyses.

To assess sociodemographic variations in out-of-pocket expenditure and underinsurance experienced by insured skin cancer patients, covariate adjusted regression analyses were conducted. These analyses were conducted for all skin-cancer patients grouped together and for NMSC patients only, but not for melanoma patients due to the small sample size for that group.

A prior publication conducting descriptive analysis of 2013 Medicare Limited Dataset Standard Analytic File 5% sample estimated average cancer attributable cost of melanoma, BCC NMSC and SCC NMSC per person per annum to be $1241, $689 and $649 respectively.[17] Cancer attributable OOP is expected to be only a portion of these values. In my currently analysis, the mean NMSC OOP is almost equal to that reported melanoma attributable total cost, even after excluding non-essential services; which may be an indication that non-cancer related services make up a substantial portion of the expenditure incurred by skin cancer patients. The paper did report certain therapies that could result in extremely high total cost for a patient over a year. An example was the drug Ipilimumab in melanoma, which would incur total cost of $80,196 per patient per year. Although not evident from the adjusted average cost of the current study, the heavily right skewed nature of total OOP in the current study indicates that the cost burden could be very high on certain skin cancer patients. A study by Guy et al. reported slightly higher cancer attributable average per person cost for melanoma of $4780 based on 2007-2011 data.[69]

In this study, Guy et al. also reported the changing trend in NMSC and melanoma prevalence among male and females across age groups over time, but their cost analysis did not cover any such studies across gender or age-groups.[69] In this current study, the issue of variation in total cost by sociodemographic sub-groups of skin cancer patients has been addressed. The AMEs estimated from OOP models in the current study demonstrate differential total OOPs across sociodemographic sub-groups. When expenses from all health related sources are considered, females and individuals with a college degree show significantly higher OOP compared to males and individuals with high school education, respectively. This trend is also observed when only clinical healthcare related costs are considered. This pattern indicates that with or without non-essential services (e.g. dental and vision) females and college educated skin cancer patients are prone to incur higher total all-cause OOP expenditure compared to their counterparts.

Similar to other sociodemographic factors, there is very limited evidence in the literature concerning variation in either total or OOP expenditure across insurance types among skin cancer patients. Guy et al. reported that 43.4% and 41.1% of total national cost burden on skin cancer is borne by private insurance and Medicare respectively.[69] How different insurance types are associated with OOP expenditure is not reported in the literature. Current study demonstrates that insurance type is associated with total OOP variation among skin cancer patients, with private non-managed care covered individuals showing higher OOP expenditure irrespective of whether all-health related costs or only clinical care related costs are considered. This holds true in both scenarios when all skin-cancer cases are grouped together or when only NMSC cases are considered. This trend indicates that private managed care plans contribute in curbing overall health care costs among skin cancer patients.

The current study also shows that 60-64 years old and ≥85 years old age groups demonstrate significantly higher all-cause OOP vs. 18-49 years old age group. However, this result only shows statistical significance for all-cause OOP, but not for OOP excluding dental and vision services. This trend indicates that unrelated costs contribute substantially in elevating 60-64 years and ≥85 years old age groups' total OOP expenditure higher compared to their younger counterparts (i.e. age 18-49 years). The same trend is also observed among individuals with some college education or high income compared to skin cancer survivors with a high school education or low income, respectively. A potential explanation for this phenomenon may be the differential utilization of non-essential services among these skin cancer patients groups.

OOP expenditures for non-whites were found to be generally lower compared to non-Hispanic whites in the current analysis, but the difference was not statistically significant for either all skin cancer versus NMSC, or all-cause versus clinical-care related costs. The probability of underinsurance/high-burden was lower for non-whites in all scenarios. The inconsistencies in statistical significance in differential OOP may be due to the highly disproportionate distribution of skin cancer cases between whites versus non-whites. The weighted proportion of non-Hispanic whites were greater than 90% in all scenarios analyzed/considered in this study.

The probability of underinsurance was higher among 60-64 years age group vs 18-49 years age group and females vs males; and was lower among non-white vs whites, middle income and high income individuals vs low income individuals when all-cause expenditures were considered. The consistent trend of higher underinsurance probability among 60-64 years age group and female skin cancer patients indicates greater financial vulnerability among these sub-groups.

There are certain limitations in the current study. Since MEPS is a survey-based dataset, recall bias may be present in reported data. Additionally, clinical stage or cancer phase could not be accounted for in the study due to lack of reported clinical information in MEPS. Moreover, the cost analysis in this study focused on all health-related costs and does not differentiate between cancer attributable and non-attributable costs.

In future research, cancer attributable out-of-pocket costs for skin cancer should be identified to estimate contribution of cancer on patients' financial experience. Factors associated with cancer attributable OOP costs should also be investigated. In the current study I could not analyze before- and after-ACA change in cost trend due to the cross sectional nature of my study. State identifiers were absent in the MEPS data and availability of post-2014 data was also too limited to make differences in differences analysis feasible. With availability of more comprehensive data, that research avenue should be explored.

Although certain skin cancer types may not be as deadly as other cancers, patients suffering from this condition may be subject to significant out-of-pocket burden: both clinical healthcare related and unrelated. In this study I have examined the OOP expenditure, high-burden related to OOP and the sociodemographic predictors of both these parameters among skin cancer patients.

4. AN ANALYSIS OF THE OUT-OF-POCKET EXPENDITURE BURDEN EXPERIENCED BY HEPATOCELLULAR CARCINOMA PATIENTS

4.1. INTRODUCTION

Liver cancer, unlike most of other cancer types, is showing a steady rise in incidence and prevalence in the USA. In fact, the annual number of Liver and Intrahepatic Bile Duct cancer has never dropped since 1999 and this condition caused an estimated 31,780 deaths in the USA in 2019.[80,81] Hepatocellular carcinoma (HCC) is the major liver cancer subtype. Although there is rising trend in HCC prevalence, there has been increasing efforts to provide better treatment options for HCC. Drug availability is slowly increasing and very recent approval of Lenvatinib for unresectable HCC is an example of the change.[82] Influenced by this changing landscape, the treatment pattern and the expenses associated with HCC may also change. Thus, it is vitally important to conduct assessment of the expenses related to HCC.

In my third study, I examined out-of-pocket expenditure burden affecting HCC patients and its predictors using Surveillance, Epidemiology and End Results (SEER)-Medicare linked data.

4.2. BACKGROUND

The medication and overall expenses related to hepatocellular carcinoma (HCC) in USA is a sparsely studied topic. Among several reported studies in the USA some are based on older data and others face generalizability issues.[83,84] Two studies by Lang et al. and White et al. analyzed total economic burden of HCC using SEER-Medicare data;

however, both studies are nearly a decade old.[83,85] Lang et al. estimated total national burden and per patient burden of HCC to be $454.9 and $32907, respectively, expressed in 2006 US$.[83] White et al. estimated per patient per month direct cost incurred by HCC patients to be $7863, expressed in 2009 US$.[85] The longitudinal retrospective cohort study that Tapper et al. conducted was based on a small cohort size of 100 study-subjects with HCV cirrhosis.[84] A more recent study by Kaplan et al. analyzed cost among cirrhotic veterans with HCC but the study cohort is male dominated.[86] Although one recent SEER-Medicare based study reported phase specific burden of HCC, none of the HCC economic burden studies looked at the out-of-pocket burden of this cancer condition.

These studies provided valuable information, but an out-of-pocket focused study is warranted to analyze how patients are affected economically due to HCC. The aim for my third study was to investigate the out-of-pocket economic burden of HCC and its predictors.

4.3. DATA AND METHODS

4.3.1. Data Source

For this study SEER-Medicare database was used. The cancer registry part of this linked database comes from SEER, which is a program by the National Cancer Institute (NCI) that comprises of several population based cancer registries. SEER areas cover more than 30% of the US population.[87] The second part of the SEER-Medicare link database comes from Medicare insurance claims database. Medicare is also a population based data source that includes enrollment and claims information on all Medicare beneficiaries in the US. The Medicare part in SEER-Medicare database contains information on cancer patients residing in the SEER areas. Person level identifiers for SEER and Medicare are not provided to the researchers but the linking part is managed by the National Cancer Institute (NCI) and the Centers for Medicare & Medicaid Services (CMS). This linking process was first conducted in 1991 and the links have been updated in 1995, 1999, 2003, 2006, 2009, 2012, 2014, 2016 and 2018. Higher than 95% successful linking was obtained between the SEER and the Medicare database in each linkage cycle. NCI stated policy is to update the linkage every two years and update the claims in the intermediate year. The data files that NCI makes available to the researchers, contain information on these linked individuals and NCI provides common id (synthetic, not the actual person level id) across files to enable linking between enrollment and claims files.[88]

The SEER portion provides initial cancer diagnosis and demographic information, and the Medicare portion provides longitudinal claims information till death or loss of eligibility for included individuals. Since almost all of the ≥65 years US individuals enroll in Medicare, it is a convenient source to conduct studies on this age-group of patients. Medicare data files contain inpatient/skilled nursing facility (SNF) (part A), outpatient (part B) and prescription medication (part D, since 2007) related claims information. Expenditure data form Medicare managed-care, which constitutes around 30% of Medicare enrollees, are not reported to CMS and thus are not available in SEER-Medicare datasets.[89] Medicare also includes <65 years old disabled or end stage renal disease (ESRD) patients, but those individuals were not be included in my current study.

SEER-Medicare data is de-identified and is provided in multiple files. The Patient Entitlement and Diagnosis Summary File (PEDSF) contains Medicare matched patients' demographic, initial cancer diagnosis, Medicare eligibility and HMO enrollment information. A non-cancer cases file, called Summarized Denominator (SUMDENOM) file, is also provided which contains data on randomly drawn sample of 5% Medicare beneficiaries residing in SEER areas. This file contains demographic and Medicare eligibility information which can be linked to Medicare claims data. Claims data on cancer patients are arranged by service type and provided in the following files: inpatient/SNF claims (MEDPAR), physician/supplier claims (NCH), outpatient claims (OUTPATIENT), home health claims (HHA), hospice claims (Hospice), durable medical equipment claims (DME) and prescription medication claims (Part D). In the current study, MEDPAR, NCH, OUTPATIENT, and DME files were used. The analysis focused on clinical care in inpatient, outpatient and physician's office settings, so MEDPAR, NCH and OUTPATIENT files were included. The DME file contains information on chemotherapies, so this file was included in the analysis. Prescription medication data were not available for the whole duration of the study period, so Part D file was excluded. Rest of the claims files were not included because they are not directly related to clinical care, rather are related to post-acute care.

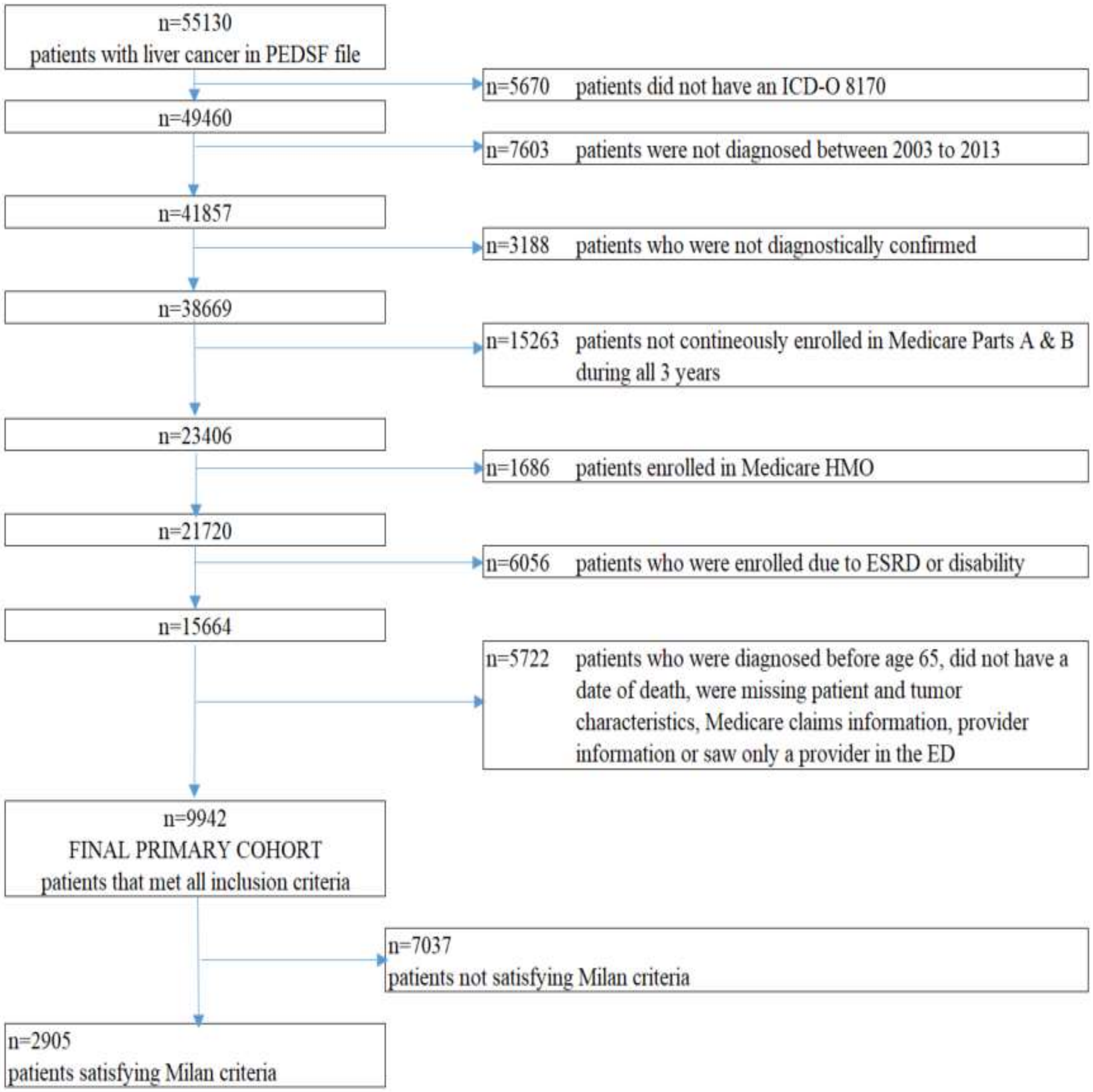

Figure 4-1: Construction of analytic cohort (HCC) - dataflow

4.3.2. Study Sample

For the current analysis all HCC patients who were 65 years or older and were diagnosed between 2003-2013 were considered in-scope. Individuals who had continuous part A and B enrollment, did not have Medicare managed care coverage, were not initially included in Medicare due to disability or end stage renal disease (ESRD) and were diagnostically confirmed with HCC were included in the analytic sample. Around 8% of the initial sample had missing date of death and they were excluded from the analysis. These cases were excluded because, including right censored cases may underestimate average cost.

HCC patients were identified using International Classification of Diseases-Oncology (ICD-O) code 8170 and relevant Healthcare Common Procedure Coding System (HCPCS) codes. Source of payment in each claims file in SEER-Medicare database is identified as Medicare, other primary payer and patient payment. For this analysis, patient payment variables were used to generate OOP amounts. Each event level files were summarized to person level file by aggregating all claims for an individual across the survival period. Each of the files from SEER and Medicare side contains common IDs, which were used to link individuals across files.

Total sample size was 9942. The full sample was stratified by patient's eligibility to receive liver transplant, expressed by the Milan criteria. When this criteria was applied, 2905 patients were in the cohort fulfilling the Milan criteria and 7037 patients were in the other cohort not fulfilling the Milan criteria (Figure 4-1).

4.3.3. Measures

OOP expenditure per person per month (PPPM). Since survival time varies for individual patients, per person per month OOP amount was used as the primary outcome variable in my analysis. For each individual, total OOP costs across their survival duration were summed to get the total lifetime OOP costs. The total lifetime OOP cost was divided by duration of survival in months to get per person per month OOP expenditure amount. In the claims files payments made by Medicare or other primary payers are reported and charges filed by the provider are also reported. In total cost analysis the charges usually are converted to costs using a cost-to-charge ratio. In my analysis, I focused solely on out-of-pocket expenditure, which is the liability of the patient in full. So, no cost-to-charge adjustments were necessary for this analysis. Patient coinsurance and deductible liability for inpatient, outpatient, physician's office and chemotherapy were summed together to obtain the total out-of-pocket liability of the patient. All dollar values were inflated to 2018 US$ using consumer price index and values were rounded.[51]

Covariates. For the current analysis, sociodemographics, comorbid status, stage at diagnosis and liver correlated conditions at baseline were included as covariates in each model. All covariates were categorical. The categories of the covariates were as follows: sex (male, female), race/ethnicity (white, Hispanic, black, Asian, other), metro area (non-metro, metropolitan), year of diagnosis (2003-2013), census poverty indicator (0%-<5% poverty, 5% to <10% poverty, 10% to <20% poverty, 20% to 100% poverty), stage at diagnosis (unknown, localized, regional, distant), live correlated conditions (none, Hepatitis B, Hepatitis C, alcohol related, other, >1 conditions), duration of cirrhosis (no cirrhosis, diagnosed within 3 years, diagnosed before 3 years), NCI comorbidity index (low (1-2), moderate (3-4), high (≥5)), hepatic encephalopathy (no, yes) and ascites (no, yes). Significance of a certain category of a covariate compared to the reference category was determined using average marginal effect.

4.3.4. Analysis

For my analysis month of diagnosis for each individual was set as the index month. Duration from index to death were calculated in months. Cumulative OOP costs for this whole duration and PPPM OOP costs for each patient were determined. The method described by Kaplan et al. was be adapted for an11-year period and adjusted PPPM OOPs were estimated directly, instead of first estimating adjusted cumulative costs.[86] All diagnosed HCC cases in the 2003-2013 SEER-Medicare data files were included in analytic cohort after applying the inclusion/exclusion criteria (i.e. continuous Medicare coverage in one year period before diagnosis, continuous part A and B coverage and not covered by Medicare HMO).

Adjusted PPPM OOP estimation was conducted using a generalized linear model (GLM) with log link and gamma distribution. Modified park test and Pregibon's link test were conducted to check the model specification. Although the link test was indicating an inverse Gaussian model for the outcome, in actual estimation, the adjusted outcome values using a gamma distribution or an inverse Gaussian distribution were very similar. So, gamma distribution was adopted for the base case. Statistical significance in variation between levels of an independent variable was examined using Average Marginal Effect (AME) measure.[79] Statistical significance of the coefficients in the GLM model were also examined. Overall significance of a predictor variable was assessed using Wald test. Significance was set at 5% for all the analyses.

Analyses were performed for the overall sample and stratifying the sample by Milan criteria. Milan criteria is a clinical criteria first proposed by Mazzaferro et al. that categorizes HCC patients' suitability for transplant based on the expected health outcome.[90] Only those patients who are expected to have better health outcome are recommended for transplant according to this criteria. Size and number of tumors are the factors considered to determine transplantation eligibility under Milan criteria.[90,91] Since, this criteria can be proxy for health status of a HCC patient, and thus the effects of covariates on costs may change significantly across this criteria, my analysis was stratified using Milan criteria. All the data processing and analyses were performed using Stata and SAS.

Sensitivity analysis. As described above, a sensitivity was conducted assuming Poisson distribution instead of gamma distribution, which resulted in very similar estimates.

4.4. RESULTS

4.4.1. Descriptive Statistics

Mean unadjusted PPPM OOP was $902 [SD, $ 1062] for the complete sample. When stratified by Milan criteria, patients satisfying the criteria had lower mean ($790 [SD, $1014]) PPPM OOP compared to those who did not satisfy the criteria ($947 [SD, $1078]).

The percent distribution of complete cohort, cohort satisfying Milan criteria and cohort not satisfying Milan criteria by covariates are presented in Table 4-1 and Table 4-2.

Table 4-1: Sociodemographic characteristics of HCC patients.

Variable and Categories	Full sample (n=9942)	Milan criteria = 0 (n=7037)	Milan criteria = 1 (n=2905)
Age Category			
65-69 years	9.2%	8.4%	11.0%
70-74 years	27.3%	26.2%	30.0%
75-79 years	28.6%	28.3%	29.2%
80-84 years	21.6%	22.3%	20.0%
≥85 years	13.3%	14.8%	9.8%
Sex			
Male	63.5%	64.8%	60.2%
Female	36.6%	35.2%	39.8%
Race/ethnicity			
White	63.5%	64.4%	61.4%
Hispanic	12.3%	11.9%	13.4%
Black	6.7%	6.8%	6.6%
Asian	11.0%	10.7%	11.6%
Other Race	6.4%	6.2%	7.0%
Metropolitan status			
Non-Metropolitan	6.7%	7.3%	5.2%
Metropolitan	93.3%	92.7%	94.8%
Year of diagnosis			
2003	7.3%	7.1%	7.7%
2004	7.1%	7.3%	6.7%
2005	8.0%	8.0%	7.8%
2006	8.2%	8.2%	8.0%
2007	8.9%	8.8%	9.2%
2008	11.0%	10.8%	11.3%
2009	9.8%	9.9%	9.7%
2010	10.3%	10.3%	10.3%
2011	9.5%	9.7%	9.1%
2012	10.9%	11.1%	10.4%
2013	9.1%	8.8%	9.9%
Census tract poverty			
0%-<5% poverty	22.3%	22.3%	22.3%
5% to <10% poverty	26.1%	26.3%	25.5%
10% to <20% poverty	30.9%	31.1%	30.4%
20% to 100% poverty	20.7%	20.3%	21.8%

Note: Descriptive statistics based on the analysis of SEER-Medicare data (2003-2013).

Table 4-2: Clinical characteristics of HCC patients.

Variable and Categories	Full sample (n=9942)	Milan criteria = 0 (n=7037)	Milan criteria = 1 (n=2905)
NCI comorbidity			
none	11.2%	12.3%	8.4%
low	25.9%	27.5%	22.0%
moderate	25.6%	25.8%	25.3%
high	37.4%	34.5%	44.3%
Stage at diagnosis			
Unknown	4.1%	4.1%	4.2%
Localized	48.9%	40.6%	68.9%
Regional	30.3%	34.8%	19.6%
Distant	16.7%	20.5%	7.4%
Cirrhosis duration			
No Cirrhosis Dx	66.8%	74.7%	47.4%
Cirrhosis Dx within 3 Years	18.4%	14.8%	27.0%
Cirrhosis Dx before 3 Years	14.9%	10.4%	25.6%
Liver correlated conditions			
None	60.5%	68.1%	42.0%
HBV	2.0%	2.0%	2.2%
HCV	10.9%	9.1%	15.2%
Alcohol related	3.9%	3.2%	5.5%
Other liver disease	8.0%	7.4%	9.5%
>1 conditions	14.8%	10.3%	25.5%
Hepatic encephalopathy			
No	94.3%	96.3%	89.5%
Yes	5.7%	3.7%	10.5%
Ascites			
No	91.7%	93.7%	86.8%
Yes	8.3%	6.3%	13.2%

Note: Descriptive statistics based on the analysis of SEER-Medicare data (2003-2013).

4.4.2. Estimates and Predictors of PPPM OOP

The adjusted mean PPPM OOP for the full sample, cohort satisfying Milan criteria and cohort not satisfying Milan criteria were $903 [SE, $11], $797 [SE, $22] and $949 [SE, $14] respectively.

Wald test ran after multivariable GLM model revealed that among the following covariates were statistically significant predictors of PPPM OOP in overall sample: race/ethnicity ($p<0.01$), Metro/non-metro status ($p<0.01$), NCI comorbidity index ($p<0.01$), stage at diagnosis ($p<0.01$), cirrhosis duration ($p<0.01$) and presence of ascites ($p<0.01$). In case of the cohort satisfying Milan criteria, same covariates were demonstrated to be statistically significant with the exception of Metro/non-metro status ($p>0.05$). In case of the cohort not satisfying Milan criteria, sex ($p<0.05$), and all the significant variables identified in the full sample, was a significant predictor of PPPM OOP.

In the sociodemographic sub-group analysis, Hispanics consistently demonstrated lower PPPM OOP compared to whites, either when the full sample was analyzed (Δ PPPM OOP -$114, $p<0.01$) or when the sample was stratified by Milan criteria (Δ PPPM OOP -$99, $p<0.05$, when Milan criteria = 0 and Δ PPPM OOP -$177, $p<0.01$, when Milan criteria = 1). Similar trend was observed for cirrhosis duration, where patients having cirrhosis diagnosed within 3 years of HCC diagnosis demonstrated lower PPPM OOP expenditure compare to those without cirrhosis diagnosis (Δ PPPM OOP -$163, -$145 and -$150 for full sample, Milan criteria = 0 and Milan criteria = 1, respectively, all $p<0.01$). In case of the patients who had been diagnosed with cirrhosis at least 3 years before diagnosis, statistically significant lower PPPM OOP was observed among the full sample and among those satisfying the Milan criteria (Δ PPPM OOP -$92 and -$140 for full sample and Milan criteria = 1, respectively, both p<0.05), but not among the patients who did not satisfy the Milan criteria. Stage of diagnosis was also associated with differential PPPM OOP, where patients with a distant staging had significantly higher PPPM OOP compared to the patients with unknown stage. This trend was true for full sample and stratified sample analysis. Patients with a previous diagnosis of ascites also demonstrated significantly higher PPPM OOP compared to those without a diagnosis; and this trend was true for full sample and stratified analysis. No significant differential PPPM OOP for liver related conditions were observed. Although in the full sample analysis alcohol-related conditions showed lower expenditure compared to no conditions, the statistical significance was lost when the sample was stratified by Milan criteria.

Significantly higher PPPM OOP was observed in case of the patients not satisfying Milan criteria but not in case of the patients satisfying Milan criteria among females (Δ PPPM OOP $64 vs males, p<0.05), non-metropolitan residents (Δ PPPM OOP $156 vs metropolitan residents, p<0.01) and patients with regional staging of cancer (Δ PPPM OOP $170 vs unknown stage, p<0.01).

For patients with Asian and other race/ethnicity, those satisfying Milan criteria showed significantly lower PPPM OOP compared to whites (Δ PPPM OOP $152 and $270; p<0.05 and <0.01, respectively), but those not satisfying Milan criteria did not show such pattern.

Table 4-3: Per person per month (PPPM) incremental OOP expenditure incurred by HCC patients, by selected variables, full sample and stratified by Milan criteria.

Variable and categories	Full sample (n=9942)		Milan criteria = 0 (n=7037)		Milan criteria = 1 (n=2905)	
	Δ PPPM OOP ($)	***p***	**Δ PPPM OOP ($)**	***p***	**Δ PPPM OOP ($)**	***P***
Sex						
Male [ref.]						
Female	42	0.069	64	0.024	24	0.569
Race/ethnicity						
White [ref.]						
Hispanic	-114	0.000	-99	0.013	-177	0.002
Black	-32	0.490	-79	0.132	69	0.489
Asian	0	0.990	70	0.151	-152	0.017
Other Race	-103	0.015	-25	0.652	-270	0.000
Metropolitan status						
Non-Metropolitan [ref.]						
Metropolitan	-166	0.002	-156	0.009	-197	0.083
NCI comorbidity						
none [ref.]						
low	255	0.000	250	0.000	301	0.000
moderate	386	0.000	355	0.000	482	0.000
high	702	0.000	683	0.000	756	0.000
Stage at diagnosis						
Unknown [ref.]						
Localized	-11	0.828	40	0.502	-56	0.571
Regional	163	0.002	170	0.005	100	0.357
Distant	334	0.000	272	0.000	665	0.000
Cirrhosis duration						
No Cirrhosis Diagnosis [ref.]						
Cirrhosis Dx within 3 Years	-163	0.000	-145	0.001	-150	0.017
Cirrhosis Dx before 3 Years	-92	0.028	-15	0.789	-140	0.048
Liver correlated conditions						
None [ref.]						
HBV	44	0.607	31	0.760	154	0.378
HCV	-15	0.698	61	0.238	-83	0.176
Alcohol related	-154	0.005	-135	0.063	-155	0.064
Other liver disease	25	0.570	32	0.550	37	0.645
>1 conditions	2	0.960	10	0.851	60	0.402
Ascites						
No [ref.]						
Yes	205	0.000	212	0.004	176	0.020

Note: †Incremental adjusted mean from a GLM model with log link and gamma distribution. Estimation model was adjusted for age, sex, race/ethnicity, metropolitan status, year of diagnosis, census tract poverty level, NCI comorbidity, cancer stage at diagnosis, cirrhosis duration, liver correlated conditions, presence of hepatic encephalopathy and presence of ascites.

PPPM OOP did not vary significantly across age, year of diagnosis and census tract poverty level; or due to prior diagnosis of hepatic encephalopathy. Variables with significant variations are presented in Table 4-3 and complete results representing all the variables is presented in the appendix (Appendix A, Table 6 and Appendix A, Table 7).

4.4.3. Future Work

In this current study I have examined per person per month average OOP expenditure incurred by HCC patients. This study provided valuable estimates and associated predictors of total OOP incurred by HCC patients. There, however are several potential research questions that might be explored in future research to get a more comprehensive overview of this important care related issue. My analysis was focused on total OOP costs, but HCC attributable costs compared to cirrhosis patients can also be estimated using claims data. Since, cirrhosis is very common etiological condition among HCC patients, an analysis of the differential costs may be of practical interest. Additionally, as reported for several other cancer types, the cost incurred due to HCC may also fluctuate over a patient's survival period.[92] In case of several other cancer types, studies have observed very high cost in the initial phase right after diagnosis that sharply decline and reach to a plateau and rise again during end-of-life care.[93] This U-shaped cost pattern is a reflection of variability in need for care across phases of care. Phase specific OOP cost analysis for HCC is not reported in the literature and should be investigated in future research work.

The DME (i.e. durable medical equipment) file that was one of the data source for this analysis, provided chemotherapy related cost information. However, cost data for other prescription medications purchased may be available from the part D claims file. Since part D data was reported starting from 2007, this was not available for the complete duration of my study period (2003-2013 HCC diagnosis). As such, prescription medication data was not included in the current study. In future analysis, prescription medication related data should be included to have a broader cost related overview. With availability of more years of data in CMS's updated data release, restricting the study period from 2007 should not reduce sample size substantially.

4.5. DISCUSSION

In the current study I have estimated per patient per month OOP expenditure incurred by elderly (age ≥65 years) HCC patients. OOP expenditure related to inpatient/SNF, outpatient, physician's office and chemotherapy related services were included in the analysis. The full sample and the sample stratified by Milan criteria, were subject to all conducted analyses. Descriptive analysis revealed that HCC patients who satisfied the Milan criteria incurred significantly lower OOP cost compared to those who did not satisfy the criteria. This pattern was retained even after adjusting for the demographic and clinical covariates.

In the adjusted analysis covariates with significant association with PPPM OOP variation were identified. OOP expenditure did not vary significantly across age categories (Appendix A, Table 6).

PPPM OOP was significantly higher among the female HCC patients not satisfying the Milan criteria. This may indicate that female patients who are ineligible for liver transplant have elevated health needs, which might translate into higher OOP expenditure. Although overall mortality rate of liver cancer is higher among males,[92,94] current study shows that gender variation in financial vulnerability may not follow gender variation in mortality pattern.

In the current analysis Hispanic patients were found to have significantly lower OOP expenditure per month compared to whites, irrespective of them satisfying or not satisfying the Milan criteria. This Pattern is most likely a reflection of care disparities experienced by Hispanic HCC patients. Studies have shown that minority patients, including Hispanics, are less likely to receive HCC directed care, such as a liver transplant, hepatectomy or ablation.[95,96] HCC mortality risks for Hispanics are also higher compared to whites.[97] Lower services receipt coupled with worse outcomes clearly indicates access to services issues rather than lower health needs as the reason behind lower costs incurred by Hispanic HCC patients.

The higher OOP per month observed in the analysis for patients with higher comorbidity index (low/moderate/high vs. none), advanced stage cancer at diagnosis (distant vs. unknown) and presence of ascites during diagnosis was consistent with the potential higher health needs due to worse health conditions persistent among these groups. HCC survival decreases significantly from localized to regional to distant staging of cancer.[20] Ascites, which is often present in HCC patients with liver cirrhosis, is associated with larger tumor burden and higher mortality risk.[98] HCC patients may require higher health services utilization due to the worsening health effects associated with these factors and that may lead to higher utilization and higher OOP expenses incurred.

Several previous studies reported lower likelihood of getting HCC related surgeries for patients with low socioeconomic status (SES) or low income.[99,100] Unlike these survival and treatment receipt pattern, the current analysis did not demonstrate any variation in PPPM OOP across patient groups with different census tract income level (Appendix A, Table 6). This may either mean no association of SES with OOP expenditure, which is unlikely; or, this might be a result of ecological fallacy caused due to attributing area level income data on individual patients.[101] In any case, further examination of association between SES factors and HCC related OOP expenditure is necessary.

5. CONCLUSION

5.1. INTRODUCTORY REMARKS

With extensive efforts to fight cancer, several novel therapeutic and care approaches are being introduced every year. In many cases, this newly introduced therapies have a very high associated costs. In addition to that, overall rising cost of healthcare delivery is contributing in the higher cost of cancer care. Although public insurance schemes and private insurance plans pay a substantial part of the cancer care cost for covered individuals, the remaining patient responsibility is not insignificant. In addition to cancer related costs, patients may have to pay for their additional healthcare needs, which may exacerbate their already stressed financial situation. To deal with this financial burden of cancer, concerted efforts to contain increasing cost is warranted. The three studies presented in this dissertation will contribute in the exiting knowledge related to financial toxicity affecting cancer patients and will inform cost containment efforts.

5.1.1. Significance of the Three Studies

In the first study presented in this dissertation I have estimated the OOP burden and underinsurance affecting all cancer patients. This study would help identify the general patterns associated with financial toxicity of cancer. This will present healthcare providers and policy makers a broader perspective of the OOP cost issues. My second study examined similar research questions pertaining to skin cancer, a cancer type that has relatively lower mortality rate. The findings from the study that the skin cancer survivors incur substantial amount of total OOP cost and a significant part of them are at the risk of being underinsured highlight the need for better addressing the financial aspects related to this cancer. My third study examining a cancer with high mortality-HCC- underscores the need to extend financial support to patients suffering from this condition. In all three studies I identified the factors associated with high OOP, which will help identify patient groups with heightened needs. This may help better formulate intervention efforts targeting the most financially vulnerable patients.

5.1.2. Potential Limitations

Since my studies were focused on examining total financial burden affecting patients, I did not differentiate between cancer-attributable versus non-attributable costs. For policy decisions pertinent to cancer attributable burden, cancer attributable cost could be estimated using the same study designs presented in this dissertation by incorporating non-cancer control groups in each study. Another limitation pertaining to my first two studies is that because these studies utilized survey derived data they may be subject to recall and social desirability bias.

The analytic approach presented in the studies estimate average cost and does not differentiate between phase of care. A U-shaped pattern for cancer costs have been reported in previous studies where costs incurred during right after diagnosis and at the end-of-life period are usually higher compared to the continuing treatment months.[93,102] Since MEPS does not provide phase of care information or date of diagnosis, it is not possible to conduct phase specific analysis with MEPS data. SEER-Medicare, however, provides diagnosis and survival information, which should be used in future HCC OOP cost related studies to examine phase specific pattern.

5.2. CONCLUDING REMARKS

In my dissertation I have conducted three studies that analyzed several cost aspects of cancer from patients' perspective. How sociodemographic (Section 2 and 3) and clinical (Section 2, 3 & 4) factors affect the OOP cost was also investigated. These studies focusing on three specific scenarios: all-cancer, skin cancer and hepatocellular carcinoma, will provide unique perspective to deal with the financial toxicity of these conditions. The outcomes of these three studies will inform patients, physicians, as well as policy makers, in making well informed clinical and policy decisions.

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APPENDIX A

ADDITIONAL TABLES AND FIGURES

Appendix A, Table 1: Distribution of non-elderly and elderly insured cancer patients by sociodemographics.

	all adult cancer patients	non-elderly cancer patients	elderly cancer patients
Variables	**%**	**%**	**%**
age			
18-49 years	13.2	31.6	
50-59 years	17.1	40.9	
60-64 years	11.5	27.6	
65-74 years	29.2		50.1
75-84 years	21.7		37.3
≥85 years	7.3		12.6
sex			
Male	46.2	39.5	51
Female	53.8	60.5	49
race/ethnicity			
non-Hispanic white	85.8	81.8	88.7
Black	5.8	7.1	4.9
Hispanic	5.1	7.1	3.7
Asian/others	3.2	4	2.7
marital status			
Not Married	36.6	33.2	39.1
Married	63.4	66.8	60.9
education			
HS education/diploma	37.3	29.5	42.8
Some college	26.4	30.7	23.3
College degree or above	36.3	39.8	33.8
income level			
Low income	25.2	20.1	28.8
Middle income	25.2	24	26.2
High income	49.6	56	45
insurance status			
<65 any private – MC	9.3	22.3	
<65 any private - non MC	26.1	62.5	
<65 Medicaid	3.2	7.7	
<65 Medicare/dual eligible	3.1	7.5	
65+ Medicare MC with other private	8.8		15.1
65+ Medicare MC w/o other private	10.2		17.6
65+ Medicare FFS with other private	28.2		48.4
65+ Medicare FFS w/o other private	11		19

Appendix A, Table 2: Distribution of non-elderly and elderly insured cancer patients by health condition and census region.

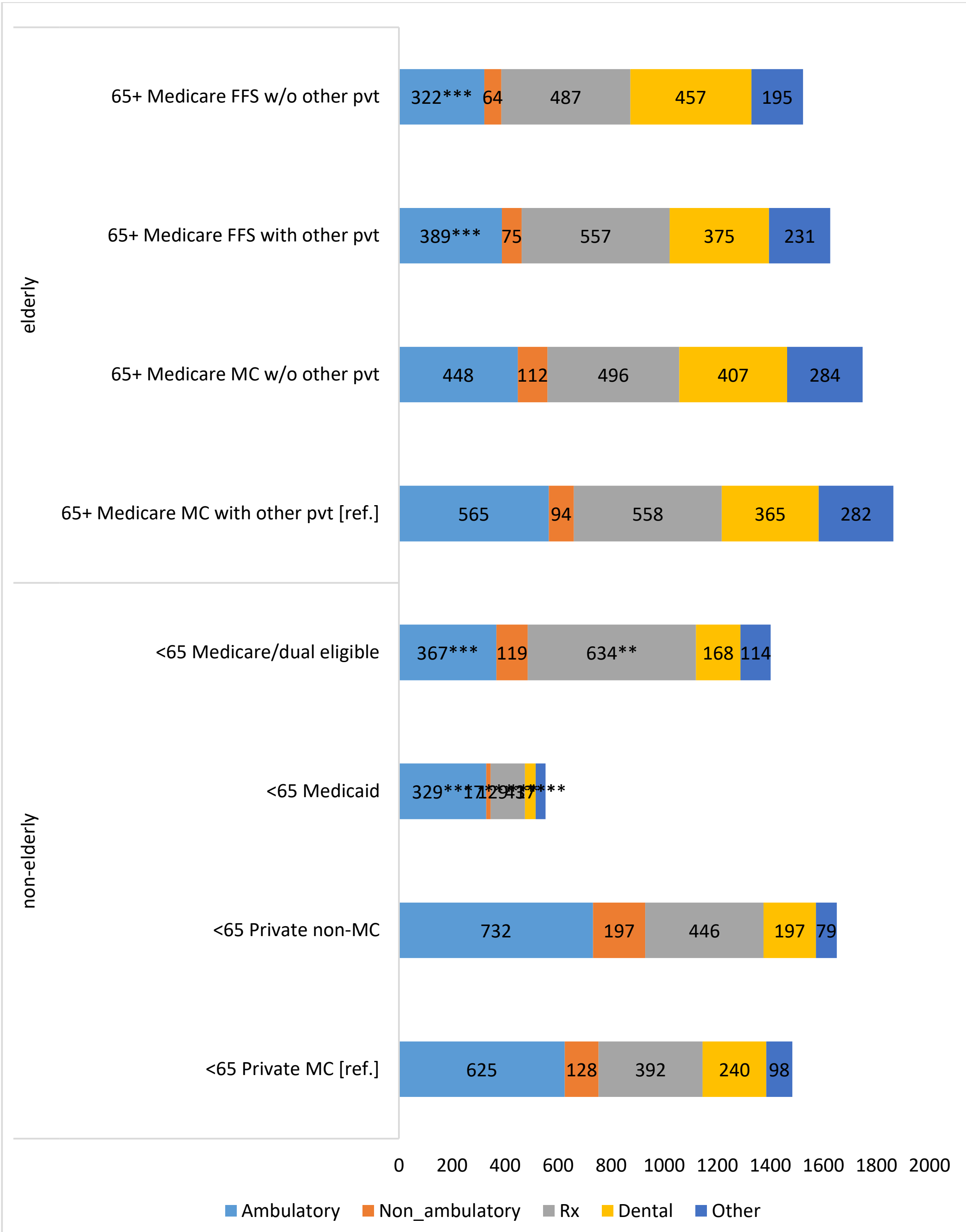
	all adult cancer patients	**non-elderly cancer patients**	**elderly cancer patients**
Variables	**%**	**%**	**%**
number of MEPS priority conditions			
none	7.6	14.6	2.6
one	12	19.9	6.3
two	16.9	19.9	14.8
three or more	63.5	45.6	76.3
census region			
northeast	18.9	20.2	17.9
midwest	23.3	22.3	24
south	36.5	34.9	37.6
west	21.4	22.6	20.5
health status			
poor or fair	22.7	22.7	22.6
good	30.3	28.4	31.7
very-good or excellent	47	48.9	45.7

Appendix A, Table 3: Mean adjusted services utilization by insured non-elderly cancer patients.

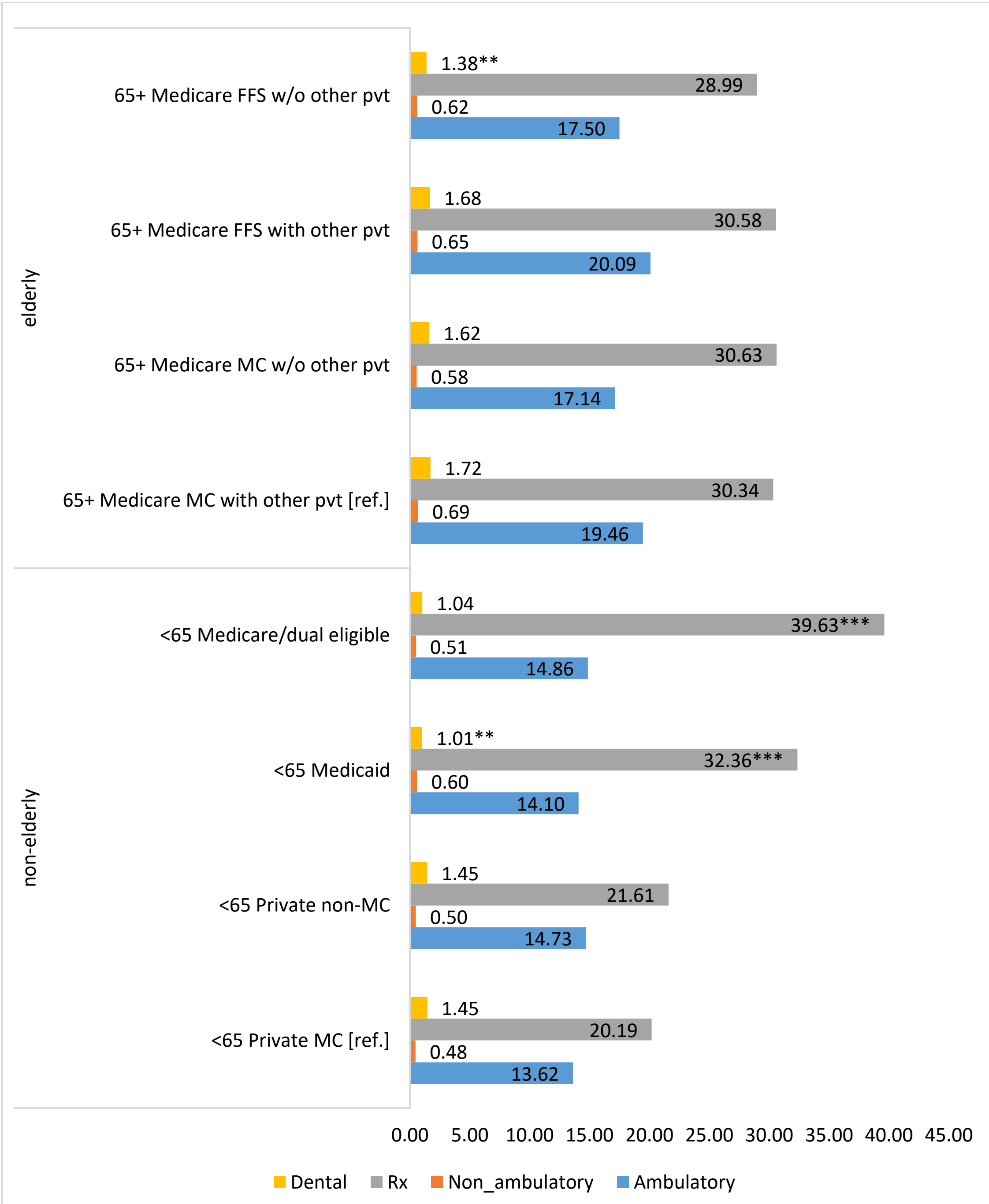
	Ambulatory†	p	Non-ambulatory†	p	Prescription med. †	p	Dental†	p
Age								
18-49 years [ref.]	13.8		0.56		21.05		1.16	
50-59 years	13.76	0.955	0.45	0.078	25.32	0.020	1.47	0.001
60-64 years	16.04	0.014	0.55	0.867	27.65	0.001	1.59	0.001
65-74 years [ref.]								
75-84 years								
>=85 years								
Sex								
Male [ref.]	11.72		0.49		21.8		1.2	
Female	16.29	0.000	0.52	0.588	27.07	0.002	1.54	0.001
Race/ethnicity								
non-Hispanic white [ref.]	14.36		0.49		25.97		1.45	
Black	14.03	0.751	0.64	0.089	20.88	0.015	1.06	0.019
Hispanic	15.09	0.564	0.58	0.301	21.68	0.052	1.2	0.121
Asian/others	15.61	0.454	0.54	0.569	20.93	0.056	1.11	0.040
Marital status								
Not Married [ref.]	13.86		0.51		25.06		1.39	
Married	14.75	0.239	0.51	0.989	24.81	0.864	1.41	0.807
Education								
HS education/diploma [ref.]	12.46		0.53		25.48		1.02	
Some college	14.3	0.023	0.51	0.797	25.81	0.874	1.34	0.010
College degree or above	16.36	0.000	0.49	0.586	23.13	0.184	1.67	0.000
Income level								
Low income [ref.]	14.52		0.59		27.42		1.17	
Middle income	12.98	0.169	0.48	0.187	24.97	0.344	1.33	0.222
High income	15.06	0.668	0.47	0.123	23.02	0.138	1.49	0.024

Appendix A, Table 4: Mean adjusted services utilization by insured elderly cancer patients.

64+ years old	Ambulatory†	p	Non-ambulatory†	p	Prescription med. †	p	Dental†	p
Age								
18-49 years [ref.]								
50-59 years								
60-64 years								
65-74 years [ref.]	19.04		0.58		31.01		1.59	
75-84 years	19.28	0.766	0.65	0.087	29.56	0.272	1.67	0.514
>=85 years	18.01	0.554	0.79	0.010	29.34	0.399	1.69	0.700
Sex								
Male [ref.]	18.28		0.65		30.54		1.49	
Female	19.8	0.028	0.62	0.617	29.87	0.608	1.78	0.009
Race/ethnicity								
non-Hispanic white [ref.]	19.45		0.64		30.15		1.68	
Black	15.17	0.001	0.58	0.484	29.63	0.755	1.05	0.000
Hispanic	15.45	0.002	0.54	0.171	29.95	0.922	1.03	0.000
Asian/others	15.95	0.072	0.62	0.839	34.02	0.306	1.37	0.274
Marital status								
Not Married [ref.]	18.98		0.68		32.56		1.5	
Married	19.01	0.973	0.61	0.194	28.63	0.006	1.7	0.043
Education								
HS education/diploma [ref.]	17.28		0.64		31.98		1.23	
Some college	18.86	0.087	0.69	0.559	27.86	0.001	1.76	0.000
College degree or above	21.43	0.000	0.58	0.359	29.25	0.090	1.97	0.000
Income level								
Low income [ref.]	18.14		0.63		32.85		1.21	
Middle income	19.59	0.073	0.66	0.637	29.73	0.035	1.7	0.000
High income	19.2	0.228	0.62	0.838	28.44	0.004	1.8	0.000



Appendix A, Figure 1: Mean OOP by insurance status and service categories, non-elderly and elderly cancer patients ($ per person per year)



Appendix A, Figure 2: Service category wise service utilization by insurance status, non-elderly & elderly cancer patients (average event count per person per year)

Appendix A, Table 5: Parameter estimates from GLM and logistic models while modeling total OOP.

	all skin cancer		NMSC		all skin cancer		NMSC	
	coef.‡	p	coef.‡	p	OR†	p	OR†	p
Age category								
18-49 years [ref.]								
50<=age<60	0.06	0.781	0.08	0.718	1.25	0.675	1.57	0.398
60<=age<65	0.34	0.047	0.45	0.029	3.05	0.044	5.26	0.002
65<=age<75	0.06	0.764	0.13	0.569	1.42	0.466	1.97	0.156
75<=age<85	0.12	0.545	0.16	0.458	1.35	0.533	1.89	0.178
85<=age	0.45	0.058	0.49	0.047	2.12	0.167	2.73	0.062
Sex								
Male [ref.]								
female	0.22	0.005	0.20	0.014	1.71	0.003	1.60	0.015
Race/ethnicity								
NHW								
non-white	-0.09	0.666	-0.52	0.009	0.24	0.003	0.10	0.000
Marital status								
marr_dmy								
married	-0.08	0.434	-0.08	0.465	1.01	0.979	1.09	0.689
Education								
HS [ref.]								
some college	0.25	0.007	0.22	0.034	1.46	0.066	1.46	0.074
≥bachelors	0.53	0.000	0.56	0.000	1.44	0.177	1.35	0.347
Income level								
low [ref.]								
middle	0.20	0.086	0.14	0.263	0.11	0.000	0.09	0.000
high	0.26	0.030	0.24	0.049	0.01	0.000	0.01	0.000
Ins. status								
pvt MC								
pvt no-MC	0.20	0.027	0.18	0.049	1.19	0.528	1.21	0.574
public	0.12	0.381	0.13	0.365	0.97	0.911	1.05	0.884
# Priority cond.								
none								
one	0.29	0.057	0.21	0.248	1.57	0.403	0.86	0.806
two	0.32	0.029	0.18	0.313	0.97	0.958	0.53	0.246
three or more	0.59	0.000	0.51	0.002	2.02	0.151	1.46	0.455
Census region								
northeast								
midwest	-0.08	0.654	-0.05	0.825	0.78	0.475	0.77	0.467
south	-0.20	0.244	-0.20	0.298	0.61	0.129	0.56	0.088
west	-0.13	0.433	-0.17	0.399	1.08	0.817	1.07	0.850
Health status								
not good								
good	-0.09	0.385	-0.04	0.738	0.97	0.920	1.13	0.668
v. good/excellent	-0.34	0.000	-0.34	0.001	0.74	0.251	0.77	0.326
_cons	6.44	0.000	6.50	0.000	0.32	0.110	0.33	0.129

‡estimated, coefficients from a gamma GLM with log link model, † odds ratio from a logistic model

Appendix A, Table 6: HCC patients' incremental PPPM OOP by sociodemographic characteristics.

Variable and categories	Full sample	p	Milan criteria = 0	p	Milan criteria = 1	p
Age category						
65-69 years [ref.]						
70-74 years	-40	0.360	-50	0.357	-20	0.791
75-79 years	-47	0.279	-46	0.401	-54	0.467
80-84 years	-37	0.416	-27	0.637	-91	0.248
≥85 years	-62	0.208	-108	0.068	33	0.738
Sex						
Male [ref.]						
Female	42	0.069	64	0.024	24	0.569
Race/ethnicity						
White [ref.]						
Hispanic	-114	0.000	-99	0.013	-177	0.002
Black	-32	0.490	-79	0.132	69	0.489
Asian	0	0.990	70	0.151	-152	0.017
Other Race	-103	0.015	-25	0.652	-270	0.000
Metropolitan status						
Non-Metropolitan [ref.]						
Metropolitan	-166	0.002	-156	0.009	-197	0.083
Year of diagnosis						
2003 [ref.]						
2004	87	0.131	54	0.441	115	0.242
2005	3	0.951	-43	0.507	87	0.336
2006	8	0.873	-60	0.354	183	0.061
2007	49	0.356	8	0.904	168	0.068
2008	93	0.072	48	0.453	168	0.054
2009	81	0.124	52	0.425	154	0.087
2010	57	0.266	-5	0.938	188	0.038
2011	47	0.362	17	0.791	100	0.256
2012	28	0.583	14	0.825	33	0.684
2013	31	0.558	0	0.996	112	0.199
Census tract poverty						
0%-<5% poverty [ref.]						
5% to <10% poverty	-36	0.257	-26	0.503	-62	0.288
10% to <20% poverty	-55	0.076	-49	0.189	-50	0.379
20% to 100% poverty	-26	0.462	-38	0.375	7	0.915

Appendix A, Table 7: HCC patients' incremental PPPM OOP by clinical characteristics.

Variable and categories	Full sample	p	Milan criteria = 0	p	Milan criteria = 1	p
NCI comorbidity						
none [ref.]						
low	255	0.000	250	0.000	301	0.000
moderate	386	0.000	355	0.000	482	0.000
high	702	0.000	683	0.000	756	0.000
Stage at diagnosis						
Unknown [ref.]						
Localized	-11	0.828	40	0.502	-56	0.571
Regional	163	0.002	170	0.005	100	0.357
Distant	334	0.000	272	0.000	665	0.000
Cirrhosis duration						
No Cirrhosis Diagnosis [ref.]						
Cirrhosis Dx within 3 Years	-163	0.000	-145	0.001	-150	0.017
Cirrhosis Dx before 3 Years	-92	0.028	-15	0.789	-140	0.048
Liver correlated conditions						
None [ref.]						
HBV	44	0.607	31	0.760	154	0.378
HCV	-15	0.698	61	0.238	-83	0.176
Alcohol related	-154	0.005	-135	0.063	-155	0.064
Other liver disease	25	0.570	32	0.550	37	0.645
>1 conditions	2	0.960	10	0.851	60	0.402
Hepatic encephalopathy						
No [ref.]						
Yes	-79	0.104	-86	0.219	-40	0.576
Ascites						
No [ref.]						
Yes	205	0.000	212	0.004	176	0.020