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Association between age, substance use, and outcomes in Medicare enrollees with prostate cancer

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ABSTRACT

Objective: To analyze the association between age, substance use, and outcomes in fee-for-service Medicare enrollees with advanced prostate cancer.

Methods: Retrospective longitudinal cohort study of elderly men diagnosed with advanced prostate cancer using SEER-Medicare data between 2000 and 2009. Substance use disorder was identified using claims for alcoholic psychosis, drug psychoses, alcohol dependence syndrome, drug dependence, and non-dependent use of drugs. We compared health service use, cost, and 5-year mortality across two age-groups: young–old (66–74 years) and old–old (≥ 75 years).

Results: Cohort consisted of 8484 young–old and 5763 old–old patients with advanced prostate cancer. Prevalence of substance use was 12.4% in young–old and 7.4% in old–old group. For the young–old group, the 'drug psychoses and related' category had the highest inpatient, outpatient, and ER usage as well as the highest hazard of mortality (HR = 2.2; CI = 1.5, 3.1), compared to those without substance use. Compared to the no substance use group, those with substance use in the follow-up phase had higher inpatient and ER visits, and those with substance use in treatment phase had higher outpatient visits and highest hazard of mortality (HR = 1.6; CI = 1.4, 1.9). For the old–old group, the 'drug psychoses and related' category was associated with highest inpatient and outpatient use; and 'Non-dependent use of drugs' were associated with highest ER use, compared to those without substance use.

Conclusion: Intersection of cancer and substance use disorder in elderly patients with advanced prostate cancer covered by Medicare is age specific. An integrated and multidisciplinary approach to screen, refer, and treat substance use in patients with prostate cancer may improve outcomes and reduce costs.

1. Introduction

The US population is aging, and it is expected that by 2050, there will be 70 million individuals aged 65 years or older who will constitute 20% of the population.[1] Additionally, the life expectancy of those aged 65 years or older has increased, and thus, the number of persons over 85 years of age is expected to double by 2050, along with the number of centenarians. The

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unique combination of physical and psychosocial comorbidities experienced by elderly patients will have substantial impact on the healthcare sector. Substance use is an important psychosocial comorbidity; however, its presence among elderly patients remains under-appreciated .[2,3]

By 2020, the number of older Americans with a substance use disorder is expected to reach 5.7 million.[4,5] Alcohol and drug abuse was found to be an issue among elderly patients with trauma.[6] Treatment episode data between 1998 and 2008 showed a rise in the proportion of older adults who sought substance abuse treatment for the first time, compared to the younger population.[7] Non-cancer related pain,[8–13] insomnia, and anxiety are experienced by many elderly patients.[13] Currently, prescription drug use is reported to be second most common form of illegal substance use in the US.[14–16] In elderly prescription opioid misusers, under treatment of pain was one of the reasons that led to prescription misuse.[12] Among community-dwelling elderly patients covered by Medicare, about 22% used at least one prescription medication with addiction potential.[17]

Advancing age is a risk factor for cancer, and therefore the aging of the US population will translate into a very large cohort of elderly patients with cancer.[18] The intersection of age, substance use, and cancer has the potential to create a substantial burden on the healthcare system; however, currently we have limited knowledge of the extent and implications of substance use among patients with cancer.[19–23] For effective cancer treatment, it is critical to have the knowledge of patients' substance use as it can affect the course of treatment and outcomes.[19,21,23–32] In patients with lung cancer, research has shown a positive association between alcohol use and mortality.[27,33] Similar association was also observed in patients with head and neck cancer,[26] colorectal cancer,[33] and esophageal cancer.[30] Longer hospitalizations and higher cost was reported among patients with head and neck cancer who abused alcohol.[29] Impaired outcomes were associated with alcohol dependence among laryngectomized patients.[32] Among patients with myelogenous leukemia, cocaine users had higher mortality.[19] Substance use was prevalent among elderly patients with advanced prostate cancer and was associated with higher health service use, cost, and mortality.[25]

These findings make important contribution to the area of cancer and substance use; however, most of these studies did not focus on elderly patients with cancer to determine if the experience of substance use differed between 'young–old' (65–74 years) vs. 'old–old' (≥75 years). Survival of older patients with cancer is now spanning to 30 or more years, and the health experiences of the 'young–old' and 'old–old' groups are different.[34] The overall objective of this study was to determine the burden of substance use disorder among 'young–old' and 'old–old' patients who are Medicare fee-for-service plan enrollees with advanced prostate cancer. We also sought to determine the association between type and timing of substance use and outcomes.

2. Methods

2.1. Data

For this retrospective cohort study, we used the Surveillance, Epidemiology, and End Results (SEER)-Medicare data from the National Cancer Institute (NCI). The SEER-Medicare data links two large population-based sources of data and provide detailed information about Medicare enrollees with cancer who reside in the SEER regions. The SEER program collects data on cancer incidence, treatment, and mortality from sixteen SEER sites and encompasses 26% of the population of the USA. Of the elderly patients (aged ≥65 years) who are diagnosed with cancer and enrolled in SEER registries, 93% have been matched with Medicare enrollment records. The local institutional review board approved this study.

2.2. Study cohort

We created a cohort of men aged ≥66 years who were diagnosed with advanced prostate cancer between 2001 and 2004. The variable 'Summary stage 2000' (summ2k1) from the SEER Patient Entitlement and Diagnosis Summary file (PEDSF), was used to identify advanced prostate cancer. As claims for the year prior to prostate cancer diagnosis are necessary to determine comorbidity, we included those who were at least 66 years old at diagnosis. We defined following phases of care: pre-diagnosis phase (1 year prior to prostate cancer diagnosis), treatment phase (1-year post prostate cancer diagnosis), and follow-up phase (4 years post treatment phase).

2.2.1. Non-cancer controls

A cancer-free comparison group with and without substance use disorder was used to analyze the incremental burden of co-occurring substance use among patients with advanced prostate cancer, above and beyond that associated with advanced prostate cancer alone or substance use alone groups. For our cohort of advanced prostate cancer, we extracted a frequency matched (age and race) control group of men form the Medicare 5% non-cancer files.

2.2.2. Age-groups

For our cohort of advanced prostate cancer and controls, we created two age related sub-groups: young–old (aged 66–74 years) and old–old (aged ≥75 years).

2.2.3. Substance use disorder

For advanced prostate cancer cohort and the controls, substance use disorder was identified using following International Classification of Diseases, 9th Edition (ICD-9) codes: 291.xx (alcoholic psychosis and related); 292.xx (drug psychoses and related); 303.xx (alcohol dependence syndrome); 304.xx (drug dependence); and 305.xx (non-dependent use of drugs). For each sub-group (young–old and old–old), we identified those with substance use disorder (at least one inpatient or outpatient claim for any of the above ICD 9 codes for substance use disorder) and those without substance use disorder. For the advanced prostate cancer cohort with substance use disorder, we also developed three exclusive time-based categories of substance use as substance use in pre-phase, treatment phase, or follow-up phase.

2.3. Outcomes

Three main outcomes were health services use, cost, and mortality. Health service use was number of inpatient,

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outpatient and emergency room visits. We operationalized cost as reimbursements from Medicare. Sum of reimbursements for inpatient hospitalizations, outpatient hospital visits, physician or provider services, durable medical equipment, home health services, and hospice care were the total cost. All-cause mortality data were obtained from PEDSF files for advanced prostate cohort and from SUMDENOM files for control group. Prostate cancer-specific mortality was obtained from PEDSF file. Since SEER only reports month and year of death, we assigned middle of the month, i.e., 15 as the day of death to construct SEER date of death. For Medicare, reported mortality, Medicare day, month, and year of death were used to create Medicare date of death. The patient was coded as deceased if SEER and/or Medicare reported him so. Those who were alive at the end of 5-year follow-up period were censored.

2.4. Covariates

The covariates were socio-demographic attributes (race and ethnicity, marital status, census tract median income, census tract proportion with college education, geographic area), disease severity, comorbidity, and prostate cancer treatment. We used Medicare inpatient claims from the 1-year before prostate cancer diagnosis to develop Elixhauser comorbidity index. We identified four exclusive categories of treatments: surgery, radiation therapy, multimodal therapy (combination of surgery and/or radiation and/or hormone therapy and/or chemotherapy) and no treatment/watchful waiting.

2.5. Statistical analysis

For the two sub-groups of elderly (young–old and old–old) patients with advanced prostate cancer, we used *t*-tests and χ^2-tests to compare the demographic and clinical characteristics of those with and without substance use disorder. For assessing health service use, negative binomial regressions were used. Dependent variables for these regressions were count data on number of total inpatient hospitalizations, outpatient hospital visits, and ER visits. Association between substance use disorder and cost was analyzed using two-part models. In a two-part model, part 1 determines the odds of incurring any cost, and part 2 is restricted to those with non-zero costs. Part 2 consists of a generalized linear model (GLM) with log-link and gamma distribution variance function to analyze the association between substance use and cost. We used Cox regression models to study the association between substance use disorder and mortality. Assignments of advanced prostate cancer treatments are non-random and may affect outcomes of care. Thus, we used propensity score analysis to minimize the bias due treatment. Using multinomial logistic regression, we calculated the propensity of receiving a given advanced prostate cancer treatment as a function of patient demographic and clinical characteristics. The propensity score was used it as a covariate in the analysis. The degree of matching was compared using *t*-statistics for these covariates before and after adjustment with propensity score. For all analyses, 'those without a substance use disorder' was the reference category. Additionally, for all analysis we adjusted for the following covariates: race and ethnicity, marital status, education, geographic area, comorbidity, and median income.

To analyze the association of outcomes with advanced prostate cancer cohort (with and without substance use) and cancer-free controls (with and without substance use), we created four groups as following: non-cancer /non-substance use group (Group 1), substance use alone group (Group 2), advanced prostate cancer alone group (Group 3), and advanced prostate cancer with substance use group (Group 4). We compared unadjusted service use, cost, and mortality between these four groups. Next, logistic regression models were used to study the association between health service use and group membership. Finally, Cox models were used to study the association between all-cause mortality and group membership. The analyses adjusted for race and ethnicity, marital status, income, education, geographic area, and comorbidity. Separate analyses were performed for young–old and old–old groups. Statistical Analysis System (SAS) Version 9.4 (SAS Institute, Cary, NC, USA) was used for data analysis.

3. Results

Our cohort consisted of 8484 young–old (aged 66–74 years), and 5763 old–old (aged ≥75 years) patients who are Medicare fee-for-service enrollees diagnosed with advanced prostate cancer between 2001 and 2004. The prevalence of substance use disorder was 12.4% (n = 1050) among the young–old and 7.4% (n = 429) among the old–old. Among those with substance use, *non-dependent use of drug* was the most frequent type of substance use disorder for both young–old and old–old groups. The second most frequent type of substance use disorder was *alcohol dependence syndrome* for the young–old (n = 96), and *drug psychoses and related* for the old–old (n = 75). Number of patients with *alcoholic psychosis and related* and *drug dependence* for both sub-groups was very small and therefore these categories were excluded.

The frequency matched non-cancer cohort consisted of 8275 young–old (aged 66–74 years) and 5756 old–old (aged ≥75 years). The prevalence of substance use disorder was 10.2% (n = 842) in the young–old group and 7.3% (n = 421) in the old–old group. For both 'young–old' and 'old–old' groups, compared to non-cancer/non-substance use group (Group 1), substance use alone group (Group 2) had lower proportion of Caucasians, lower proportion of metro residents, and higher proportion of those with one or more comorbidity.

For the advanced prostate cancer cohort, in Table 1, we present a comparison between patients with and without substance use disorder within the two sub-groups (young–old and old–old). For both sub-groups, mean age was comparable of between those with and without a diagnosis of substance use disorder. Those with substance use disorder were less likely to be white, married, be from a metropolitan area, and have median census tract income of greater than $45,000. Additionally, those with substance use disorder had higher comorbidities and were more likely to have received multimodal treatment, compared with those who did not have a substance use disorder.

Table 2 presents unadjusted outcomes for advanced prostate cancer cohort and controls for the two sub-groups (young–old and old–old). For the young–old group, compared

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Table 1 – Demographic and clinical attributes (advanced prostate cancer cohort).

	Advanced-stage prostate cancer cohort			
	Young–old (age 66–74 years)		Old–old (age ≥ 75 years)	
	No substance use (n = 7434)	Substance use (n = 1050)	No substance use (n = 5334)	Substance use (n = 429)
Mean age in years (SD)	69.6 (2.5)	69.4(2.5)	81.0(5.0)	79.8.7(4.3)
Race/ethnicity (%) *				
White	5867 (78.9)	773 (73.6)	4341 (81.4)	332 (77.4)
African American	812 (10.9)	190 (18.1)	618 (11.6)	70 (16.3)
Hispanic	755 (10.1)	87 (8.2)	375 (7.0)	27 (6.3)
Geographic area (%) *				
Metro	6565 (88.3)	861 (82.0)	4625 (86.7)	347 (80.9)
Non-metro	869 (11.7)	189 (18.0)	709(13.3)	82 (19.1)
Comorbidity index (%) *				
0	6938 (93.3)	894 (85.1)	4508 (84.5)	309 (72.0)
1–2	328 (4.4)	85 (8.1)	434 (8.1)	56 (13.1)
≥ 3	168 (2.3)	71 (6.8)	392(7.4)	64 (14.9)
Marital status (%) *				
Married	5682 (76.4)	767 (73.0)	3356 (62.9)	213 (49.7)
Other	1473 (19.8)	239 (22.8)	1712 (32.2)	191 (44.5)
Unknown	279 (3.8)	44 (4.2)	266 (4.9)	25 (5.8)
Mean % of persons with at least 4 year college (SD) *	32.1 (67.7)	27.5 (70.0)	30.9 (68.2)	31.5 (90.2)
Median income for census tract (2000 census survey) (%) *				
≤$45,000	45.2	59.2	48.8	60.4
>$45,000	54.8	40.8	51.2	39.6
Grade (%) *				
Moderately	3049 (41.0)	363 (34.6)	1093 (20.5)	93 (21.7)
Poorly differentiated	3645 (49.0)	529 (50.4)	2587 (48.5)	208 (48.5)
Undifferentiated	110 (1.5)	34 (3.2)	127 (2.4)	15 (3.5)
Other	630 (8.5)	124 (11.8)	1527 (28.6)	113 (26.3)
Treatment (%)	2387 (32.1)	199 (18.9)	282 (5.3)	28 (6.5)
Surgery alone *	651 (8.8)	92 (8.8)	607 (11.4)	46 (10.7)
Radiation alone	3590 (48.3)	678 (64.6)	2539 (47.6)	260 (60.6)
Multimodal *	806 (10.8)	81(7.7)	1906 (35.7)	95 (22.1)
No treatment/watchful waiting *				

* Significant at 0.05 level.

to the non- cancer/non- substance use group (Group 1), advanced prostate cancer cohort with substance use disorder (Group 4) had highest health service utilization (impatient, outpatient, and ER), highest cost, and mortality. Additionally, the presence of substance use alone (Group 2) or advanced prostate cancer alone (Group 3) was associated with higher health serve use, cost, and mortality compared to the non-cancer/non-substance use group (Group 1). Similar patterns were observed for the old–old group: co-occurring substance use disorder in patients with advanced prostate cancer was associated with highest health service use, cost, and mortality compared to the non-cancer /non-substance use group (G1).

Table 3 presents the results of logistic regressions and survival models to study the association between outcomes and group membership (advanced prostate cancer cohort with and without substance use). For the young–old group, it was observed that compared to the non-cancer/non-substance use group (Group 1), other groups had higher odds of having an inpatient stay and ER visit. However, these odds were highest for the advanced prostate cancer group with co-occurring substance use disorder (Group 4). Also for Group 4, the odds of having an inpatient visit, an outpatient visit, and an ER visit were 17 times higher, two times higher, and eight time higher, respectively, compared to the non-cancer/non-substance use group (Group 1). Similarly, the hazard of mortality was highest for the advanced prostate cancer group with co-occurring substance use disorder (Group 4), compared to the non-cancer/non-substance use group (Group 1). Comparable results were observed for the old–old group. The presence of co-occurring substance use disorder in patients with advanced prostate cancer was associated with higher health service use, over and above that associated with advanced prostate cancer alone group (Group 3) and substance use alone group (Group 2).

3.1. Association between substance use disorder and health service use (advanced prostate cancer cohort)

3.1.1. Inpatient hospitalizations

As seen from Table 4, for the young–old group, the category *drug psychoses and related* was associated with higher inpatient hospitalizations (odds ratio [OR] = 2.9; 95% confidence interval

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Table 2 – Unadjusted, health service use, costs, and mortality (advanced prostate cancer cohort and controls).

	Age 66–74 years				Age ≥ 75 years			
	Prostate cancer cohort		*Controls*		*Prostate cancer cohort*		*Controls*	
	Substance use (*n* = 1050), *n* (%) (Group 4)	No substance use (*n* = 7434),*n* (%) (Group 3)	Substance use (*n* = 842), *n* (%) (Group 2)	No substance use (*n* = 7433), *n* (%) (Group 1)	Substance use (*n* = 429), *n* (%) (Group 4)	No substance use (*n* = 5334), *n* (%) (Group 3)	Substance use (*n* = 421), *n* (%) (Group 2)	No substance use (*n* = 5335), *n* (%) (Group 1)
***Any health service use n* (%)**								
Inpatient hospitalizations	908 (86.5)	4674(62.9)	470 (55.5)	2018 (27.1)	342 (79.7)	2966 (55.6)	164 (38.9)	1331 (24.9)
Outpatient hospital visits	693 (66.0)	2974 (40.0)	543 (64.4)	3705 (49.8)	320 (74.6)	2649 (49.7)	186 (44.7)	1938 (36.3)
ER visits	769 (73.2)	4395 (59.1)	383 (45.2)	1990 (26.5)	257 (59.9)	2187 (41.0)	145 (34.4)	1215 (22.8)
Costs in $								
Mean	77,247	47,852	57,505	26,439 (53,561)	60,760	38,845	60,089	32,579
(SD)	(43,337)	(91,710) 21,946	(81,732)	7093	(97,268)	(76,750) 13,953	(75,766)	(52,280)
Median	111,141		33,374		28,730		35,954	13,788
***Mortality n* (%)**								
All-cause	380 (36.2)	1783 (23.9)	177 (20.9)	792 (10.5)	284 (66.2)	3537 (66.3)	184 (43.7)	1894 (35.5)
Prostate cancer specific	230 (21.9)	1221 (16.4)			176 (41.0)	2417 (45.3)		

[CI] = 2.3–3.8), compared to those without a substance use disorder. Additionally, those who were identified with substance use disorder in the follow-up phase had highest inpatient hospitalization (OR = 1.9; 95% CI = 1.7–2.1), compared to those without a substance use disorder. Similar results were observed for the old–old group.

3.1.2. *Outpatient hospital visits*

A pattern similar that for inpatient hospitalizations was observed for outpatient visits. For both young–old and old–old, the category *drug psychoses and related* category was associated with the higher outpatient visits (OR = 3.2; 95% CI = 1.9–5.2, and OR = 1.9; 95% CI = 1.3–2.8, respectively). For the young–old group, substance use disorder that was identified in the follow-up phase had a statistically significant association with outpatient visits (OR 1.9; 95% CI = 1.7–2.1). On the other hand, substance use disorder in the treatment phase was associated with higher outpatient visits for the old–old group (OR = 2.1; 95% CI = 1.7–2.6).

3.1.3. *Emergency room (ER) visits*

For the young–old group, compared with those without a substance use disorder, those in the category *drug psychoses and related* had higher ER visits (OR = 1.9; 95% CI =1.3–3.1). For the old–old group, those with *non-dependent use of drugs* had higher ER visits (OR = 1.6; 95% CI = 1.2–2.1). Finally, those who had substance use disorder in the follow-up phase had the highest ER visits for the young–old group as well as for the old–old group, compared to those without substance use (OR = 1.8; 95% CI = 1.5–2.1; and OR = 1.5; 95% CI = 1.1–2.3, respectively).

3.2. Association between substance use disorder and cost of care (advanced prostate cancer cohort)

Results from the 2-part models for cost are presented in Table 5. Part 1 of the two-part model is the logistic regression where dependent variable is any cost. For young–old group, compared with the reference category 'no substance use disorder', those with *alcohol dependence syndrome* had 8.5 higher odds of incurring any cost. For the old–old group, *drug psychoses and related* category has highest odds of incurring any cost (OR = 4.2; 95% CI = 1.5–12.1). For both sub-groups (young–old and old–old), substance use disorder during the cancer treatment phase had highest odds of incurring any cost (OR = 11.2; 95% CI = 5.7–21.9; and OR = 4.5; 95% CI = 2.3–8.8, respectively).

Part 2 of the two-part model consists of GLM model with log-link and gamma distribution and is limited to those with non-zero costs. As observed, costs were higher for all types of substance use compared to those without a substance use disorder. Among the young–old group, those in the category *drug psychoses and related* had 110% higher costs compared to those without a substance use disorder. Among the old–old group, those with *non-dependent use of drugs* had 30% higher cost. Additionally, for both sub-groups (young–old and old–old), patients whose substance use disorder was identified in the follow-up phase had 60% higher costs compared with those in the reference category of 'no substance use disorder'.

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Table 3 – Association between substance use and outcomes (advanced prostate cancer cohort and controls). [a]*

	Hospitalizations OR (95% CI)	Outpatient visits OR (95% CI)	ER visits, OR (95% CI)	All-cause mortality [b], HR (95% CI)
Age 66–74 years (adjusted for socio-demographic characteristics, comorbidity, and geographic region)				
Prostate cancer + substance use (Group 4)	17.9 (14.9, 21.7)	1.9 (1.6, 2.1)	7.8 (6.7, 9.0)	3.8 (3.4, 4.3)
Prostate cancer only (Group 3)	4.9 (4.6, 5.3)	0.68 (0.63, 0.72)	4.2 (4.0, 4.6)	2.7 (2.6, 3.1)
Substance use only (Group 2)	3.1 (2.6, 3.5)	1.5 (1.3, 1.8)	2.1 (1.8, 2.5)	1.6 (1.4, 1.9)
Non-cancer/non-substance use (Group 1, reference)	–	–	–	–
Age ≥ 75 years (adjusted for socio-demographic characteristics, comorbidity, and geographic region)				
Prostate cancer + substance use (Group 4)	11.7 (9.2, 15.1)	4.9 (3.9, 6.1)	5.1 (4.1, 6.2)	2.4 (2.1, 2.7)
Prostate cancer only (Group 3)	3.9 (3.6, 4.1)	1.7 (1.5, 1.8)	2.4 (2.1, 2.5)	3.0 (2.7, 3.2)
Substance use only (Group 2)	1.9 (1.5, 2.3)	1.3 (1.0, 1.6)	1.8 (1.4, 2.2)	1.1 (0.94, 1.3)
Non-cancer/non-substance use (Group 1, reference)	–	–	–	–

[a] Logistic models.
[b] Cox proportional hazard model.

3.3. Association between substance use disorder and mortality (advanced prostate cancer cohort)

As shown in Table 5, among young–old, the category of *drug psychoses and related* was associated with the highest hazard of all-cause mortality (HR = 2.2; 95% CI = 1.5–3.1), compared to those without a substance use disorder. For the old–old group, non-dependent use of drug had protective effect on mortality, compared to those with no substance use (HR = 0.8; 95% CI = 0.7–0.9). For the young–old, the hazard of mortality was high for substance use disorder in the treatment phase (HR = 1.6; 95% CI, 1.4–1.9), compared to those with no substance use disorder. We observed comparable results from an analysis that focused on advanced prostate cancer-specific mortality (data not shown).

4. Discussion

Our results provide strong and timely evidence regarding intersection of age, advanced prostate cancer and substance use disorders. The prevalence of substance use disorder in our cohort of elderly patients with advanced prostate cancer who are Medicare fee-for-service enrollees, differed by age-group. It was higher for the young–old (aged 66–74 years) compared to the old–old (≥75 years). Compared to the non-cancer/non-substance use controls, the presence of substance use alone or advanced prostate cancer alone was associated with higher health service use, cost, and mortality. However, the co-occurring substance use in the advanced prostate cancer cohort intensified the effects on outcomes for both the young–

Table 4 – Association between health service use and substance use (advanced prostate cancer cohort).

	Hospitalizations, [a] OR (95% CI)	Outpatient visits, [a] OR (95% CI)	ER visits, [a] OR (95% CI)
Type of substance use disorder			
Age 66–74 years (adjusted for socio-demographic characteristics, treatment, clinical characteristics, and propensity score)			
Alcohol dependence syndrome	2.0 (1.7, 2.5)	2.0 (1.3, 2.9)	1.3 (0.9, 1.9)
Drug psychoses and related	2.9 (2.3, 3.8)	3.2 (1.9, 5.2)	1.9 (1.3, 3.1)
Non-dependent use of drugs	1.6 (1.5, 1.7)	1.9 (1.7, 2.2)	1.5 (1.3, 1.7)
Age ≥ 75 years (adjusted for socio-demographic characteristics, treatment, clinical characteristics, and propensity score)			
Alcohol dependence syndrome	1.5 (1.1, 2.2)	1.2 (0.7, 2.0)	0.9 (0.5, 1.9)
Drug psychoses and related	1.9 (1.4, 2.5)	1.9 (1.3, 2.8)	0.8 (0.5, 1.4)
Non-dependent use of drugs	1.6 (1.4, 1.9)	1.4 (1.1, 1.7)	1.6 (1.2, 2.1)
Period in which substance use disorder was identified			
Age 66–74 years (adjusted for socio-demographic characteristics, treatment, clinical characteristics, and propensity score)			
Pre prostate cancer diagnosis	1.4 (1.2, 1.6)	1.9 (1.5, 2.6)	1.1 (0.9, 1.5)
Cancer treatment phase	1.7 (1.5, 1.9)	2.1 (1.7, 2.6)	1.5 (1.3, 1.8)
Follow-up phase	1.9 (1.7, 2.1)	1.9 (1.6, 2.4)	1.8 (1.5, 2.1)
Age ≥ 75 years (adjusted for socio-demographic characteristics, treatment, clinical characteristics, and propensity score)			
Pre prostate cancer diagnosis	1.5 (1.2, 1.8)	1.3 (0.9, 1.8)	1.2 (0.8, 1.9)
Cancer treatment phase	1.6 (1.3, 1.9)	1.4 (1.1, 1.8)	1.3 (0.9, 1.9)
Follow-up phase	1.9 (1.6, 2.5)	1.7 (1.3, 2.3)	1.5 (1.1, 2.3)

[a] Negative binomial models.

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Table 5 – Association between cost, mortality, and substance use (advanced prostate cancer cohort).

	Total cost (two-part model)[a] Estimate (SE)		All-cause mortality[b] HR (95% CI)
	Part 1 OR (95% CI)	Part 2 OR (95% CI)	
Type of substance use disorder			
Age 66–74 years (adjusted for socio-demographic characteristics, treatment, clinical characteristics and propensity score)			
Alcohol dependence syndrome	8.4 (2.7, 26.9)	1.3 (0.9, 1.6)	1.4 (1.1, 1.8)
Drug psychoses and related	2.9 (1.2, 7.7)	2.1 (1.5, 2.8)	2.2 (1.5, 3.1)
Non-dependent use of drugs	4.9 (3.6, 6.9)	1.3 (1.2, 1.4)	1.2 (1.1, 1.4)
Age ≥ 75 years (adjusted for socio-demographic characteristics, treatment, clinical characteristics and propensity score)			
Alcohol dependence syndrome	2.2 (0.8, 5.7)	1.4 (0.9, 2.1)	0.8 (0.6, 1.2)
Drug psychoses and related	4.3 (1.5, 11.9)	1.3 (0.9, 1.7)	1.2 (0.9, 1.6)
Non-dependent use of drugs	3.4 (2.2, 5.3)	1.3 (1.1, 1.5)	0.8 (0.7, 0.9)
Period in which substance use disorder was identified			
Age 66–74 years (adjusted for socio-demographic characteristics, treatment, clinical characteristics and propensity score)			
Pre prostate cancer diagnosis	2.9 (1.7, 5.2)	1.1 (0.9, 1.3)	1.4 (1.2, 1.8)
Cancer treatment phase	11.2 (5.7, 21.9)	1.2 (1.0, 1.3)	1.6 (1.4, 1.9)
Follow-up phase	3.8 (2.5, 5.7)	1.6 (1.4, 1.7)	0.9 (0.7, 1.1)
Age ≥ 75 years (adjusted for socio-demographic characteristics, treatment, clinical characteristics and propensity score)			
Pre prostate cancer diagnosis	2.0 (1.1, 3.6)	1.1 (0.9, 1.4)	0.9 (0.7, 1.1)
Cancer treatment phase	4.5 (2.3, 8.8)	1.2 (0.9, 1.5)	1.2 (0.9, 1.4)
Follow-up phase	4.4 (1.9, 9.6)	1.6 (1.3, 1.9)	0.5 (0.4, 0.7)

[a] Two-part model. Part 1 is logistic model and Part 2 is Generalized Linear Model, gamma distribution with log-link.
[b] Cox proportional hazard model.

old and old–old. Another important finding is that the type of and timing of substance use disorder had strong association with outcomes for both age-groups. Overall, the association between substance use disorders and all outcomes was stronger for the young–old group. On the other hand, substance use disorders in the old–old group appeared to have association with health service use and cost of care. Also for the old–old group, hazard of mortality was lower for *'non-dependent use of drug'* category, compared to those without substance use. A complex interaction of personal level factors (intensity of usage, length of usage, treatment for substance use, and advanced prostate cancer) and provider level factors (physician and hospital characteristics, quality of care) may have contributed to the lower hazard of mortality in the old–old group.

Our findings make an important contribution to the research on substance use among patients with cancer. Alcohol use and withdrawal among patients with head and neck cancer was associated with longer length of hospitalization and higher costs.[29] Research has established association between alcohol, cocaine, areca nut, and mortality. For example, in patients with Myelogenous Luekemia, lifetime cocaine use was associated with a six-fold increase in mortality risk.[26] Quantity and frequency of drinking was associated with mortality in multiple cancers.[33] In patients with esophageal squamous cell carcinoma, use of substance was shown to result in poorer survival prognosis.[30] The risk of cancer increases with age and substance use is on the rise among the elderly.[4,7,21,23,31,35–38] Our results show that the effect of substance use disorder on outcomes varies across the age spectrum. For the young–old, the association between substance use and outcomes is stronger than that for old–old group.

We note following limitations of our study. Our study sample consisted of white, African American, and Hispanic patients aged 66 years and older who are enrolled in the Medicare fee-for-service plan, residing in a SEER region. SEER-Medicare linked database does not include elderly patients who are enrolled in Medicare advantage or Part C, and people younger than 65 (except for those who are Medicare eligible because they receive Social Security Disability Insurance benefits). Medicare Advantage plans are mostly offered by Health Maintenance Organizations (HMOs). These plans are not required to report service utilization data or claims,[39] and their patients tend to be healthier.[39] Younger patients eligible for Medicare generally qualify for disability and report poorer health status.[40] For these sub-groups, the synergy of age, advanced prostate cancer, and substance use disorder may be of different nature, and thus affect generalizability of our results. Additionally, mortality rates derived from SEER data may not be representative of the national cancer mortality rates.[41] Data on census tract level median income and percent with high school or college education are available from SEER-Medicare files. However, individual or patient level income and education data are not available in SEER-Medicare. Administrative data are important sources of information on public health and health services research; however, these data are subject to error.[42] Our definition of substance use disorder did not include 'surrogate' alcohol disorders. History of substance use prior to age 65 is not available in SEER-Medicare data and thus ascertaining total length of substance use is not feasible. Additionally, our study analyzed health service utilization at aggregate level and not for specific types of services (i.e., substance use related and non-substance use related). Finally, some substance use disorder codes or

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substance use disorders in general may be under-reported in the Medicare claims, leading to conservative prevalence estimates.

5. Conclusion

The experience of substance use among patients with advanced prostate cancer varies over the age continuum and further complicates the interaction of substance use and cancer. Future research needs to focus on specific and tailored strategies to screen, refer, and treat substance use in patients with advanced prostate cancer, with special consideration to patients' age. An integrated and multidisciplinary approach with tailored strategies to screen, refer, and treat substance use in patients with advanced prostate cancer is essential. Collaboration between health (primary care physicians, geriatricians, specialists, psychiatrist, nurse practitioners and other health providers) and non-health (social workers, aging service providers, community organizations) service systems are critical to address the silent epidemic of substance use among elderly patients with prostate cancer and to improve outcomes and reduce health care costs.

Disclosures and conflict of interest statements

The authors have no conflicts of interest to disclose.

Author contributions

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Study Design: R Jayadevappa, S Chhatre.
Data Acquisition: R Jayadevappa, S Chhatre.
Quality Control of Data and Algorithms: R Jayadevappa, S Chhatre.
Data Analysis and Interpretation: R Jayadevappa, S Chhatre.
Statistical Analysis: R Jayadevappa, S Chhatre.
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